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RESPONSIBLE MANAGER

Prof. Dr. Bülent BAYRAKTAR
Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkiye

CORRESPONDENCE ADDRESS

Istanbul University, Istanbul Faculty of Medicine Deanery, Publication Commission
Turgut Özal Caddesi 34093 Çapa, Fatih, Istanbul, Turkiye
Phone: +90 (212) 414 21 61
E-mail: tr-ent@istanbul.edu.tr
https://dergipark.org.tr/tr/pub/trent
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RESEARCH ARTICLES

RESEARCH ARTICLE
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Low Amplitude of Ocular Vestibular-Evoked Myogenic Potentials Can Denote Poor Prognosis in Patients with Idiopathic Sudden Sensorineural Hearing Loss

Ayça Başkadem Yılmazer[1], Sabire Sitare Sarıçam[1], Güler Berkiten[1], Öykü İzel Onaran[1], Melis Ece Arkan Anarat[1], Belgin Tutar[1], Hüseyin Sarı[1], Ömür Biltekin Tuna[1]

[1]University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Otorhinolaryngology, Head and Neck Surgery, İstanbul, Türkiye

ORCID ID: A.B.Y. 0000-0001-9967-8046; S.S.S. 0000-0003-4666-3259; G.B. 0000-0002-1532-6113; Ö.İ.O. 0000-0002-3697-4275; M.E.A.A. 0000-0002-6702-8820; B.T. 0000-0001-7783-0908; H.S. 0000-0003-4088-4739; Ö.B.T. 0000-0002-5946-6396

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ABSTRACT

Objective: To assess vestibular evoked myogenic potentials (VEMP), both cervical (c-VEMP) and ocular (o-VEMP), in patients diagnosed with unilateral sudden hearing loss and presenting with vestibular symptoms and to determine whether these responses can serve as predictive parameters for recovery.

Materials and Methods: Patients diagnosed with unilateral sudden sensorineural hearing loss (SSHL) and vertigo and healthy volunteers without ear pathology were included. All participants underwent ear tests, including pure tone audiometry and c-VEMP and o-VEMP tests.

Results: When comparing the VEMP values of the patients who showed improved hearing with those who did not, it was observed that the o-VEMP amplitude of non-improved patients was statistically lower ($p=0.013$). Moreover, in the non-improved group, the c-VEMP P1 latencies were lower, and the amplitude asymmetry ratio (AAR) of c-VEMP was significantly higher than that in the control group, significantly ($p=0.006$ and $p<0.001$, respectively; Mann Whitney U test with Bonferroni Correction $p<0.017$).

Conclusion: In patients with SSHL and vertigo, VEMP testing is beneficial for detecting the vestibular component of the disease. There was no asymmetry in VEMP responses between the affected and unaffected ear sides. Patients with SSHL who have vertigo have poor hearing loss recovery rates in the case of low-amplitude o-VEMP responses.

Keywords: Hearing loss sudden, vestibular evoked myogenic potentials, prognosis

INTRODUCTION

Sensorineural hearing loss is a significant issue affecting many individuals, with an estimated 300 million adults and 32 million paediatric cases worldwide. Idiopathic sudden sensorineural hearing loss (SSHL) refers to the rapid onset of hearing loss within a span of three days, typically affecting one ear but occasionally bilateral, with a minimum threshold shift of 30 dB across three consecutive frequencies on pure-tone audiometry (1, 2). The management of sudden hearing loss without a discernible cause remains challenging in otolaryngology, as its underlying histopathological basis is not well understood and is still being explored through various studies.

Histological examination of patients with SSHL revealed the most common degeneration in the saccule (3). Numerous studies have demonstrated that patients with SSHL exhibit vestibular manifestations even in the absence of overt symptoms (3, 4). Approximately 30%–40% of patients with SSHL simultaneously experience vertigo, and these patients have a worse prognosis for hearing recovery than those without vertigo (5, 6).

