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RESEARCH ARTICLE
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Evaluation of the Relationship Between Vitamin D Receptor Gene Polymorphism and Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Objective: The paradoxical relationship between cancer and vitamin D has been known since 1990. Vitamin D receptor (VDR) is found in several tissues and, in contrast to popular belief, it is not only responsible for calcium and phosphorus metabolism but also associated with several other metabolic events. We conducted this study to investigate the effects of these factors on head and neck cancers by examining vitamin D, calcium, and phosphorus levels and polymorphisms of the VDR genes FokI and Bsm in patients with head and neck cancer.
Material and Methods: A total of 51 patients with head and neck squamous cell carcinoma aged 31-88 years and 51 healthy individuals aged 33-89 years who applied to the otorhinolaryngology outpatient clinic of Mersin University Faculty of Medicine were included in this study.
Results: No difference was observed in the distribution of the genotype ratios of the VDR genes FokI and Bsm between the two groups. However, a statistically significant difference was found in calcium levels between the two groups.
Conclusion: An individual with known VDR gene polymorphisms can provide possible risk information regarding which disease risk group he/she is in, and VDR gene polymorphism can be used as a biomarker.
Keywords: Vitamin D, genes, neoplasms, calcium, phosphorus, real-time polymerase chain reaction

INTRODUCTION

Head and neck cancers can be found in a wide range of anatomical areas, including the salivary glands, parts of the upper aerodigestive system, and parts of the ear (1).

Several studies conducted after 1990 found important evidence of an inverse relationship between cancer and vitamin D (2). After calcitriol enters the cell, it clenches the vitamin D receptor (VDR), creating an active complex that subsequently binds to nuclear chromatin, viz., the area on the DNA known as the vitamin D response element (VDRE) (3). VDR is one of the factors responsible for regulating vitamin D transcription. The human VDR gene, which is located on chromosome 12q12-q14, is a protein of 50 kD, consisting of 427 amino acids. Four different polymorphisms of VDR gene have been identified, viz., *FokI*, *Bsm*, *ApaI*, and *TaqI* (4).

The hematopoietic and immune system; heart, skeletal, and smooth muscle tissues; brain; liver, breasts, endothelium, skin (keratocytes, melanocytes, and fibroblasts), and endocrine glands (pituitary gland, parathyroid glands, and pancreatic islet beta cells); adrenal cortex and medulla thyroid; and ovaries and testicles are among the tissues with VDRs. In this manner, the antiproliferative effect of $1,25(OH)_2D$ responds to malignancies developed in these tissues (5).

Polymorphism is used to determine risk levels in people for diseases such as cancer, coronary heart disease, and diabetes and for the prenatal diagnosis of genetic diseases and detecting

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heterozygous carriers, tissue typing for organ transplantation, paternity testing, and forensic studies. In this regard, polymorphism is currently defined as a genetic marker (6).

Polymorphism of VDR genes is considered effective to determine cancer development or progression. VDR plays an important role in cell signaling pathways and cellular interactions that result in cancer progression (7).

A positive correlation has been found between *FokI* polymorphism and breast cancer. A comparative study in Europe involving 5,284 cases and 7,500 controls showed a significant increase in breast cancer risk in subjects with *FokI* polymorphism (8). It has been believed that inherited VDR variants exert an impact on cancer risk. Furthermore, a relationship may exist between the disease stage and survival rate and VDR polymorphism in patients with lung malignant neoplasm (small cell) (9). Another study reported an increase in the 245th codon mutation rate and VDR gene polymorphism in the Ff/ff genotype (10).

One study of patients with prostate cancer reported that calcium sensor receptor, estrogen receptor alpha, and VDR polymorphisms exert an effect on carcinogenesis and proliferation in prostate glands. Polymorphism of the VDR gene *Bsm* and especially the Bb/BB genotype were found to increase the risk of developing prostate cancer (11).

Regarding VDR, calcium sensor receptor polymorphism, and colorectal cancer risk, despite research on polymorphisms of the VDR genes *FokI* and *Bsm*, and although no relationship was observed between *FokI* and colorectal cancer, it was reported that a relationship might exist between *Bsm* polymorphism and colorectal cancer risk (12). A study conducted in Japan demonstrated that calcium and vitamin D levels were associated with breast malignancies in postmenopausal and premenopausal women (13). Another study reported that calcium, vitamin D, and retinol exert an effect on pancreatic cancer (14).

Consumption of 1,000–2,000 IU/day to reach at least 30 ng/ml of vitamin D, provided that daily calcium intake is not more than 1,000 mg/day, was found to be effective in preventing colorectal cancer (15).

We conducted this study to identify the possible relationships between VDR gene polymorphisms and head and neck squamous cell cancers.

MATERIAL and METHODS

The study sample consisted of 102 participants, with 51 individuals (patient group, Group 1, 8 women and 43 men, age 31–88 years) diagnosed with head and neck squamous cell carcinoma, who applied to the otorhinolaryngology outpatient clinic of Mersin University Medical Faculty Hospital, and 51 individuals (control group, Group 2, 9 women and 42 men, age 33–89 years) who have never been diagnosed with head and neck squamous cell carcinoma and do not have a history of any systemic disease.

When selecting the control group, key demographic factors such as age, gender, and geographical location were considered, providing a baseline for comparative analysis against the patient group.

Peripheral venous blood samples of the participants were collected into EDTA tubes, and their sera samples were collected into uncontained biochemistry tubes for separation.

Vitamin D3 levels in the blood samples collected in EDTA tubes were determined using the Cobas 800 autoanalyzer at the medical biochemistry laboratory of Mersin University. The

Table 1: Gender distribution of patient and control groups

Region	Number of people	%	Male/Female ratio
Larynx	31	60.78	14.5/1
Lip	4	7.84	4/0
Tongue	3	5.89	2/1
Retromolar Trigone	3	5.89	1/2
Parotid gland	2	3.92	1/1
External auditory canal	1	1.96	0/1
Paranasal Sinuses	1	1.96	1/0
Tongue Base + epiglottis	1	1.96	1/0
Squamous cell carcinoma of unknown primary in the head and neck (supraclavicular area)	1	1.96	1/0
Buccal	1	1.96	0/1
Floor of mouth	1	1.96	1/0
Nasal vestibule	1	1.96	1/0
Gingiva and alveolar arch	1	1.96	0/1

Table 2: Distribution of VDR *FokI* polymorphisms among genotypes in patient and control groups

			Group		Total
			Control	Patient	
FokI	Allele C	Number of people	24	24	48
		% *FokI*	50.0%	50.0%	100.0%
		% In groups	48.0%	47.1%	47.5%
		% Total	23.8%	23.8%	47.5%
	Allele T	Number of people	6	6	12
		% *FokI*	50.0%	50.0%	100.0%
		% In groups	12.0%	11.8%	11.9%
		% Total	5.9%	5.9%	11.9%
	Heterozygous	Number of people	20	21	41
		% *FokI*	48.8%	51.2%	100.0%
		% In groups	40.0%	41.2%	40.6%
		% Total	19.8%	20.8%	40.6%
Total		Number of people	50	51	101
		% *FokI*	49.5%	50.5%	100.0%
		% In groups	100.0%	100.0%	100.0%
		% Total	49.5%	50.5%	100.0%

Table 3: Distribution of VDR *Bsm* polymorphisms among genotypes in patient and control groups

			Group		Total
			Control	Patient	
Bsm	Allele G	Number of people	25	26	51
		% *Bsm*	49.0%	51.0%	100.0%
		% In groups	50.0%	51.0%	50.5%
		% Total	24.8%	25.7%	50.5%
	Allele A	Number of people	8	10	18
		% *Bsm*	44.4%	55.6%	100.0%
		% In groups	16.0%	19.6%	17.8%
		% Total	7.9%	9.9%	17.8%
	Heterozygous	Number of people	17	15	32
		% *Bsm*	53.1%	46.9%	100.0%
		% In groups	34.0%	29.4%	31.7%
		% Total	16.8%	14.9%	31.7%
Total		Number of people	50	51	101
		% *Bsm*	49.5%	50.5%	100.0%
		% In groups	100.0%	100.0%	100.0%
		% Total	49.5%	50.5%	100.0%

blood samples in the EDTA tubes were stored at +4°C until DNA isolation. Calcium and phosphorus levels of the serum, which was separated by centrifugation at 3,000 rpm for 600 s, and peripheral venous blood samples were kept in frameless biochemistry tubes for 600 s and then examined in the Cobas 400 autoanalyzer.

Statistical analysis

Statistical analyses were conducted using the STATISTICA 7.0 package program. Numerical data were subjected to the Kolmogorov–Smirnov normality test. Independent t-test and Mann–Whitney U test were used for comparing two groups.

Table 4: Distribution of VDR *FokI* polymorphisms between genotypes and biochemical parameters in patient and control groups

FokI	Group		Number	Mean	Standard deviation
Allele C	Control	Ca	24	12.872	8.487
		D3	24	14.589	10.156
		Valid N	24		
	Patient	Ca	24	9.013	0.752
		D3	24	11.718	5.064
		Valid N	24		
Allele T	Control	Ca	6	20.848	11.041
		D3	6	9.950	1.413
		Valid N	6		
	Patient	Ca	6	9.036	0.160
		D3	6	16.658	9.716
		Valid N	6		
Heterozygous	Control	Ca	20	10.354	4.564
		D3	20	14.994	9.917
		Valid N	20		
	Patient	Ca	21	9.417	0.540
		D3	21	15.316	9.529
		Valid N	21		

Table 5: Distribution of VDR *Bsm* polymorphisms between genotypes and biochemical parameters in patient and control groups

Bsm	Group		Number	Mean	Standard deviation
Allele G	Control	Ca	25	12.098	6.432
		D3	25	10.421	4.550
		Valid N	25		
	Patient	Ca	26	9.235	0.565
		D3	26	13.661	6.780
		Valid N	26		
Allele A	Control	Ca	8	15.233	12.480
		D3	8	18.011	11.815
		Valid N	8		
	Patient	Ca	10	9.345	0.834
		D3	10	9.982	4.783
		Valid N	10		
Heterozygous	Control	Ca	17	12.752	8.015
		D3	17	17.947	11.699
		Valid N	17		
	Patient	Ca	15	8.983	0.643
		D3	15	16.715	9.924
		Valid N	15		

Chi-square independence test statistics were used for nominal and categorical data. Descriptive statistics were also presented and considered statistically significant when p≤0.05.

This study was approved by the Clinical Research Ethics Committee of Mersin University (Date: 12.02.20215, No:38).

RESULTS

The gender distribution of the 51 patients with head and neck cancer according to the site of cancer is shown in Table 1.

There were 43 men and eight women in control patients, 42 men and nine women in the patient group. The mean age of subjects in the control group was 61.59±12.766 years, and that of subjects in the patient group was 64.49±11.231 years, with no significant difference in terms of age distribution (p=0.200).