Vestibular evoked myogenic potential (VEMP) testing is a method used to measure the electrophysiological reflex arc in muscles through stimulation of peripheral vestibular organs and muscles (7, 8). Generally, two reflex arcs, vestibulo-

Corresponding Author: Ayça Başkadem Yılmazer **E-mail:** aycabaskadem@hotmail.com

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collic and vestibulo-occular reflex arcs, are used in testing. The biphasic surface potential recorded from the ipsilateral sternocleidomastoid muscle is called cervical VEMP (c-VEMP), and it tests the function of the saccule, inferior vestibular nerve, and inferior vestibular nucleus. VEMP recorded from extraocular muscles is called ocular VEMP (o-VEMP), and it tests the function of the utricle and superior vestibular nerve (8-11).

In the existing literature, VEMPs have been used to investigate the potential impact of idiopathic SSHL on the vestibular system, whether or not it is accompanied by vertigo. Researchers have observed that the saccule is affected more than the semicircular canals in patients with vertigo and SSHL (3). Despite extensive investigations into labyrinthine functions using various neurophysiological tests, no consensus has been reached.

This study aims 1) to assess both c-VEMP and o-VEMP responses in patients diagnosed with unilateral sudden hearing loss and presenting with vestibular symptoms and 2) to determine whether these responses can serve as predictive parameters for recovery. By evaluating these parameters, researchers can gain insights into the involvement of the vestibular system in SSHL and its potential implications for prognosis and treatment.

MATERIALS and METHODS

This retrospective clinical study was conducted at a tertiary referral centre. Patients diagnosed with both SSHL and vertigo and healthy volunteers without ear pathology were included. The participants were between 18 and 75 years old and had type A tympanogram. Patients who presented with external or middle ear pathologies, central nervous system pathologies, head trauma, other vestibular diseases, recurrent or bilateral sudden deafness, or uncontrolled comorbid diseases (hypertension or diabetes mellitus); those who did not receive treatment for 2 weeks after sudden deafness; or individuals lost to follow-up were excluded.

Sudden deafness was defined as a rapid drop in sensorineural hearing loss of more than 30 dB for at least three consecutive frequencies that occurred in less than three days and had no discernible explanation. All patients were regularly monitored at the clinic and underwent audiometry. Before treatment, all patients underwent an otoscopic examination and a battery of inner-ear tests, including tympanometry, pure tone audiometry, c-VEMP, and o-VEMP tests. Upon admission, all patients received systemic steroid treatment and hyperbaric oxygen therapy for 20 sessions.

This study was approved by the Okmeydanı Research and Education Hospital and was designed according to the Declaration of Helsinki. The study group patients gave their informed consent for participation in the study (Date: 16.04.2019, No: 1258).

Audiometry

Pure-tone audiometry was conducted at 500, 1000, 2000, and 4000 Hz. According to the modified Siegel's criteria proposed by Cheng et al. the audiograms were categorised as grade 1 (<25 dB), grade 2 (26–45 dB), grade 3 (46–75 dB), grade 4 (76–90 dB), and grade 5 (>90 dB) using the ICS_CHARTR EP 200 system (Baastrup, Denmark) (12). The audiometric evaluations were conducted in a soundproof AC 40 audiometry cabin calibrated to ISO 9001 standards. Air and bone conduction were tested at octave intervals from 250 to 8000 Hz and 500 to 4000 Hz.

According to Cheng et al.'s modified Siegel criteria, post-treatment hearing recovery was categorised as complete recovery (final hearing level<25 dB), partial recovery (hearing gain>15 dB and final hearing level 26–45 dB), slight improvement (hearing gain>15 dB and final hearing level 46–75 dB), no improvement (hearing gain<15 dB and final hearing level 76–90 dB), and non-serviceable ear (final hearing level>90 dB) (12).

VEMPs

Both c-VEMP and o-VEMP tests were performed on all participants to evaluate their vestibular symptoms using the ICS-CHARTER EP 200 evoked potential system (CN Otometrics North America, Schaumburg, IL, USA. VEMP waves were analysed to compare the patients with the control group based on the latencies, amplitudes, and the amplitude asymmetry ratio (AAR) of c-VEMP (P1, N1) and o-VEMP (N1, P1). The AAR was calculated as AAR = 100 x (Ar - Al) / (Ar + Al), where Al and Ar represent the left and right amplitudes, respectively. According to the normal values of VEMP levels obtained from healthy control subjects for 95 dB at our laboratory, a peak limit of 34.2% for c-VEMP and 35% for o-VEMP was defined for the AAR, and values exceeding these limits were considered abnormal.

Acoustic stimulation for both o-VEMP and c-VEMP was performed using an ICS Medical Insert Earphones (ER 3A/5A Insert Earphone 300 ohms). The impedance difference between the electrodes remained below 3 kOhm. An amplitude value of 0 was assigned to ears with no response.

c-VEMP

The reference electrode was placed over the sternum, and the ground electrode was placed on the nasion close to the hairline in the midline. The active electrodes were placed over the sternocleidomastoid muscle and nasion. Rest periods were provided to alleviate fatigue, if necessary. The parameters recorded included 500-Hz tone bursts with a repetition rate of 5.1 tone bursts per second, a minimum of 50 sweeps per waveform, an intensity level of 95 dB HL (decibel hearing level), rise-plateau fall times of 2.0–1.0–2.0 ms, and at least two waveforms per condition. After the stimulus, the initial negative-positive biphasic waveform included the peaks P1 (positive) and N1 (negative).

o-VEMP

All participants were instructed not to contract their facial muscles and to maintain a gaze at a predetermined point approximately two metres away while keeping their heads in a fixed position and looking upward at an angle of 30° 40°. The reference electrode was positioned in the infraorbital position at a distance of 3 cm, and the ground electrode was placed on the forehead. The active electrodes were placed over the infraorbital position on the face at distances of 1 and 3 cm. The parameters recorded included 500-Hz tone bursts with rise-plateau-fall times of 1.5–0–1.5 ms, a repetition rate of 5.1 tone bursts per second, a minimum of 50 sweeps per waveform, and an intensity level of 95 dB HL. After the stimulus, the first biphasic waveform peaks were negative (N1) and positive (P1).

Statistical analysis

Descriptive statistical methods (mean, median, standard deviation [SD], frequency, percentage, minimum, and maximum) were used to evaluate the data. Pearson's chi-square test was used to compare the qualitative variables. The Shapiro–Wilk test was used to analyse the quantitative variables' normal distributions. The Student's t-test was used to compare two independent groups whose quantitative variables were normally distributed, while the Mann–Whitney U-test was used to compare groups whose distributions were not normally distributed. The Wilcoxon test was used when distributions varied from normal; a paired t-test was performed for dependent groups. Accepted criteria for statistical significance were $p<0.05$.

RESULTS

Clinical manifestations comprised hearing loss and vertigo/dizziness in all 40 patients. Our study was conducted with 64 cases, of which 37.5% (n=24) were healthy controls and 62.5% (n=40) were patients. Among the cases, 54.7% (n=35) were female and 45.3% (n=29) were male. The ages ranged from 18 to 74 years, with a mean age of 45.37±12.47 years. There were no statistically significant differences in age and gender distribution between the groups ($p>0.05$). In the patient group, 47.5% (n=19) had problems in their right ear, while 52.5% (n=21) had problems in their left ear (Table 1). Additionally, no differences were observed between the subgroups according to the hearing level of the patients by age (Table 2).

According to pure tone audiometry, the mean hearing levels were 69.7+27.9 dB in the patient group and 12.5+5.7 dB in the control group. The patient group's mean hearing level was significantly high ($p<0.001$).

Before treatment, hearing loss in the patient group was as follows: 17.5% (n=7) had grade 2, 27.5% (n=11) had grade 3, 30% (n=12) had grade 4, and 25% (n=10) had grade 5 hearing loss (Table 2).

Table 1: Demographic data

		SSHL Patients			Control (n=24)	p value
		Right side (n=18)	Left side (n=12)	Total (n=40)		
Gender (n)	Male	7	12	19	10	0.553*
	Female	11	10	21	14	
Age (mean±SD)		47.5±11.6	44.3±16.3	45.75±14.3	44.8±8.9	0.697**

*Pearson Chi-Square test, **Student t Test, SSHL: Sudden sensorineural hearing loss, SD: Standard deviation

Table 2: Hearing status of patients with SSHL

Characteristics of the SSHL group (n=40)		Age (mean±SD)	p value
Pre-treatment hearing loss	Mild (n=7)	43.0±5.8	0.798*
	Moderate (n=11)	52.2±9.8	
	Severe (n=12)	42.6±14.2	
	Complete (n=10)	44.4±21.0	
Post-treatment Modified Siegel Classification	Class1 (n=7)	41.3±10.8	0.397*
	Class2 (n=3)	44.3±26.5	
	Class3 (n=13)	45.8±12.7	
	Class4 (n=17)	47.8±15.3	
Recovery status	Recovered (n=23)	44.2±13.7	0.438**
	Not-recovered (n=17)	47.8±15.3	