Serum Ca levels did not show a normal distribution in the control group (p=0.001) but showed a normal distribution in the patient group (p=0.200), with differences being observed between the study groups (p=0.001). Serum phosphorus levels exhibited a normal distribution in the control group (p=0.200) but not in the patient group (p=0.040); however, there was no difference in phosphorus levels between the groups (p=0.864). Vitamin D3 levels showed a normal distribution in both groups (p=0.001 in the control group, p=0.019 in the patient group), with no difference being detected between the groups (patient vs control p=0.848).

Tables 2 and 3 show the percentage distribution of polymorphisms of the VDR genes *FokI* and *Bsm* among the genotypes in the study groups. There was no difference between the groups in the genotype ratio distribution of *FokI* (p=0.903) and *Bsm* (p=0.837). No difference was observed in the relationship between the groups in terms of *FokI* (p=0.993) and *Bsm* (p=0.754).

VDR *FokI*: The CC genotype rate was 47.1% in Group 1 and 48% in Group 2. The heterozygous (CT) genotype rate was 41.2% in Group 1 and 40% in Group 2. The TT genotype rate was 11.8% in Group 1 and 12% in Group 2.

VDR *Bsm*: The AA genotype rate was 19.6% in Group 1 and 16% in Group 2. The heterozygous (GA) genotype rate was 29.4% in Group 1 and 34% in Group 2. The GG genotype rate was 51% in Group 1 and 50% in Group 2.

No difference was detected between the groups in terms of the percentage distributions of allele C, allele T, and heterozygous genotype (p=0.903). Ca levels were different between the groups in individuals carrying the T allele (p=0.034). Vitamin D levels were different between groups in individuals carrying the A allele (p=0.028). Tables 4 and 5 show the distribution of polymorphisms of the VDR genes *FokI* and *Bsm* between genotypes and biochemical parameters.

DISCUSSION

VDR mediates the activity of vitamin D and participates in a variety of processes, including the regulation of cell proliferation and differentiation in normal tissues and cell death and cell adhesion in neoplastic cells. VDR gene and its polymorphism and vitamin D levels may be associated with malignancy. Vitamin D possesses extremely strong antineoplastic features. Calcitriol is an anti-reproductive and prodifferentiation factor for several cell types, including human squamous cells. *FokI* and *Bsm* are several polymorphisms of the VDR gene (16).

Gandini et al. investigated the relationship between vitamin D levels and gastrointestinal, endocrine, and genitourinary cancer (colorectal, breast, and prostate cancer) and observed an inverse relationship between vitamin D levels and colorectal cancer risk. An insignificant decrease in the risk of developing breast malignant tumors was found, but other studies have detected no relationship between vitamin D levels and breast cancer. Moreover, no relationship was detected between vitamin D levels and prostate cancer (17, 18).

Polymorphisms in the gene encoding VDR may exert an effect on cancer risk (19). Although numerous studies have analyzed VDR polymorphisms, their general relationship with carcinogenesis remains controversial. Significant relationships have been reported between VDR gene polymorphisms and breast (*FokI*, *Bsm*, and *ApaI*), prostate (*FokI*, *Bsm*, and *TaqI*), colorectal (*FokI*, *Bsm*, and *TaqI*), and skin (*FokI*, *Bsm*, *TaqI*) (20) cancers. There is only one study in the English literature on the relationship between head and neck cancers and polymorphism of the VDR gene *FokI*, whereas there is no study on *Bsm*. Liua et al. examined 719 patients with otorhinolaryngological squamous cell carcinoma for VDR polymorphism (FokI ff homozygous) in Texas and found a difference in polymorphism between patient and control groups. However, in our study, there was no relationship between VDR gene polymorphisms (*FokI* and *Bsm*) and head and neck squamous cell carcinoma (21). This difference between our study and that by Liua et al. may be due to difference in the number of study subjects.

A study by the European Prospective Investigation into Cancer and Nutrition (EPIC) demonstrated that patients who have an adequate level of vitamin D concentration in their blood circulation have a reduced risk of developing head and neck cancer and exhibit a higher rate of survival after diagnosis (22). A high phosphorus content is responsible for tumor growth and progression (23, 24).

In our study, no difference was detected between Group 1 and Group 2 in the levels of vitamin D (control: 14.110±9.374, patients: 13.90±7.656) and phosphorus (control: 3.405±0.628, patients: 3.441±0.785). These differences may be related to environmental factors (exposure to sunlight, nutrition). Hypocalcemia occurs in approximately 30% of all patients diagnosed with prostate cancer (25).

CONCLUSION

Hypocalcemia was observed in 15.68% of the patients. When calcium levels and genotype distributions of *FokI* polymorphisms were examined, individuals with *FokI* T allele and patients with HNSCC have lower blood calcium levels

than subjects in a randomly selected group. A comparison of calcium levels and *FokI* polymorphism alleles in our total sample of 102 participants revealed that individuals with the T allele have lower levels of calcium. When the *Bsm* VDR gene polymorphism was examined, the vitamin D level showed a statistically significant difference in individuals with the A allele. The different results obtained in studies on the relationship between *FokI* and *Bsm* polymorphisms and patients with HNSCC in different ethnic populations are not yet sufficient to explain the pathophysiological mechanism of the event. Our findings indicate that the investigated biochemical parameters (vitamin D, phosphorus, and calcium) are associated with the activity of VDR gene polymorphisms (*FokI* and *Bsm*). Confirmation of these findings through larger studies by including more participants and all exons, introns, and promoter regions Finding the VDR gene would make this study highly valuable.

Although the sample size for this study was determined based on available resources and time constraints, we acknowledge that future studies using larger sample groups may further confirm our findings. The results of our study differ from some findings in the literature. We believe that these discrepancies arise from variations in the genetic diversity of study populations, methodological approaches, or the specific polymorphisms analyzed. Our study did not extensively investigate environmental and lifestyle factors that could affect vitamin D levels and VDR gene polymorphisms. Future research should consider factors such as sun exposure, dietary habits, and smoking status. The specific biological mechanisms by which VDR gene polymorphisms might affect the risk of developing HNSCC remain unclear; however, considering the role of VDR in regulating cell growth and differentiation, these gene variations could be hypothesized to play a significant role in cancer development.

According to our results, an individual with known VDR gene polymorphisms can be informed about which disease risk group he/she is in, and VDR polymorphisms can be used as a bioindicator. Therefore, by being aware of their risk group in advance, individuals can have a better quality of life by making changes in their lifestyle and diet.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Mersin University (Date: 12.02.20215, No:38).

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

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Author Contributions: Conception/Design of Study- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Data Acquisition- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Data Analysis/Interpretation- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Drafting Manuscript- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Critical Revision of Manuscript- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Final Approval and Accountability- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Material or Technical Support- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.; Supervision- S.C., Z.N.Ü., K.K.B., H.G., O.İ., M.Ü.

Conflict of Interest: The authors have no conflict of interest to declare.

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RESEARCH ARTICLE
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Clinical Outcomes of Supraglottic Laryngeal Cancer: Insights from a Decade of Surgical Treatment

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ABSTRACT

Objective: This study sought to retrospectively examine the clinical outcomes of patients treated for supraglottic laryngeal cancer at a single center over a decade, assess the efficacy of surgical interventions, and evaluate survival rates in comparison to current literature.

Materials and Methods: A retrospective analysis was conducted on 84 patients diagnosed with supraglottic laryngeal cancer who underwent surgical treatment between January 2008 and December 2018. Nonlaryngeal head and neck malignancies and inaccessible patient records were excluded. The study evaluated factors including tumor location, tumor stage, lymph node metastasis, surgical approach, complications, histopathological findings, and adjuvant therapy. Statistical analysis involved descriptive methods, frequencies, and ratios, with outcomes compared to existing literature.

Results: The cohort primarily consisted of male patients (91.7%) with an average age of 58.04 years. Squamous cell carcinoma was the predominant histopathological type (98.8%), exhibiting various degrees of differentiation. Most patients presented with advanced-stage disease (III or IV), with 53.6% undergoing total laryngectomy. Neck dissection was performed in 95.2% of cases, and 69% received postoperative radiotherapy. The 5-year overall survival rate was 72.2%, with a recurrence rate of 7.1%.

Conclusion: This study reveals that supraglottic laryngeal cancer, predominantly affecting older males, is frequently diagnosed at advanced stages. Surgical intervention resulted in a 5-year survival rate consistent with existing literature. Despite the limitation of its retrospective design and the small, single-center sample, the findings support current treatment modalities while underscoring the importance of early detection and further research.

Keywords: Supraglottic laryngeal cancer, squamous cell carcinoma, neck dissection, total laryngectomy, partial laryngectomy

INTRODUCTION

Laryngeal cancer ranks as the second most prevalent type of tumor among upper aerodigestive tract tumors (1), with squamous cell carcinoma representing approximately 95% of cases. Noteworthy risk factors for laryngeal cancer include tobacco smoking and alcohol consumption (2). Predominantly, laryngeal cancers occur in the glottis, followed by the supraglottic region, while subglottic localization is exceptionally rare (3).

For supraglottic laryngeal cancers, a single treatment modality is favored for T1 and T2 tumors, whereas combined treatment is often necessary for T3 and T4 tumors. Surgical options for supraglottic cancers encompass partial laryngectomy and total laryngectomy. Partial laryngectomy is typically utilized for T1 and T2 and selected T3 tumors, while total laryngectomy is reserved for T3 and T4 tumors (4, 5). Supracricoid partial laryngectomy with cricohyoidopexy is particularly indicated for supraglottic carcinomas involving the glottic level or preepiglottic space, demonstrating reduced vocal fold mobility, or displaying limited thyroid cartilage invasion (6). Specifically, total laryngectomy is recommended for supraglottic cancers with interarytenoid extension, extralaryngeal spread, involvement of the posterior supraglottic region, or extensive extension of the tongue root (7).

Supraglottic squamous cell carcinoma (SCC) typically presents with evident clinical signs, and occult regional metastases are frequently observed, with a tendency to spread to levels II, III, and IV. Pathological investigations have indicated that the rates of cervical metastasis vary according to the stage of the

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disease, with percentages of 10% for T1, 29% for T2, 38% for T3, and 57% for T4 stages of supraglottic lesions (8). Bilateral metastases are also prevalent (9). Due to these differing metastasis rates, the standard approach for managing the neck in supraglottic SCC involves bilateral selective neck dissection of levels II–IV (10).

This retrospective study analyzed patients diagnosed with supraglottic laryngeal cancer who received treatment at our clinic. The objective was to evaluate the efficacy of different treatment modalities across various stages of the disease.