*One-Way ANOVA, **Student t Test, SSHL: Sudden sensorineural hearing loss, SD: Standard deviation

Table 3: Comparison of VEMP parameters between the SSHL and control groups

		SSHL patients (n=40)		Control (n=48)	p* value
		Recovered (n=23)	Non-recovered (n=17)		
c-VEMP (mean±SD)	P1 latency	12.12±7.49	11.99±6.72	16.14±1.32	0.009
	N1 latency	19.66±11.42	19.24±11.47	25.66±2.18	0.039
	Amplitude	140.15±143.93	126.69±130.97	156.22±123.83	0.382
	AAR	47.26±36.66	60.19±33.90	24.99±20.04	0.721
o-VEMP (mean±SD)	P1 latency	12.99±6.19	9.70±8.37	15.47±1.15	0.782
	N1 latency	8.64±4.21	6.80±5.94	10.50±1.12	0.002
	Amplitude	7.96±6.90	3.07±3.95	7.74±5.62	0.004
	AAR	39.80±33.80	57.59±41.83	24.49±17.73	0.063

*Kruskal–Wallis test, VEMP: Vestibular evoked myogenic potential, SSHL: Sudden sensorineural hearing loss, AAR: Amplitude asymmetry ratio, SD: Standard deviation

After treatment, the outcomes of the patients were as follows: complete recovery with 7.7% (n=7), partial recovery with 7.5% (n=3), slight improvement with 32.5% (n=13), and no improvement with 42.5% (n=17) of the cases. In total, 57.5% of the cases showed improvement, whereas 42.5% showed no improvement (Table 2).

In both the control and patient groups, there was no statistically significant difference between the ear sides for either the c-VEMP or o-VEMP parameter (p>0.05; Wilcoxon test). In comparing VEMP responses between the SSHL and control groups, the P1 and N1 latencies of c-VEMP were lower in the SSHL group (p=0.009, p=0.039, respectively). Moreover, the amplitude of o-VEMP was lower in the SSHL group (p=0.002), and both the AAR of c-VEMP and o-VEMP were higher in the SSHL group (Table 3).

When comparing the VEMP values of the patients who improved hearing with those who did not, it was found that the o-VEMP amplitude of non-improved patients was statistically lower (p=0.013). Moreover, in the non-improved group, the c-VEMP P1 latencies were lower, and the AAR of c-VEMP was significantly higher than that in the control group (p=0.006, and p<0.001, respectively; Mann–Whitney U test with Bonferroni correction p<0.017).

DISCUSSION

The results of VEMP testing on SSHL with vertigo. We observed that both the c-VEMP and o-VEMP responses were abnormal in patients with idiopathic SSHL, and a low amplitude of o-VEMP may predict poor prognosis.

The present study evaluated hearing before and after treatment according to Cheng et al.s modified Siegel criteria (12). Cheng et al. reported that 51% of 110 patients with SSHL experienced hearing improvement. In our study, 57.5% of 40 patients with SSHL experienced hearing improvement after treatment.

VEMP results may vary according to age (13, 14). Khan et al. compared the c-VEMP results among different age groups and observed that the c-VEMP response rate was extremely high in adolescents (13). Additionally, Jha et al. studied the differences in VEMP results according to age. They concluded that c-VEMP decreased only at 500 and 750 Hz, whereas o-VEMP changed at all frequencies according to age (14). Age and sex did not differ in our study between the two groups or across the patient group subgroups, therefore that these factors had no bearing on outcomes.

Accompanying the cochlear system, the vestibular system has been shown to be affected in SSHL based on c-VEMP, o-VEMP, or both c-VEMP and o-VEMP testing (15-18). However, some studies also used caloric tests in addition to VEMP tests. Iwasaki et al. studied SSHL with vertigo using VEMPs and caloric tests. They observed that caloric tests provide information about the function of the semicircular canals, whereas VEMPs provide information about the saccule. Moreover, in SSHL, the saccule is affected more than the semicircular canals; thus, VEMP testing is more sensitive than caloric tests for detecting vestibular function in SSHL (3). Liang et al. used both VEMP and caloric tests to detect the recovery of patients with SSHL and claimed that caloric tests were not predictive of the prognosis of SSHL (19). Thus, our study focused on VEMP tests (both c-VEMP and o-VEMP) to analyse SSHL patients.

Many studies on SSHL with or without vertigo using VEMP tests have shown that VEMP tests are abnormal in SSHL, and the saccule and utricle, as well as the cochlea, are included in the pathophysiology of SSHL. Jiang et al. compared patients with SSHL with and without vertigo using the VEMP test but did not include a healthy control group. SSHL patients with vertigo had severe hearing loss and higher abnormal VEMP results (20). Lim et al. demonstrated that abnormal o-VEMP was significantly more related to hearing loss in patients with SSHL and vertigo. They concluded that this was because the arterial supply of the saccule included more collateral arteries than the utricle, thereby causing resistance to ischaemia (21). Yigider et al. also

studied VEMP responses in patients with SSHL. Their study group had no vestibular symptoms, and the healthy control group was not included. They compared patients' bilateral ears and determined that c-VEMP responses differed between the ears bilaterally, whereas o-VEMP responses were similar (22).

In this study, we used both c-VEMP and o-VEMP levels to compare patients with SSHL with vertigo and a healthy control group. We observed that both the VEMP and control test results in patients with SSHL were abnormal. However, the VEMP responses were similar bilaterally between the ear sides. Kizkapan et al. also found no bilateral ear differences using VEMP testing (23).

VEMP testing has been used in the literature to evaluate not only the diagnosis but also the prognosis of SSHL (19, 23). Kizkapan et al. studied the prognosis of SSHL using caloric and VEMP tests and compared the caloric test results with the degree of hearing loss before and after treatment. However, they compared the VEMP results between the control and case groups, not considering the degree of hearing loss. They concluded that the VEMP responses were abnormal before treatment but improved after SSHL treatment (23). Similarly, Liang et al. evaluated the prognosis of SSHL using the VEMP test. They compared patients according to hearing improvement. They concluded that abnormal VEMP levels may predict poor prognosis in patients with SSHL (19). The study aim was to investigate VEMP results before treatment and the predictive value of hearing recovery after treatment. We observed that only low-amplitude o-VEMP was correlated with a poor prognosis of SSHL. Patients with low-amplitude o-VEMP showed less hearing recovery. Therefore, hearing loss may be permanent and unresponsive to treatment if the utricle and superior vestibular nerve are affected in patients with SSHL.

The small sample size in our study is a major limitation. Although caloric testing was less vulnerable to detect vestibular function in SSHL than VEMP testing, it might be included in the differential diagnosis of vertigo. Moreover, to evaluate the changes in vestibular function after SSHL treatment, VEMP responses might be analysed in the patients' follow-up periods.

CONCLUSION

VEMP testing is beneficial for detecting the vestibular component of SSHL with vertigo. There was no asymmetry in VEMP responses between the affected and unaffected ear sides. Patients with SSHL and vertigo have poor recovery rates of hearing loss in cases of low-amplitude o-VEMP responses.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences, Okmeydanı Training and Research Hospital (Date: 16.04.2019, No: 1258).

Informed Consent: The study group patients gave their informed consent for participation in the study.

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Immediate Effects of Vocal Warm-Up on the Acoustic and Aerodynamic Parameters of Speech-Language Pathology Students

Merve Aydoğuş[1], Elçin Tadıhan Özkan[2]

[1]İstanbul Kent University, Faculty of Health Science, Department of Speech Language Therapy, İstanbul, Türkiye
[2]Anadolu University, Faculty of Health Science, Department of Speech Language Therapy, Eskişehir, Türkiye