MATERIALS and METHODS

The research involved 84 patients diagnosed with and surgically treated for supraglottic laryngeal cancer between January 2008 and December 2018. Ethics committee approval was secured for the study (Approval Date: 20.10.2022, No: 331). It was conducted retrospectively through a review of patient records. Patients with head and neck malignancies other than laryngeal cancer, those with tumors located in the glottis or subglottis, and those with inaccessible files were excluded. Data on tumor location, size, and stage were collected, along with assessment of lymph node metastasis. Detailed records were kept on surgical procedures, postoperative complications, histopathological findings (including surgical margins, lymphovascular invasion, perineural invasion), and postoperative radiotherapy.

Postoperative monitoring of patients included monthly head and neck examinations and laboratory tests during the first year after surgery, followed by examinations every 3 months in the subsequent year and then every 6 months thereafter.

Statistical analysis

The primary data variables, encompassing demographic and clinical characteristics, histopathologic findings, surgical procedures, and treatment results, underwent thorough analysis. Basic statistical techniques were employed to assess data distribution and central tendencies (including mean, median, standard deviation, etc.). Frequency distributions for categorical variables such as tumor staging, degree of differentiation, and surgical interventions performed were determined, and the associations among these variables were illustrated through percentage distributions and ratios. Descriptive statistics were utilized to present the data, and the outcomes derived within this framework were compared with similar findings from analogous studies in existing literature.

Table 1: Patient demographics and clinical characteristics

		n=84	%
Age		58.04±8.92	
Sex	Male	77	91.7
	Female	7	8.3
Histopathology	Squamous cell carcinoma	83	98.8
	Pleomorphic Adenoma	1	1.2
Stage	Stage I	4	4.7
	Stage II	9	10.7
	Stage III	52	62
	Stage IV	19	22.6

RESULTS

In this study, a total of 84 patients were examined. Among these individuals, 77 (91.7%) were male, while 7 (8.3%) were female. The average age of the patients was 58.04 years (SD: 8.92). Histopathological analysis revealed pleomorphic adenoma in only one patient, with SCC diagnosed in the remaining 83 patients (98.8%). Among the SCCs, 24 (28.9%) were classified as well differentiated, 43 (51.8%) as moderately differentiated, and 16 (19.3%) as poorly differentiated. In terms of tumor staging, 4 (4.7%) tumors were categorized as stage 1, 9 (10.7%) as stage 2, 52 (62%) as stage III, and 19 (22.6%) as stage IV, indicating advanced stage (Table 1).

Among the 45 patients who underwent total laryngectomy, the primary factor guiding this decision was the presence of extralaryngeal spread, which was observed in 32 patients. Total laryngectomy was also conducted for eight patients due to involvement of the interarytenoid region and for five patients due to extensive involvement of the base of the tongue. Supracricoid laryngectomy was performed on 15 patients, primarily indicated for 9 patients with supraglottic carcinomas affecting the glottic level and for 6 patients with limited invasion of the thyroid cartilage. These surgical determinations were based on comprehensive preoperative evaluations, including imaging and histopathological evaluations. Additionally, 25 patients (29.7%) underwent supraglottic laryngectomy, and 1 patient (1.2%) underwent vertical hemilaryngectomy. Neck dissection was carried out in 80 patients (95.2%), while 4 patients did not undergo this procedure. These patients were at the T1 stage with no clinical or radiological evidence of metastatic lymph nodes. However, this approach was not universally applied to all T1 patients with similar clinical and radiological findings, as decisions were based on meticulous evaluation of clinical and radiological aspects. Postoperative adjuvant radiotherapy was administered to 58 patients (69%),

Table 2: Treatment methods and clinical follow-up outcomes

	Patients (n, %)
Total laryngectomy	45 (53.6)
Supraglottic laryngectomy	25 (29.7)
Supracricoid laryngectomy	13 (15.5)
Vertical hemilaryngectomy	1 (1.2)
Neck dissection +	80 (95.2)
Neck dissection	4 (4.8)
Adjuvant radiotherapy	58 (69)
Concurrent chemoradiotherapy	19 (22.6)

with concurrent chemotherapy provided to 19 of these patients (Table 2).

Recurrence was observed in 6 (7.1%) patients during the post-treatment follow-up period. Among them, one patient experienced local recurrence and subsequently underwent total laryngectomy. Regional recurrence occurred in five patients, with two having metastatic lymph nodes in the left neck region (levels 3–4), measuring 2 cm and 3 cm, respectively, and two others having metastatic lymph nodes in the right neck region (levels 4–5), measuring 3 cm and 4 cm, respectively. In one patient, a 3-cm metastatic lymph node was identified at level 2A in the right neck region. Excision was performed for patients with regional recurrence. The average follow-up duration was 68.8±31.53 months. Analysis of patient survival rates revealed a 5-year overall survival of 72.2% across all stages (Figure 1).

Pharyngocutaneous fistula formation occurred in 7 (15.6%) out of 45 patients who underwent total laryngectomy. Stoma narrowing necessitating tracheostoma revision surgery was observed in three (6.7%) of the total laryngectomy patients. Aspiration pneumonia was reported in 4 out of 15 patients (26.7%) who underwent supracricoid laryngectomy and 4 out of 25 patients (16%) who underwent supraglottic laryngectomy. Hematoma developed in 4 out of 80 patients (5%) who underwent neck dissection, requiring reoperation for bleeding control.

DISCUSSION

The larynx is composed of three primary regions: the glottis, supraglottic, and subglottic. Supraglottic region cancers represent approximately 50% of all laryngeal cancers (11). Cancers in the supraglottic site are typically identified later than those in the glottic site, often resulting in more advanced disease stages. Patients frequently seek medical attention at an advanced stage, primarily due to the nonspecific symptoms of the disease (12, 13). Consistent with the literature, most patients in our study (74.6%) were diagnosed at stage III or IV.

Laryngeal cancers are more prevalent in men than in women (14). Studies have reported that estrogen receptors offer protective effects in women (15). The most common age group affected is individuals over 50 years old (14). In our study, over 90% of the patients were male and the average age exceeded 50 years. These findings align with those reported in existing literature.

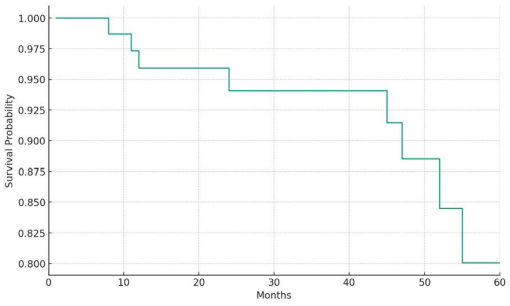

Figure 1: Survival curve by Kaplan–Meier

Literature reports indicate that up to 95% of laryngeal cancers manifest as SCCs (2). Similarly, in our study, 98.8% of patients received a diagnosis of SCC based on histopathological evaluations. This underscores the predominance of SCC in most cases of supraglottic cancer. Furthermore, it has been noted that a majority of SCCs exhibit moderate differentiation (16). Correspondingly, intermediate differentiation was the most common finding in our study.

In the treatment of laryngeal cancers, surgery or radiotherapy is typically favored as the primary intervention. Following surgery, neoadjuvant radiotherapy and chemotherapy may be administered based on histopathological findings. Treatment planning takes into account factors such as tumor location, disease stage, patient's nutritional status, overall health, and individual preferences (17-19). Cancers affecting the supraglottic region can be managed with either partial or total surgical approaches. Numerous studies in the literature have explored this topic. Partial surgery has shown comparable efficacy to total laryngectomy in patients meeting appropriate criteria (20-24). In our study, partial surgery was chosen for patients deemed suitable candidates.

Assessing the neck is crucial in managing supraglottic cancers, as the likelihood of lymphatic metastasis increases significantly from 15% at T1 stage to 75% at T4 stage (25). Supraglottic tumors have the potential to spread bilaterally to the neck (26). Recurrence in the neck region can lead to treatment failure. Due to the approximately 20% risk of occult metastasis in N0 stage supraglottic cancers, elective neck dissection is generally recommended (27). In our study, neck dissection was conducted, and radiotherapy was administered based on histopathological examination results of surgically removed tissue samples, considering factors like positive surgical margins, cartilage invasion, and lymph node metastasis.

The 5-year survival rate for supraglottic laryngeal cancers is around 70%, with survival rates decreasing as the stage advances (28, 29). In our investigation, the 5-year survival rate across all was 72.2%, consistent with literature findings.

In existing literature, the incidence of pharyngocutaneous fistula formation following total laryngectomy ranges from 8.7% to 22% (30). In our research, fistula formation was observed in 15.6% of total laryngectomy patients. Reported rates of tracheostomy stenosis vary between 4% and 40% in the literature (31). In our study, 6.7% of patients experienced tracheostomal stenosis, necessitating surgical intervention in all cases. Aspiration pneumonia rates after supraglottic and supracricoid laryngectomy may exceed 20% (32). Similarly, in our investigation, rates of aspiration pneumonia following these procedures aligned with literature findings. The literature reports a risk of neck hematoma after major head and neck surgery at approximately 4%, a potentially life-threatening complication (33). Consistent with existing literature, our

study observed hematoma development at a rate of 5%, with successful management of bleeding in all cases.

This study has several limitations. First, it utilized a retrospective design, which typically introduces more bias compared to prospective studies. The retrospective review of patient files may have influenced the results due to potential missing information or biases in the records. Second, the study sample consisted of 84 patients, which might not adequately represent variations observed in larger patient populations. Lastly, the study was conducted at a single center, raising concerns about the generalizability of the findings to the broader population or other healthcare facilities. These limitations should be taken into account when interpreting the study results.

CONCLUSION

This study conducted a retrospective analysis of patients diagnosed with supraglottic laryngeal cancer, indicating a higher incidence among men, predominantly diagnosed at advanced stages, with SCC being the most prevalent type. The study emphasized the effectiveness of treatment regimens, underscored the significance of neck dissection and adjuvant therapies, and found that 5-year survival rates were consistent with existing literature. However, limitations such as the retrospective design, limited patient cohort, and data collection from a single center restrict the generalizability of the results. These findings are pertinent for evaluating treatment strategies, guiding future prospective research, and stressing the importance of early detection and tailored treatment approaches. While the observed survival rates support the efficacy of current treatments, they also indicate the necessity for more comprehensive investigations to enhance the management of this cancer subtype and develop personalized therapies.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences, Ümraniye Training and Research Hospital (Approval Date: 20.10.2022, No: 331).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflict of interest to declare.

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RESEARCH ARTICLE
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A Comparative Study of Laryngopharyngeal Reflux Disease and Migraine: Insights From a Hospital-Based Analysis

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ABSTRACT

Objective: There has been ongoing discussion regarding the diagnosis of headaches stemming from multiple causes. Migraine and laryngopharyngeal reflux disease (LPRD) are frequently overlooked contributors to headaches, necessitating increased attention. Patients exhibiting diverse headache manifestations require tailored treatment options as part of their regular care. This study aims to determine whether LPRD and migraines occur concurrently or have distinct origins for headaches, as well as whether variations in lifestyle have an impact on health and well-being.

Materials and Methods: Four hundred fifty patients were assessed through clinical diagnosis, and conservative treatment was recommended, with a strong emphasis on adopting favorable lifestyle practices.

Results: The treatment outcomes were monitored during followup appointments, and data were tabulated to identify any correlation between LPRD and migraines.

Conclusion: This study suggests that LPRD and migraines coexist as contributing factors to headaches rather than representing entirely separate entities.

Keywords: Coexist, intermingle, LPRD, lifestyle measures, migraine

INTRODUCTION

Headache represents a prevalent symptomatology encountered by ENT practitioners globally. Regardless of gender and age, most adults experience headaches at some point, ranging from mild to severe, as documented in literature. Headaches may stem from hyperactivity in pain-sensitive regions, classified as primary type such as migraines or secondary due to conditions like laryngopharyngeal reflux disease (LPRD) that trigger these pain-sensitive areas. Amidst our hectic lifestyles and pursuit of luxury, we often overlook minor headache triggers and focus on less common sources of headaches. By redirecting attention toward adopting pertinent lifestyle adjustments, a lasting solution to the underlying cause of most headaches can be attained (1, 2).

Objective

- To investigate potential synergy between LPRD and migraine
- To examine whether LPRD and migraine mutually influence each other
- To raise awareness about the role of lifestyle modifications in enhancing overall health

MATERIALS and METHODS

A prospective followup study involving 450 patients was conducted at a Tertiary Care Hospital in Karnataka from September 2020 to October 2023. These patients had been experiencing headaches for more than 3 months. A comprehensive assessment of all participants was carried out to determine the underlying cause of their headaches, following the acquisition of informed consent. Subsequently, a treatment plan was devised after undergoing institutional ethical review, with registration number ECR/1358/Inst/KA/2020.

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Inclusion criteria

- Only two causes for headaches, namely migraine and LPRD, were considered for inclusion in the study.
- No gender bias was applied.
- Only adults aged between 18 and 60 years were included.

Exclusion criteria

- Any other potential causes of headaches were excluded from consideration in the study.
- Individuals younger than 18 or older than 60 years of age were not included.

RESULTS

Among the patients categorized by headache type, 278 individuals exhibited a combination of primary and secondary (PriSec) headaches. The remaining 67 patients experienced migraine as the primary type of headache, while 105 patients presented with LPRD as the secondary type of headache.

DISCUSSION

There have been frequent and significant changes occurring daily, complicating simple survival. In the whirlwind of life, we often disregard or prioritize our health to chase our dreams. The challenge lies in achieving the impossible and reaching greater heights rapidly, often at the expense of our well-being in this laidback lifestyle (3, 4). Stress accumulates within us unnoticed, erupting suddenly as headaches. The saying "Health is Wealth" has reversed in today's reality (5-7).

In the monotonous routine, headaches have become a prevalent symptom in these stress-filled times. Studies indicate that nearly everyone experiences at least one headache episode in their lifetime, necessitating prompt treatment after identifying the underlying cause (8, 9). LPRD and migraines are now recognized as common causes of headaches, previously overlooked (10, 11).

Healthcare providers, primarily focused on managing primary headache causes like migraines, often overlook secondary causes such as LPRD. Headaches can originate from overactivity in pain-sensitive areas such as nerves, blood vessels, and muscles in the head and neck, or from chemical activity changes in the brain (12, 13).

Over 30% of the population silently suffers from LPRD due to their habits. Gastric contents regurgitate after food intake, leading to irritation of the esophagus, which can progressively damage its mucosal lining over time. Sedentary lifestyles and stress contribute to approximately 20% of adults experiencing heartburn at least once a week and 10% experiencing it daily (14, 15).

Migraine, a debilitating neurological condition, affects 2% of the general population. Those with chronic migraine endure headaches on 15 or more days per month, often accompanied by additional symptoms. They experience frequent headache attacks with aura and a gradual increase in headache frequency over months to years (16, 17).

After evaluating all patients, the study made the following observations regarding the conditions: 278 patients exhibited a PriSec type of headache in the ENT OPD. The remaining 67 patients presented with primary headaches, while 105 patients showed secondary headaches. These finding aligns with the study's objectives. Additionally, 26 patients (6%) with headaches from other causes were excluded from the study.

Among the patients, 56% (252 patients) were diagnosed with both LPRD and migraine. The remaining 23% (105 patients) were diagnosed with LPRD, and 15% (67 patients) were diagnosed with migraines as the cause of their headaches. This suggests a strong connection between LPRD and migraine, with LPRD often overlapping with migraine, as depicted in Figure 1.

All patients in the study were recommended oral medications and lifestyle modifications. Oral medications, particularly proton-pump inhibitors (such as pantoprazole) combined with peripheral selective dopamine D2 receptor antagonists (like domperidone), demonstrated effectiveness in the study. Lifestyle alterations proved to be a pivotal factor, yielding favorable outcomes.

For LPRD, the suggested regimen includes:

1. Proton-pump inhibitor (pantoprazole) + peripheral selective dopamine D2 receptor antagonist (domperidone) (Tablet: Pan-D/Panmask-DSR)
2. Local anesthetic solution (aluminum hydroxide, magnesium hydroxide, and oxetacaine) (Syrup: Mucaine gel/Tricaine MPS)
3. Vitamin supplements (Capsule: Becadexamin)

For the treatment of migraine, the following medications were recommended:

1. Calcium antagonist (flunarizine) (Tablet: Sibelium 10 mg HS)
2. Tablet Pan-D (as previously mentioned)
3. Tablet Dolo 650 mg (paracetamol)

Lifestyle modifications adopted by the patients in the study are outlined as follows (18-20):

1. Avoidance of specific food products known to trigger gastric reflux, such as avocado, artificial sweeteners, alcohol, chocolates, corn, caffeine, citrus fruits, dairy items, egg whites, frozen foods, nicotine, onions, seafood, soda, sugar-containing foods, and smoking.
2. Consumption of fresh fruits and vegetables and preference for less spicy, oily, bitter, and sweet foods.

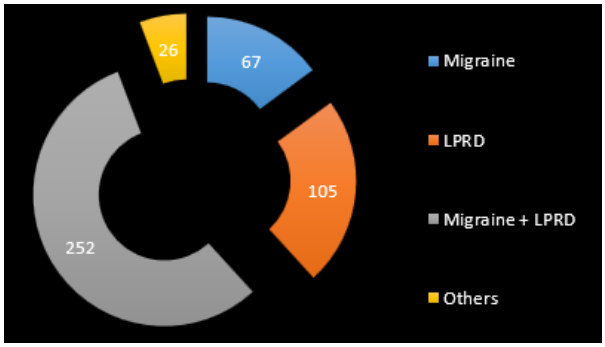

Figure 1: Headache causes illustrated in donut chart

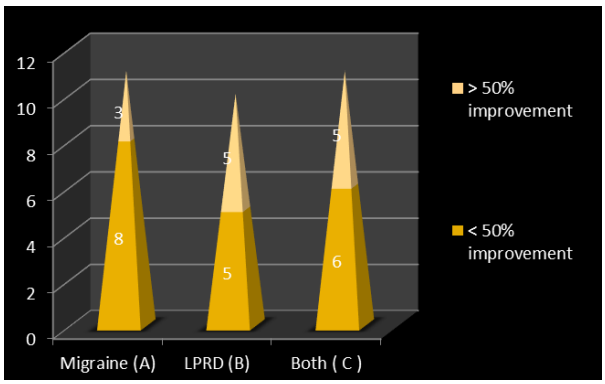

Figure 2: Treatment response after 15 days of followup

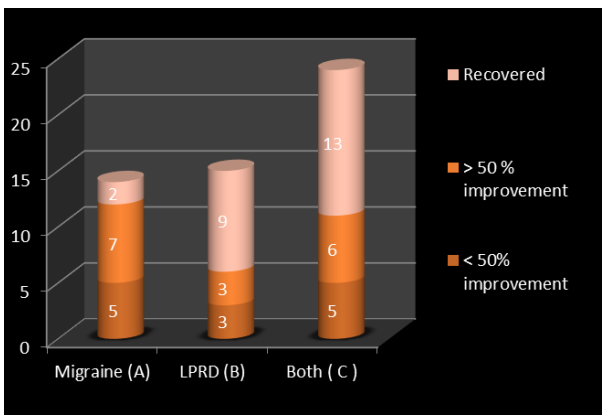

Figure 3: Treatment response after 30 days of followup

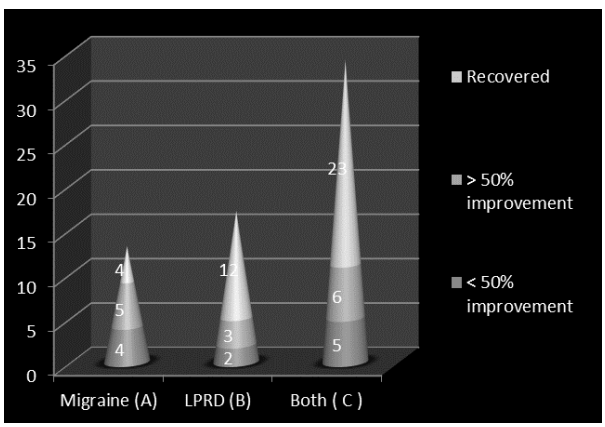

Figure 4: Treatment response since 45 days of followup

3. Inclusion of foods rich in dietary fiber and natural sugars for weight management.
4. Avoidance of skipping meals, fasting, or crash diets.
5. Consumption of meals at frequent intervals with no more than a 3-hour gap.
6. Consumption of small amounts of food at frequent intervals.
7. Adjustment to weather changes by wearing layered clothing to adapt to varying temperatures.
8. Wearing comfortable and loose-fitting clothing, avoiding tight attire.
9. Engagement in stress-relieving activities such as meditation, yoga, and regular exercise for 30 minutes, three times per week.
10. Avoidance of sunglasses for photophobia and usage of headphones/earplugs for phonophobia.
11. Use of antiglare screens for desktops/laptops.
12. Use of appropriate light bulbs at home.
13. Avoidance of 3D glasses if feeling dizzy while watching movies.
14. Choosing to sit in the front seat of the car to avoid motion sickness.
15. Avoidance of reading while in a moving vehicle.
16. Engagement in rejuvenating activities, indoor or outdoor.
17. Avoidance of unnecessary medications.
18. Ensuring 7–8 hours of sleep per night and avoidance of immediate post-lunch and dinner naps. Elevating the head end side by 15–30 degrees while sleeping on the back. Maintaining proper posture by sitting straight and avoiding hunching the back.
19. Chewing mints/gums to prevent bruxism and clenching teeth. Using a proper mouth guard to reduce stress on the jaw.