ORCID ID: M.A. 0000-0002-6628-6633; E.T.Ö. 0000-0003-3154-5305

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ABSTRACT

Objective: Although vocal warm-up is vital for singers and other professional voice users, no consensus has been reached regarding its underlying physiological effects, especially for the non-singing community. Accommodating speech and language pathology (SLP) students, this research aimed to investigate the effects of vocal warm-up on the acoustic and aerodynamic parameters of voice.
Material and Methods: A quasi-experimental, pre-test–post-test research design was used. A total of 28 SLP students performed a 20-minute session of vocal warm-up based on breathing, stretching, phonation, and resonance exercises. Data analysis consisted of instrumental analysis in which the Multidimensional Voice Programme (MDVP) and Phonatory Aerodynamic System (PAS) were used to measure acoustic and aerodynamic parameters before and after vocal warm-up.
Results: A significant decrease in jitter and shimmer values was detected after the vocal warm-up period. Additionally, significantly higher values were found in the subglottal pressure estimate.
Conclusion: Following vocal warm-up, acoustic and aerodynamic parameters improved to normal values. The findings indicate that vocal warm-ups improve the objective voice quality.
Keywords: Acoustic analysis, aerodynamic analysis, phonatory aerodynamic system, voice quality, warm-up

INTRODUCTION

A professional voice user is anyone who relies on their voice for their livelihood. This population includes not only singers and actors, but also teachers, salespeople, telemarketers, and anyone who needs to maintain optimum vocal quality as part of their profession (1). Considering the higher prevalence of voice disorders among professionals with heavy vocal demand, the development of preventive strategies, such as voice training, is of critical importance (2). Research findings revealed that speech language pathology (SLP) candidates as future professional voice users exhibit more voice-related problems (12%) than the general population (3–9%) (3). The manner of SLP voice use differs from routine conversation level, as SLPs must demonstrate voice therapy techniques and provide vocal coaching (4).

The analogy of vocal athletes is commonly used to refer to professional voice users who rely on their voices for earning their livelihood; such as singers, teachers, and performers (5). Professional voice users are required to warm up their voices before vocally demanding activities in much the same manner that athletes prepare their muscles for sports performance (6, 7). Studies have shown that warming up the voice affects the physiology of the vocal mechanism (8-17), in addition to helping mental preparation for the upcoming activity (18). Positive changes in both objective measurements and subjective/perceptual evaluations (8-17, 19-24) were documented following vocal warm-up. Although it is widely acknowledged that a vocal warm-up is essential for optimal voice function, relatively little progress has been made in describing the underlying physiological effects and their impact on the acoustic and aerodynamic parameters of the voice.

Corresponding Author: Merve Aydoğuş **E-mail:** aydogusmerve@gmail.com
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Acoustic analysis, as an objective and non-invasive measurement tool, assesses vocal fold function and tracks changes over time (25). Research has demonstrated that vocal warm up has positive effects on acoustic parameters, including improvement in fundamental frequency (F0) and formant values, decrease in perturbation values, improvement in noise-to-harmonic ratio, increase in singer's formant amplitude and spectral energy (8-14, 16), establishment of singer's formant cluster, and increase in vocal range profile (12-17). On the other hand, no significant changes in the abovementioned acoustic parameters following vocal warm-up have been reported in the literature (8, 9, 11). A study recruiting untrained singers found no significant changes in acoustic measurements following straw phonation as a vocal warm-up, whereas decreased shimmer along with increased fundamental frequency were reported following traditional vocal warm-ups (8). In another study with speech language pathology students, the vocal warm-up yielded no improvements in perturbation values, whereas an overall increase in objective vocal quality represented by the Dysphonia Severity Index was noted (11).

Although used less frequently in relevant literature, aerodynamic analysis provides valuable data on laryngeal valve mechanisms, airflow during sound production, and subglottal air pressure, which are related to underlying voice physiology (26). Studies investigating the effects of vocal warm-up on aerodynamic parameters have yielded inconclusive results, especially regarding the phonation threshold pressure, which is defined as the minimum subglottal pressure required to initiate phonation vocal fold oscillation (27). After vocal warm-up, the phonation threshold pressure increased or decreased in some studies, whereas in others, inter-subject variability, gender variability, or no change was observed (7, 8, 19, 21, 28-31). Portillo et al. compared the effects of vocal exercises using the semi-occluded vocal tract (SOVT) and open vocal tract (OVT) as a vocal warm-up for contemporary commercial music singers (19). Decreased sound pressure level, increased airflow, and decreased aerodynamic efficiency were found for the latter; and the findings were interpreted by the authors as indicative of vocal fatigue. In another study by Saldias et al., both water resistance therapy (a type of SOVTE) and OVT warm-up decreased the subglottic pressure and inspiratory airflow duration, whereas the sound pressure level decreased only in the OVT group (32). Although increased self-perceptions of vocal quality were reported for both conditions, SOVTEs were shown to be more effective in preparing vocal mechanisms for an upcoming vocal load, leading to a more economic voice. While determining the optimal vocal warm-up protocols, their potential effects on the physiology of vocal mechanisms should also be considered, in addition to the psychological component.