As illustrates in Figure 2, all patients who underwent treatment were monitored for their response every 2 weeks. Due to the chronic nature of their conditions, a fortnight (15 days) was deemed insufficient to determine recovery rates conclusively. While the treatment duration leaned toward prophylaxis in the long term, patient A showed no significant response. However, patients B and C exhibited comparable response rates. Thus, during followup, more than 50% improvement was observed in 41% (15 out of 32). With extended follow-up duration, both the number of patients and their response to treatment increased. Patients B and C demonstrated increased response rates, with patient C showing the highest response rate among all three groups at 1 month. During follow-up, 45% (24 out of 53

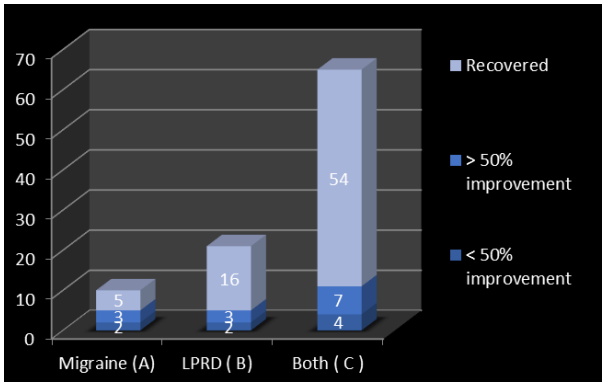

Figure 5: Treatment response after 60 days of followup

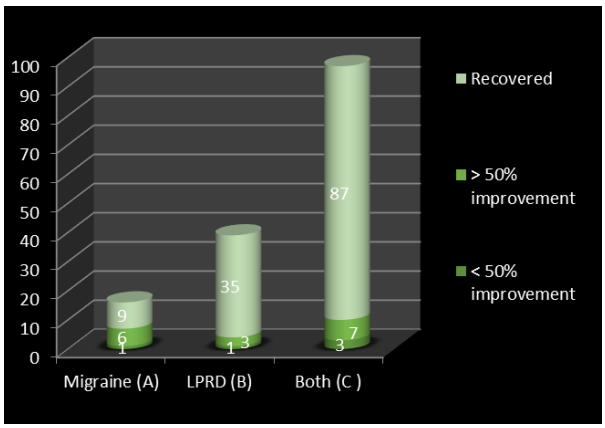

Figure 6: Treatment response after more than 90 days of followup

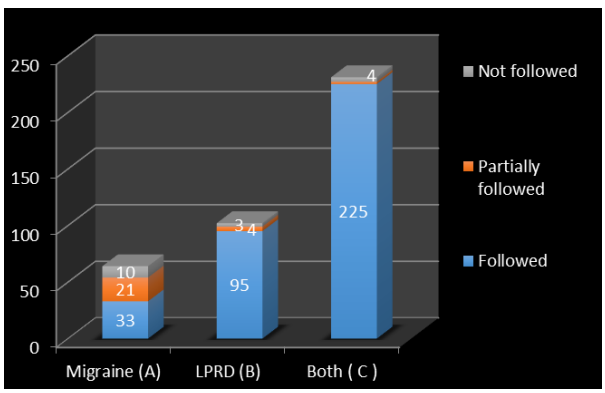

Figure 7: Implementation of lifestyle modifications

patients) achieved complete recovery by implementing simple lifestyle changes. Consequently, the study's expectations were supported by the data.

As depicted in Figure 4, a significant increase in treatment response was observed among patients during follow-up after 1.5 months (45 days). Moreover, 61% (39 out of 64 patients) exhibited good recovery, indicating a favorable response to treatment. Patients B and C showed recovery rates exceeding 65%. Patient feedback indicated satisfaction with the daily modifications aimed at improving health, aligning with the study's principles.

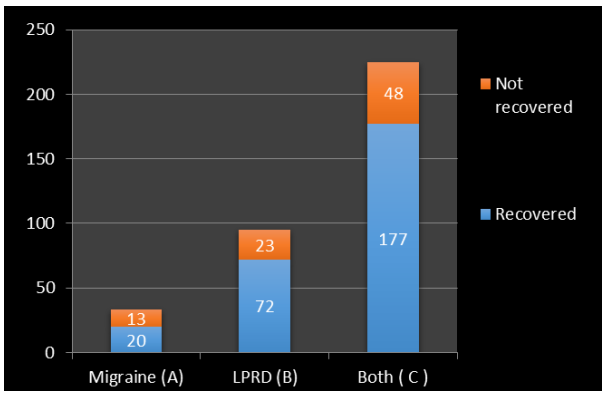

Figure 8: Recovery rates after lifestyle modification followup

Furthermore, 78% (75 out of 96 patients) showed a positive response to conservative treatment during a 2-month follow-up (60 days), with notable improvement in patients B and C as depicted in Figure 5. This indicates that patients accepted the measures provided after understanding the condition's pros and cons, affirming the study's assumptions. This observation underscores both treatment response and patient follow-up.

Out of 152 patients, 131 (86%) exhibited significant recovery after more than 3 months (90 days) of followup. As illustrated in Figure 6, aligning with the initial study assumptions, 87 out of 97 patients in group C and 35 out of 38 patients in group B also responded positively to treatment.

This data is consistent with the study's objectives, as depicted in Figure 7, where 353 out of 397 patients (89%) diligently followed lifestyle changes that had a significant impact on their daily routines. Moreover, 7% (27 patients) attempted to incorporate simple measures but were unable to sustain them for unknown reasons, while 4% (17 patients) acknowledged not adopting any measures during treatment.

In Figure 8, the tabulated data supports the study's aim, wherein the evaluation of 353 patients was based on the implementation of lifestyle interventions and their recovery response. Further, 76% (269 patients) exhibited favorable recovery rates, indicating that promoting practical lifestyle changes has yielded positive outcomes. However, 24% (84 patients) did not recover despite lifestyle modifications, requiring additional oral medications to achieve recovery.

CONCLUSION

PriSec headaches are the most prevalent among the 450 patients with headaches, while secondary headaches rank second. It is now evident that secondary causes of headaches, either alone or as part of PriSec, surpass primary causes. This finding indicates a significant synergy and connection between LPRD and migraine, with LPRD often overlapping with migraine. Twenty-six patients with other headache causes were excluded from the study. All patients were monitored for 90 days to assess their response to treatment when a combination of oral medications and lifestyle changes was introduced to improve their health. Moreover, 27 out of 424 patients were no longer

part of the study, with 14 being unresponsive to treatment and 13 lost to followup. At the end of 3 months, the study revealed a robust interrelation between LPRD and migraine, confirming the coexistence of LPRD and migraine. The implementation of lifestyle modifications, in addition to oral medications, was directly correlated with patient response and recovery, yielding results close to or exceeding 75% in the study. These adaptations not only resolved the patients' conditions but also provided a new perspective on addressing such conditions in the future.

Ethics Committee Approval: This study was approved by the Subbaiah Institute of Medical Sciences (ECR/1358/Inst/KA/2020).

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

Peer Review: Externally peer-reviewed.

Conflict of Interest: The author have no conflict of interest to declare.

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RESEARCH ARTICLE
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The Current Publication Rate of Audiology Master's and Doctoral Theses in Peer-Reviewed Journals: 2023

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ABSTRACT

Objective: This study aims to compare the publication rates of audiology master's and doctoral theses completed in 2017 and to investigate the effectiveness of the "publication of theses before graduation" rule applied by some universities.
Materials and Methods: The participants' age range, gender, degrees, graduation year, private/state university graduation, institutions where they proceeded to their business life, and publication status of their master's and doctoral theses were questioned using a survey consisting of 16 multiple-choice as well as two open-ended questions. The study comprised 71 participants who completed their master's or doctoral degrees in audiology in 2017 and later. The descriptive statistic and Chi-Squared test were used for statistical analysis using the Statistical Package for the Social Sciences (SPSS) version 23.0.
Results: Thirty-five of the 62 (56.45%) master's theses were presented at an international (n=21, 33.87%) or national (n=14, 22.58%) congress as oral/poster presentations. Thirty-three of the 62 (53.22%) master's theses were published as articles in national and international peer-reviewed journals. Additionally, of the 16 doctoral theses, two (12.5%) were presented as oral/posters at a national and five (31.25%) at an international congress. Ten of the 16 theses (62.5%) were published in an international SCI/SCIE journal.
Conclusion: The rate of publication of master's and doctoral theses in national journals has decreased while the rate of publication in international journals has more than doubled. It was concluded that the "publishing theses before graduation" rule significantly increased the publication rates in international journals.
Keywords: Publication, thesis, dissertation, Audiology

INTRODUCTION

Master's and doctoral degrees are gateways to an academic life. In all branches of science, master's and doctoral degrees are awarded to candidates for completion within a certain period. Candidates generally complete their theses at the end of a process in which the literature is scanned based on a hypothesis, data are systematically collected, necessary statistical analysis is performed, and the findings are written on paper. At the end of this process, candidates develop academic study disciplines and skills in using scientific language.

In addition, thesis studies are one of the important indicators of the scientific productivity of universities (1, 2). However, for these to reach wider audiences, they must be published in international academic databases. Articles published in scientific journal databases such as the Web of Science (WoS), Scopus, and Emerging Science Citation Index (ESCI) reach wider audiences and contribute more effectively to the literature (3).

However, not all theses or dissertations have been published in peer-reviewed scientific journals for various reasons. According to a 2015 study in "Neurosurgery," the rates were insufficient in graduation theses in Turkiye. While only 5% of theses completed between 2004 and 2013 were published as SCI/SCIE publications, 13% were published in national journals (4). Of the 538 theses in "Public Health" in Turkiye, 18% were published in national journals and 11.9% of these were published in international journals (5). In a study conducted in 2020, publication rates of graduation theses in the field of general surgery in Turkiye were examined between 1998 and 2018. According to the study findings, 20.5% of the dissertations were published in a journal, whereas only 14.4% were published in an SCI/SCIE journal (6). Additionally, the rates

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of publication in national and international journals were 26.1% and 36.3% in "Otolaryngology", respectively (7).

There have been a few studies on the publication rates of master's and doctoral theses in other countries. Only 21.6% of theses completed in the Family Medicine field between 1982 and 2014 were published in Egypt. While 68.9% of these were published in national journals, 31.1% were published in international journals (8). In the US, a study reported that approximately half of the completed doctoral theses in Library and Information Science up to the year 2000 were published as articles (9). In addition, in a study performed in 2018 in the US, the overall weighted estimate showed that 25.6% of psychology doctoral theses were published in peer-reviewed journals within the period 0-7 years following their completion (10). There has been no research in international journals on the publication rate of master's and doctoral theses completed in audiology. In our research published in a national journal in 2016, the publication rate of master's and doctoral theses in the field of audiology in an international journal was 15.9% for master's degrees, while the rate was 26.6% for doctoral theses. The publication rates in national journals are 18.1% and 13.3%, respectively (11).

From 2017, some universities in Turkiye require theses to be published in national/international peer-reviewed journals before the thesis final exam for master's and doctoral graduation in audiology depending on the university. Therefore, this study aims to investigate the publication rates of audiology master's and doctoral theses completed in 2017 and later in national/international journals and the effectiveness of the "publication of the theses" rule.

MATERIAL AND METHODS

Participants

The study sample consisted of individuals who completed their master's and/or doctoral degrees in audiology in 2017 and later.

Study design

Data was collected using a survey consisting of 16 multiple-choice and two open-ended questions. In this survey, the participants' age range, gender, degrees, graduation year, private/state university graduation, institutions where they proceeded to their business life, and publication status of their master's and doctoral theses were questioned. In the open-ended questions in the survey, participants who did not publish were asked "Why did not you publish your master's or doctoral theses?"

The survey questions are as follows: What is your age? What is your gender? What education did you complete in 2017 or later (master's and/or doctoral education)? In what year did you complete your master's and/or doctoral education? At which institution did you complete your master's and doctoral education ("state" or "private" university)? Are you continuing your academic career (yes or no)? Please provide information about your academic title and the institution where you work. Have you published or presented your master's and doctoral theses in a national or international journal or congress? If so, please provide details about the presentation or article. What was the topic of your thesis? If you did not publish them, could you explain why?

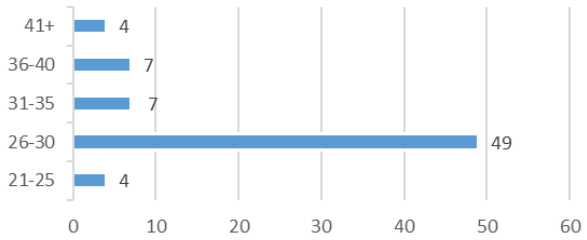

Figure 1: Age distribution of participants

The questions were presented to the participants online, with separate multiple-choice items for master's and doctoral education.

Statistical analysis

Data was analyzed using the Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) version 22.0. The Chi-square test was used to determine the differences between the publishing styles of master's and doctoral theses. In addition, descriptive statistics were used to present information on participants' status.

This study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Ethics Committee of Istanbul Medipol University (Date: 31.08.2023, No: 714).

RESULTS

A total of 71 participants who completed their postgraduate education in audiology participated in the study by completely filling out the survey. Of the participants, 54 (76.1 %) were women, and 17 (23.9 %) were men. Four participants were 21-25 (5.6%), 49 participants were 25-30 (69%), 7 participants were 30-35 (9.9%), 7 were 35-40 (9.9%), and 4 were in the 40+ (5.6%) age range (Figure 1).

A total of 78 theses completed by 71 participants between 2017 and 2023 were evaluated in this study. Of these, 62 (87.3%) were master's theses and 16 (22.5%) were doctoral theses. The distribution of these by years is shown in figure 2. Accordingly, more than half of the Master 's theses (56.45%) and most doctoral theses (81.25%) were completed in 2021 and later.

Nine participants were included in the study only with their doctoral theses because they completed their master's theses before 2017. Nevertheless, of the 71 participants, including participants who completed their master's theses before 2017, 39 (54.90%) completed their master's degree at a state university and 32 (45.10%) at a private/foundation university

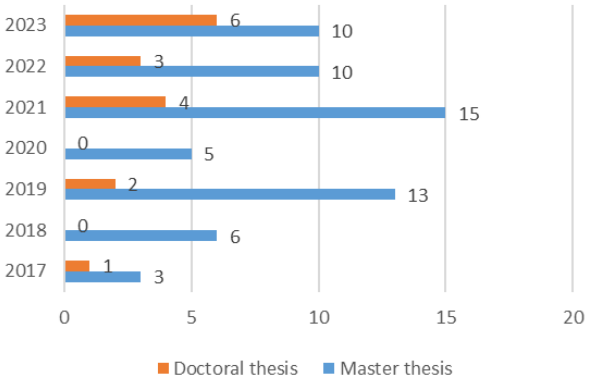

Figure 2: Distribution of graduation of master's and doctoral education

for a fee. This distribution is 12 (75%) and 4 (25%) in doctoral education.

While 43 (60.56%) of the participants who completed their master's or doctoral education proceeded to their academic careers as academics in a university, 28 (39.44%) worked in different positions. Of the participants working at a university, 16 (37.21%) were research assistants, 19 (44.19%) were lecturers, and 8 (18.60%) were assistant professors. Of the 43 universities where academic work continued, 22 (51.16%) were state universities and 21 (48.84%) were private universities. Of the participants who did not work as academics, four (14.28%) worked in a private or public university hospital, one (3.57%) worked in a state hospital, three (10.71%) worked in a private hospital, 6 (21.42%) worked in a hearing aid/cochlear implant company, seven (25%) worked in an auditory-verbal rehabilitation center, and one (3.57%) worked in a private ENT clinic. While 3 participants (10.71%) declared that they worked in a different sector other than audiology, 3 participants (10.71%) stated that they proceeded with their academic education without working in a job (Table 1).

Thirty-five of the 62 (56.45%) master's theses were presented at an international (n=21, 33.87%) or national (n=14, 22.58%) congress as oral/poster presentations. In addition, 53.22% (33 out of 62) of the master's theses were published as articles in various databases. These databases include the National Academic Network and Information Center (ULAKBIM) (12.90%), national journals other than ULAKBIM (n=1, 1.61%), SCI/SCIE international journals (n=16, 25.80%), and international journals other than SCI/SCIE (n=8, 12.90%). Additionally, 8 (12.90%) participants stated that their publication is under evaluation in a SCI/SCIE journal and the number of pending publications in international journals published in non-SCI/SCIE databases is 2 (3.22%). The number of participants who did not publish their master's theses as an article or did not attempt to publish it was 19 (30.65%) (Table 2).

Of the 16 doctoral theses completed in audiology between 2017 and 2023, 2 (12.5%) were presented as oral/posters at a national congress and 5 (31.25%) at an international congress. More than half of these theses (56.25%) were not presented at any congress. In addition, 10 of the 16 theses (62.5%) were published in an international SCI/SCIE journal, whereas one publication (6.25%) was stated to be under evaluation in an

Table 1: Distribution of participants according to their job

Work at a university	n	%	Work at different positions except a university	n	%
Research assistant	16	37.21	University hospital	4	14.28
Lecturers	19	44.19	State hospital	1	3.57
Assistant professor	8	18.60	Private hospital	3	10.71
			Hearing aid/Cochlear implant company	6	21.42
			Rehabilitation center	7	25
			Private ENT clinic	1	3.57
			Different sector other than Audiology	3	10.71
			Unemployed	3	10.71

Table 2: The publication rates of all master's and doctoral thesis

	Oral/poster presentation n=42, (59.15%)				**Article n=43, (60.56%)**							
	Oral/poster presentation at a national congress		Oral/poster presentation at an international congress		National Academic Network and Information Center (ULAKBIM)		National journals other than ULAKBIM		SCI/SCIE international journals		International journals other than SCI/SCIE	
	n	%	n	%	n	%	n	%	n	%	n	%
Master thesis	14	22.58	21	33.87	8	12.90	1	1.61	16	25.80	8	12.90
Doctoral thesis	2	12.5	5	31.25	0	0	0	0	10	62.50	0	0

Table 3: The distribution of master's and doctoral thesis topics

Topic	Master's thesis		Doctoral thesis	
	n	%	n	%
Diagnostic	10	14	2	12.5
Electrophysiology	5	7	3	18.75
Hearing aids	8	11	2	12.5
Cochlear implants	12	17	2	12.5
Bone anchored hearing systems (BAHS) & middle ear implants	0	0	0	0
Vestibular system	17	24	2	12.5
Aural rehabilitation	4	6	1	6.25
Experimental studies	4	6	1	6.25
Tinnitus	7	10	1	6.25
Central auditory processing	3	4	2	12.5
Voice disorders	1	1	0	0
Total	**71**	**100**	**16**	**100**

SCI/SCIE journal. Five participants (31.25%) did not publish their theses as articles or send them to any journal (Table 2).

The rates of participants presenting their theses orally at national/international congresses and publishing them as articles in national/international journals were analyzed using a chi-square test. Oral/poster presentations of master's and doctoral theses in national and international congresses were evaluated using Fisher's Exact Chi-Square test results. Accordingly, although master's theses are presented at more national and international congresses than doctoral theses, the difference is not statistically significant (p=0.690). In addition, the publication rates of master's and doctoral theses in ULAKBIM, national journals other than ULAKBIM, SCI/SCIE, and international journals other than SCI/SCIE were analyzed according to the Monte Carlo Chi-Square test results. According to the test results, participants tend to publish their master's and doctoral theses significantly more in SCI/SCIE journals, χ^2 (3, n=43) =8.52, p=0.036.

Considering the distribution of master's thesis topics completed in the field of audiology between 2017 and 2023, most theses concerned the vestibular system (n=17, 23.94%). Then come cochlear implant (n=12, 16.90%) and diagnostic audiology (n=10, 14.08%). This distribution is quite balanced in doctoral studies. The detailed distribution of master's and doctoral theses according to audiological topic is presented in Table 3.

In the survey, participants were also asked an optional open-ended question about their master's and doctoral theses: "Why did not you publish your master's or doctoral theses?" The answers given to this question are generally clustered under four headings: "not finding enough time", "communication problems with the advisor", "motivation problems" and "inexperience in academic studies". Academics, particularly those working in audiology clinics at university hospitals, stated that they could not find enough time for academic work. The fact that advisors do not allocate sufficient "effective" time to students has also emerged as an important reason. In addition, the stress experienced during the education and this thesis period manifests itself as a "loss of motivation" after graduation. One participant expressed this issue as follows: "Since the thesis writing process during my master's degree was tiring and stressful for me, I could not find enough energy and motivation to turn my thesis into an article and publish it". Finally, a participant expressed inexperience in academic studies in a way that was conspicuous among all participants: "By the time I felt competent in this regard, the data of my thesis was outdated."

DISCUSSION

Master's theses are doors to academic life in positive science. The theses, written after master's education, are very comprehensive practical training that includes hypotheses determination, literature review, study design, and statistics. Generally, doctoral theses consist of comprehensive study designs that significantly contribute to the literature. For this reason, presenting both theses at congresses and publishing them as articles in journals enables them to be available to large audiences. In particular, studies published in "English" in international journals appeal to a wider academic community. Additionally, publishing theses in international journals, especially SCI/SCIE journals, also proves the quality of post-graduate education and theses.

The only global study on the publication of theses in audiology was conducted by Çelikgün et al. in 2016 (11). A total of 58 theses, 45 master's theses, and 13 doctoral theses, were evaluated in the study. Accordingly, the oral/poster presentation rate of the 58 theses at a national/international congress was 62.06%. In the present study, the rate was 59.15%. While the rate of theses published as articles in a national/international journal was 36% in 2016, it was 60.56% in this study.