The findings of the aforementioned studies indicate that the literature on the effects of vocal warm-up is somewhat inconclusive. This inconsistency arises because the methodologies are quite varied. The use of a variety of warm-up exercises, the duration of the warm-up, and the measurement of voice quality using different techniques make it difficult to reach a consensus regarding the ideal warm-up protocol.

Titze suggests that the five best exercises for vocal warm-up are a) lip trill, tongue trill, humming, and tube phonation on glides, scales, or arpeggios, b) two-octave pitch glides on high vowels, c) forward tongue roll and extension, vowel sequences /a/-/i/, 4) messa di voce, 5) staccato on arpeggios (33). Furthermore, he clarifies the specific purpose each exercise serves. In parallel with Titze's proposals, vocal warm-up regimens commonly selected for research purposes include SOVTE, which consists of lip trills, tongue trills, humming, and nasal consonants, bilabial fricative, straw phonation, LaxVox, hand-over mouth, and finger kazoo technique (14). SOVTE have been hypothesised to reduce the phonation threshold pressure and perceived phonatory effort; improve acoustic qualities of voice, and lead to morphometric differences of the vocal tract that help establish healthy voice production (34).

Vocal warm-up preferences also vary across the singing and non-singing community; and the current literature mostly focuses on the singing community (13-17, 35-39). In such a study, Gish et al. investigated the characteristics of vocal warm-up regimens for 170 vocalists (40). 54% of the participants stated that they always warmed up their voice before singing. The most frequently used singing exercises were ascending/descending five-note scales, octave scales, legato arpeggios, and glissandi. Regarding the non-singing warm-up exercises; stretching muscles, breathing, and postural alignment exercises were the most preferred. As vocal warm-up is recommended to be performed by other professional groups with high vocal loads, warm-up protocols for non-singing communities should also be investigated. Vocal warm-up has a positive effect on the quality of speaking and singing voices, and warming up the voice can be beneficial for non-singing communities by preventing vocal fatigue and improving vocal economy.[8] In addition, vocal warming is proven to be effective when used for voice rehabilitation in people with voice disorders, so warm-up can also be practised as a therapeutic method or a preventive measure for occupational dysphonia (12, 41). Therefore, this study was conducted with SLP candidates because they will be required to use their voice intensively in the future due to the nature of their future employment facing an increased risk of developing voice disorder. For this purpose, this study aimed to determine whether SOVTE, as a warm-up, differentially affects the acoustic and aerodynamic parameters of voice in future SLPs. We hypothesised that vocal warm-up will have an immediate and significant improvement in vocal acoustic and aerodynamic properties.

MATERIALS and METHODS

Participants

Employing the convenience sampling method, this study employed a quasi-experimental pre-/post-interventional research design. A total of 28 undergraduate and graduate SLP students (10 female and 18 male) within the age range of 20-35 years were recruited after obtaining informed consent to participate in writing. Participants with a history of hearing

defect, surgery of the vocal apparatus, vocal pathology, head and neck trauma, neurological disorder, respiratory tract infections, or smoking were excluded from the study. None of the participants received any vocal training or previous voice therapy. There were no singers among the participants. The ethics committee of Anadolu University approved the study.

Voice assessment and equipment

The data collection process was carried out in the voice analysis laboratory of Anadolu University Research Centre for Speech and Language Disorders. A multi-dimensional voice analysis (acoustic and aerodynamic measurements) was performed before and immediately after each vocal warm-up session. The first author collected data and completed the vocal warm-ups with the participants.