In a study conducted in 2016, 45.4% of master's theses were presented orally/poster at a national congress, and 20.4% at an international congress. Additionally, 18.1% of master's theses were published as articles in a national journal and 15.9% in an international journal. In the current study, these rates are 22.58%, 33.87%, 14.51% (ULAKBIM and other national journals, respectively), and 38.7% (SCI/SCIE and other international journals).

Moreover, in a study published in 2016, 26.6% of doctoral theses were presented as oral/posters at a national congress, and 33.3% at an international congress. The rates of doctoral theses converted into articles for publication in national and international journals were 13.3% and 26.6%, respectively. In this study, national oral/poster presentation in doctoral theses is 12.5%, and international is 31.25%. In addition, the publication rate as an article in the SCI/SCIE journal is 62.6%. No publication turned into an article from a doctoral thesis among non-SCI/SCIE journals.

When both studies are looked at from a wide perspective, two important points stand out. First, the rate of presentation of master's and doctoral theses as oral/poster presentations at national congresses has decreased by approximately 50% compared to the study in 2016. While there was no significant difference between 2016 and this study in terms of oral/poster presentations of doctoral theses at international congresses, an important increase was found in terms of master's theses. The increase in "online" international meetings that started during the COVID-19 pandemic and continued afterward may be considered as a factor in the increase in master's theses presentations at international congresses. However, the pandemic and Turkiye's economic conditions in recent years may negatively affect these presentations at national congresses. Second, compared to the study conducted in 2016, while the demand for national journals decreased, interest in international journals, particularly SCI/SCIE, increased by more than 100%. All doctoral theses converted into articles were published in the SCI/SCIE journals. This may be because many universities are increasingly requiring SCI/SCIE publications for graduation, especially in doctoral education. Additionally, the increase in audiology schools with reduced clinical burden established within health sciences faculties may have also supported academic productivity (12). Moreover, the more widespread use of artificial intelligence applications and academic writing websites that facilitate article writing in English might have increased the rate of international publications (13). Additionally, individuals with a doctoral degree are more likely to continue their academic lives and produce publications (14).

In the literature, only two studies were conducted in 2020 on the topic of later conversion of theses to publication. In the first study, the authors investigated the publication rate of "general surgery" dissertations completed in Turkiye between 1998 and 2018 (6). Between these years, 1,996 theses were completed, 20.5% of which were converted into publications. Only 14.4% were published in the SCI/SCIE journal. Another study investigated the conversion rate of dissertations completed in "public health" to publication (15). When theses completed between 2000 and 2018 were reviewed, 30.3% were published as articles in a journal. The distribution of publication rates is as follows: 10.4% for SCI/SCIE, 12.9% for international journals that are not within the scope of SCI/SCIE, and 7% for national journals. When assessing studies conducted in the field of audiology in 2016 and the other studies in medicine, it is seen that the "publication of the theses before graduation" rule put into effect by some universities significantly increases the rate of publication rate of master's and doctoral theses in peer-reviewed journals.

Although the rate of publication of theses as articles, particularly in international journals, has doubled compared to 2016, it seems that it is still not enough. In addition to quantitative questions, a qualitative question was asked to participants to ask "why" this was the case. The answers to the open-ended question pointed to important solutions: saving time for academic studies by reducing academics' clinical working hours, the coaching/mentoring skills of supervisors might be increased through training provided by universities to increase the quality of communication between students and supervisors as well as keep student's motivation at a high level after graduation (16, 17). In addition, planning some additional training on academic literacy during the master's period may facilitate the publication process. Furthermore, requiring all universities in Turkiye to publish theses in national or international peer-reviewed journals prior to the final thesis examination for Masters and Doctoral degrees in all fields may ensure much better publication rates.

The distribution of postgraduate graduation was balanced between state/private university graduations in master's degrees (state university n=39, 54.9%), while most participants (n=12, 75%) graduated from a state university with a doctoral degree. The fact that the doctorate education is longer than the master's and the doctorate is more expensive compared to the master's education may have caused the doctoral graduation rate to be lower in private universities.

When the distribution of audiology postgraduate theses by subject is investigated, it is seen that most studies in master's degree are completed in the fields of the vestibular system (n=17, 24%), cochlear implants (n=12, 17%) and diagnostic audiology (n=10, 14%). In doctoral studies, it is seen that doctoral theses are distributed similarly to different fields related to audiology. Interestingly, there was no study on BAHS and middle ear implants in any of the master's and doctoral theses.

Generally, studies on the publication rate of graduation theses are conducted by searching and analyzing national and international journal databases. Our study was carried out by reaching people directly through a survey. Therefore, a larger study sample could not be reached in the study. This might be considered as a limitation of the study. However, reaching people directly through a survey also eliminated factors that

could negatively affect the study findings, such as spelling errors during database searches, changes in the author's surname because of different reasons (particularly for women due to marriage), incorrect data collection where multiple authors with similar names exist in the country, and the possibility of changing the thesis title in the article form.

CONCLUSION

As a result of the study, compared to the study published in 2016, the presentation of master's and doctoral theses as oral/poster at a national congress decreased by half, while the presentation of master's theses at international congresses increased by more than 50%. In addition, while the rate of publication of master's and doctoral theses in ULAKBIM and other national journals has decreased, the rate of publication in international journals, particularly SCI/SCIE journals, has more than doubled. In general, it was observed that the rule of "publishing theses before graduation" significantly increased the publication rates in international journals.

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Hospital Infections and Microbiota

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ABSTRACT

The human body hosts complex communities of microorganisms, collectively known as the "microbiota," predominantly in the lower intestine. This microbiota, which consists of bacteria, viruses, and fungi, plays a vital role in the breakdown of various nutrients and maintenance of homeostasis. The microbiome, which represents the collective genetic content of these microorganisms, is intricately associated with human health and disease. Healthcare-associated infections (HCAIs), a major public health problem, contribute to high morbidity and mortality. Exposure to antibiotics, a primary risk factor for diseases, disrupts the microbiota and compromises its protective role. Age-related changes in the microbiota affect the onset and progression of various diseases by affecting the functional capacity and fitness of the host. Inanimate surfaces in built environments contribute to HCAIs by serving as potential reservoirs for microorganisms. Promising results have been observed with fecal microbiota transplantation (FMT) for treating *Clostridium difficile* infection, which is often associated with healthcare facilities. FMT prevents disease recurrence by restoring a healthy colonic microbiota and breaking the dysbiotic cycle. Furthermore, microbiota-based interventions have the potential to control emerging multidrug-resistant pathogens such as vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae.

Keywords: Microbiota, Healthcare-associated Infections, Microbiome, vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae

INTRODUCTION

The complex communities of microorganisms that live on the body surfaces of vertebrates are termed microbiota, and the region where it is most concentrated is the lower intestine. The microbiota has evolved to break down various plant polysaccharides and other nutrients (1). The collective genome content of the microbiota was earlier known as microbiome; however, both microbiota and microbiome are currently used synonymously (2).

The gastrointestinal application of feces from healthy donors to restore the protective microbiome is known as fecal microbiota transplantation (FMT) (3). In recent years, FMT has been associated with the colonization of multidrug-resistant organisms (MDROs) such as carbapenemase-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* (MRSA) that colonize the intestine. FMT is being attempted as a treatment option to eliminate such colonization, with studies showing successful results, making FMT a promising treatment (4).

Microbiota

In ancient times, Hippocrates emphasized the importance of microbiota by stating that death is in the intestines and inadequate digestion is the source of all evil. Élie Metchnikoff, who lived during 1845–1916, proposed that most diseases begin when good bacteria in the digestive tract can no longer control bad bacteria. He named this situation dysbiosis, which implies an ecosystem in which bacteria do not live together in mutual harmony (5). Humans have evolved with different microorganisms in their microbiota. Dysbioses in the microbiome are associated with several disorders, such as inflammatory bowel disease, multiple sclerosis, diabetes (type 1 and 2), allergies, asthma, autism, and cancer (6).

The pathogenesis, development, severity, and consequences of upper respiratory tract infections may depend on the nasopharyngeal microbiome and immune defense. During early childhood, nasopharyngeal colonization by bacterial

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respiratory pathogens is a common event and constitutes the first and essential step in the pathogenesis of respiratory bacterial infectious diseases, including acute otitis media, sinusitis, conjunctivitis, chronic obstructive pulmonary disease, and pneumonia. A polymicrobial association exists between high otopathogen loads in children with otitis media or upper respiratory tract infection. The types of microbiomes in the respiratory tract include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Some strains of *H. influenzae* and *M. catarrhalis* in the middle ear secrete signals that promote biofilm formation. *M. catarrhalis* promotes the growth of *H. influenzae*, especially in the presence of *S. pneumoniae* (7).

Anaerobic bacteria found on the skin, mouth, gastrointestinal tract, and female genital tract are important members of the microbiota (8). The relative abundance of members of these phyla varies among different sites in the body (Figure 1) (9).

Effect of antibiotics on microbiota

Consuming antibiotics orally releases chemicals into the intestine that disrupt the intestinal microbiota. These disruptions may occur through interactions between the normal intestinal microbiota and opportunistic and pathogenic bacteria present in the intestine. The effects of antibiotics on the intestinal microbiota may be temporary or permanent, depending on the type of antibiotic and duration of treatment (10). Mucosal damage caused by antibiotic intake initiates the production of a cascade of inflammatory cytokines, including tumor necrosis factor, type I interferons, interleukin (IL)-1, and IL-6. These cytokines directly alter the gut microbiome and thus create an optimal environment for the development of MDRO induced infections (11).

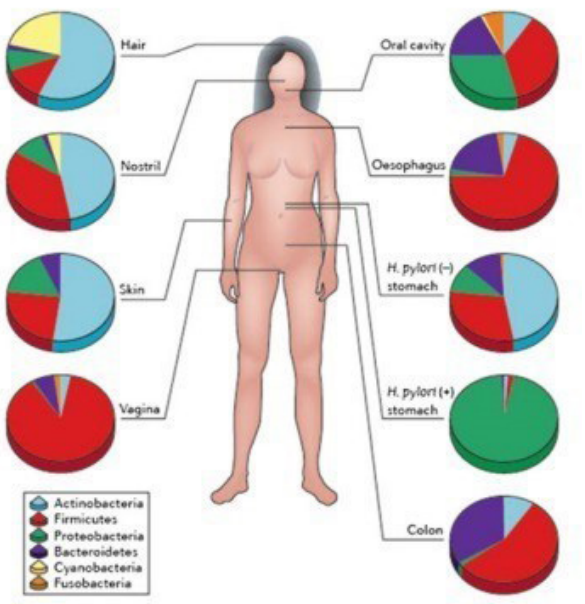

Figure 1: Compositional differences in the microbiome by anatomic site (9)

Antibiotics are released into the environment as a consequence of continuous antibiotic overuse. The release of antibiotics into the environment results in the development of antibiotic resistance genes in bacteria, which reduces the effect of antibiotics on pathogens. This is an alarming situation (12).

Antibiotic use may disrupt the microbiota in the ear, nose, and throat, causing opportunistic pathogens to proliferate in this region. In a microbiota analysis on left and right ear canal swab and nasopharyngeal swab samples obtained from 19 children, a core group of bacterial taxa was identified, including *Corynebacterium*, *Alloiococcus*, *Staphylococcus*, *Haemophilus*, *Turicella*, *Streptococcus*, and *Pseudomonas* (13).

The primary cause of severe bacterial dysbiosis observed in patients in the intensive care unit (ICU) is the widespread use of antibiotics. Nevertheless, as the current evidence is based on preclinical studies, the mechanisms in the microbiota are not completely understood. For instance, although disruption of the gut microbiota by broad-spectrum antibiotics does not affect systemic innate immune responses in healthy humans, it disrupts the host's gut microbiome balance in critically ill patients, causing dysbiosis (14). Gut dysbiosis caused by different factors (environmental factors, antibiotic use, and other factors) can trigger or aggravate inflammatory bowel syndrome, rheumatoid arthritis, obesity, diabetes, nonalcoholic fatty liver disease, depression, and Parkinson's disease (15).

Healthcare-associated infections and microbiota

Healthcare-associated infections (HCAIs) were previously known as nosocomial infections. HCAIs are defined as infections acquired in any healthcare setting, including inpatient/outpatient care (16).

The association between bacteria and humans is related to environmental changes. Anthropogenic factors that alter the environment, chemical pollution that alters microbial biodiversity, new medical technologies, increasing number of highly susceptible hosts, and controlling the access of bacteria to the host are important factors for nosocomial infections. These factors balance colonization/multidrug resistance in the nosocomial microbiota (17).

Inanimate surfaces are potential reservoirs for microorganisms, including bacteria (Gram-positive and Gram-negative), fungi, and viruses. Some microorganisms can survive on dry surfaces for days or even months. A study conducted in the ICU investigated the bacterial species on the floor, workplace, and devices and identified the following seven major bacterial phyla: *Acidobacteria*, *Actinobacteria*, *Bacteroidetes*, *Cyanobacteria*, *Firmicutes*, *Nitrospira*, and *Proteobacteria*. Moreover, the highest bacterial load was detected in hospital devices, followed by the workplace and finally the floors (18).

The microbiota of hospitalized patients is often dysbiotic because of the frequency of treatments such as antibiotics, diet, and chemotherapy (19). Dysbiosis in the gut increases susceptibility to *Clostridium difficile* infection (CDI), which

explains why most CDI cases are associated with healthcare facilities. Microbiota plays a beneficial role in the resistance and resolution stages of infection (20). There is limited research on the changes in the microbiome of patients with recurrent CDI (rCDI). For instance, in a study that investigated microbiome diversity in samples collected from healthy individuals and from patients with primary and rCDI, less bacterial diversity was detected in samples collected from patients with rCDI (21).

Another study by Sereira et al. conducted using rectal, nasal, and hand swab samples collected from 198 patients reported high abundance rates of pathogens associated with HCAIs in all sample types. During hospitalization, 50% of the patients did not experience any HCAI, 43.9% of them experienced an HCAI, and 6.1% of them were colonized by bacteria associated with HCAIs. The authors mentioned that has been an increase in the number of HCAI cases and the detection of pathogens associated with HCAIs, especially bacteria such as *Klebsiella pneumoniae*, Enterobacteriaceae, *Staphylococcus* spp., and *Acinetobacter baumannii*. The usefulness of active surveillance programs based on microbiome monitoring in the evaluation and control of HCAIs indicates the need for a multidisciplinary approach (22).

Hospital plumbing systems are potential reservoir areas for bacteria. There is extensive research demonstrating the isolation of clinically important bacteria from hospital sink and drain water. Multidrug-resistant (MDR) *Pseudomonas aeruginosa* has been widely identified in these areas (23). A study reported that the number of *Bifidobacterium* and *Lactobacillus* bacteria decreases in hospitalized critically ill patients, whereas that of *P. aeruginosa* increases logarithmically. Intestinal microflora can be altered using antibiotics, prebiotics, and probiotics or through fecal transplantation (24). A study conducted using mouse models suggests that the lung immune responses of mice with acute bacterial lung infection are altered by intestinal dysbiosis. Gut dysbiosis caused by broad-spectrum antibiotics results in changes in the IgA response in the lung, causing *P. aeruginosa* infection (25). The results reported by Bacci et al. strengthen the hypothesis of the interaction between the lung and intestinal microbiota concerning *P. aeruginosa* chronic infection (26).

The number of VRE is increasing among nosocomial infections. Stachyose supports probiotic development, and attempts are made to prevent VRE infections using stachyose. For instance, Zhu et al. reported that stachyose supplementation could cause changes in the microbiome, which could result in alterations in the expression of genes and inhibit VRE colonization (27). VRE colonization is essential in liver transplant recipients. VRE colonization as a consequence of intestinal dysbiosis may negatively affect graft function on the microbiota–liver axis and result in adverse outcomes before and after liver transplantation (28). Intestinal commensal bacteria can inhibit dense gut colonization by VRE (29).

Changes in the lung microbiome are observed in respiratory diseases. With alterations in physicochemical properties due to chronic inflammation, the temporary microbiome becomes the permanent microbiome (30). Because the intestinal microbiota can manage lung immune function through the gut–lung axis, this presents a novel option for preventing lung infectious diseases. In this regard, one study reported significant decreases in α-diversity and the presence of various beneficial bacterial species in lung microbiota analysis after MRSA infection, which indicates a decrease in butyric acid content that may play a role in lung inflammation as a result of disruption of the microbiota during MRSA infection (31). Bessesen et al. found no MRSA colonization in the presence of *Streptococcus mitis* and *Lactobacillus gasseri* in the nasal microbial communities of hospitalized patients (32).

Although a high-fat diet (HFD) plays a role in various diseases, the relationship between HFD and antibiotic effectiveness is not completely understood. Antibiotic effectiveness was investigated in a study conducted on HFD-fed mice infected with MRSA and *Escherichia coli*. Lower antibiotic sensitivity was observed in HFD-fed mice than in diet-fed mice. Fecal samples collected from HFD-fed mice were transplanted into diet-fed mice, which resulted in impaired antibiotic activity in the diet-fed mice. This study demonstrated that changes occurred in the intestinal microbiota of HFD-fed mice that played a role in reducing antibiotic activity. Analysis of fecal samples revealed decreased microbial diversity in HFD-fed mice (33).

Therefore, modern approaches require us to consider the human body as a complex ecosystem that must remain in balance to maintain health. Any disturbances to this balance may result in malfunctioning of various organs and promote the development of numerous inflammatory diseases (34).

A novel approach: treatment with microbiota

Interest in microbiota-based therapies has increased due to the success of FMT for treating rCDI. The FMT success rate in rCDI treatment was between 85% and 92% (35). Moreover, FMT was effective in decreasing the development of antibiotic resistance genes in patients with rCDI, which may be effective in reducing colonization by MDROs (36). In the study by Kuraishi et al., FMT was found to be more effective than vancomycin for treating recurrent and resistant CDI (37).

Because dysbiosis is the primary factor for rCDI, microbiome diversity changes due to the excessive use of antibiotics after CDI treatment. Restoring a healthy microbiota can eliminate the dysbiotic cycle (38). Jalanka et al. conducted a study on 84 patients with inflammatory bowel disease, cancer, autoimmune disease, allergies, and neurological diseases, including 45 patients treated with FMT and 39 in the control group receiving antibiotics due to infection. They observed that patients receiving FMT had fewer upper gastrointestinal tract symptoms and irregular bowel function. Thus, FMT was reported as a safe alternative treatment option in patients with rCDI (39).

Davido et al. applied FMT treatment to 15 patients colonized by VRE, and after 3 months, VRE colonization was detected in only three patients. The authors confirmed that FMT is safe and may exert a strong effect on VRE colonization over time (40).

In another study conducted on 17 patients with an average age of 73 years, the duration of infection with CRE and VRE was 62.5 days before FMT. At 1 week after FMT, CRE colonization disappeared in 3 of 8 patients, and VRE colonization disappeared in 3 of 9 patients. At 3 months after FMT, CRE colonization disappeared in 4 of 8 patients, and VRE colonization disappeared in 7 of 8 patients (41). Moreover, a patient with MDR *K. pneumoniae* infection was treated successfully with FMT (42).

A recent study supported a relationship between urinary tract infection and gut microbiota (43), showing that susceptibility to recurrent urinary tract infections (rUTI) may act through the bowel–bladder axis. Patients with rUTI may develop different immune symptoms against intestinal dysbiosis and bacterial bladder colonization (44). This study has demonstrated that FMT is an effective method to treat rUTI (45). Wang et al. demonstrated the benefits of FMT for treating *Escherichia coli* in their study with *E. coli*-infected mice. They recommended FMT as a therapeutic agent for intestinal infections and stomach-related diseases (46).

Bilinski et al. reported that FMT is a suitable treatment option for blood disorders. Colonization was prevented with FMT, but antibiotic treatment after FMT reduced the success rate (47). *Citrobacter murliniae*, *K. pneumoniae*, and *Enterobacter cloacae*, which are among the hospital pathogens, are important in terms of infection risk in hematopoietic stem cell transplantation (HSCT). Acute graft-versus-host disease is a major complication of allogeneic HSCT. Microbiota-based treatment options may be a good option for the prevention and treatment of graft-versus-host disease in patients with HSCT (48).

In a study by Wieërs et al., patients treated with antibiotics were administered a probiotic mixture, which resulted in a significant decrease in *Pseudomonas* colonization from 25% to 8.3% after antibiotic treatment (49).

New treatments are being developed against MDR pathogens, including carbapenem-resistant *K. pneumoniae*. These new treatment options include the application of monoclonal antibodies, use of bacteriophages, genetic editing, and FMT (50).

CONCLUSION

It is crucial to understand the relationship between microbiota and human health to develop strategies for the prevention and management of diseases. Microbiota-based therapies such as FMT are promising in treating conditions such as CDI and addressing the challenges posed by antibiotic resistance. Ongoing research in this area will provide novel insights into the role of microbiota in health and pave the way for innovative therapeutic approaches.

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AIM AND SCOPE

The Turkish Journal of Ear Nose and Throat (Tr-ENT) aims to contribute to the literature by publishing high quality original articles, case clinical reports, surgical techniques and invited reviews focusing on key subjects and contemporary developments in the field. The scope of the journal includes otology, neurootology, rhinology, head and neck, general ORL, facial plastic surgery and laryngology. The journal welcomes articles from other disciplines as well, provided that these are related to the major subject area. The target audience of the journal consists of academicians, researchers, professionals, students, related professional and academic bodies and institutions.

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  - All tables, illustrations (figures) (including title, description, footnotes)

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