The Multi-Dimensional Voice Programme (MDVP) Model 3700 (Kay Elemetrics Corp., Lincoln Park, NJ) was used to compute the acoustical data. Voice recording was performed using a unidirectional dynamic microphone (Shure SM48 Dynamic Cardioid Microphone) in a sound-attenuated room. A constant mouth-to-microphone distance of 10 cm at a 45° angle was maintained during each recording. Voices were recorded at a sampling rate of 44.1 kHz. Participants were instructed to perform sustained /a/ vowel phonation three times with comfortable pitch and loudness for three seconds. The middle second of the vowel prolongation was segmented for analysis. The acoustic parameters measured were fundamental frequency (F0, Hz), frequency perturbation (Jitter, %), amplitude perturbation (Shimmer, %), and noise-to-harmonic ratio (NHR, dB).

Aerodynamic measurements of the voice were performed using the Phonatory Aerodynamic System (PAS) Model 6600 (Medical Kay Pentax). The selected protocol within the scope of this study is the Voicing Efficiency Protocol (VOEF), which calculates a number of parameters describing glottal behaviour. Before each recording session, the researcher calibrated the measuring equipment appropriately. The participants were asked to press the mask firmly against their face to prevent air leakage, as shown in Figure 1. An intraoral tube was inserted 2 cm into their mouths to acquire oral pressure. They were instructed to repeat the syllable [pa:] seven consecutive times in a single breath at a comfortable pitch and loudness. Three trials were performed. Before the recording, the experimenter trained the participants on how to produce the syllables at an appropriate rate (1.5 to 2 syllables per second). The first and last syllables in the string were not included, and the middle five syllables in between were analysed. The subglottal pressure was estimated from peak air pressure during the production of the voiceless plosive [p], while average airflow and sound pressure level measurements were obtained during the vowel segment [a] (42). Variables analysed in this phonatory task were mean sound pressure level (SPL, dB), average airflow rate (Lit/Sec), and subglottal pressure estimate (P_{sub}, cmH2O).

Figure 1: The correct way to hold the PAS external module during data capture (picture taken from PAS instructional manual)

Vocal warm-up exercises

The vocal warm-up protocol consisted of gentle stretching exercises, breathing exercises/posture alignment, and phonation/resonance exercises. Warm-up exercises were designed based on previous research regarding vocal warm-up and adapted for the non-singing community (7, 11, 43). The entire warm-up period lasted 20 minutes. The researcher provided corrective feedback to ensure that the exercises were performed in accordance with their purposes. The participants were advised to perform the exercises without tension in the head and neck area.

A warm-up activity began with gentle stretching exercises of the muscles of the head, neck, arm, shoulders, and mandible region. Then, they transitioned to diaphragmatic breathing exercises, improving their respiratory function without excessive shoulder and neck movements. Each exercise was performed using due attention to proper body alignment. For the last part of the vocal warm-up, participants engaged in phonation and resonance exercises, increasing the flexibility of their vocal folds and facilitating voice production. Phonation and resonance exercises were performed as follows:

1) Lip and tongue trill at a habitual speaking pitch and loudness, and ascending and descending glissandos through a comfortable vocal range 2) Humming at a habitual speaking pitch and loudness, and ascending and descending glissandos through a comfortable vocal range 3) Ascending and descending scales on syllables with nasal consonant and vowel sequences 4) Gliding yawning on open-mouthed vowels.

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Corp., Armonk, NY, USA) 22.0. The Shapiro-Wilk test was used to evaluate the distribution of the selected acoustic and aerodynamic parameters. In the case of a normal distribution, the paired t-test was performed to compare pre- and post-warm-up conditions. To compare non-normally distributed data, the Wilcoxon signed-rank test was used. The level of significance was set at $p<0.05$ in all tests.

RESULTS

This study aimed to investigate the immediate effects of vocal warm-up on acoustic and aerodynamic parameters in future SLPs. The paired sample t-test and Wilcoxon signed-rank test revealed significant effects of vocal warm-up exercises on objective voice quality. The results are detailed below:

Acoustic parameters

Acoustic analysis of the six recordings could not be performed for technical reasons; therefore, the corresponding subjects were excluded from the MDVP analysis. Table 1 presents the mean and standard deviation of the acoustic parameters pre- and post-vocal warm-up. A significant difference was observed in the jitter and shimmer values with p-value <0.05 of the Wilcoxon signed-rank test. No statistically significant effect was found for fundamental frequency or noise-to-harmonic ratio (p>0.05).

Aerodynamic parameters

The aerodynamic parameters measured under pre- and post-warm-up conditions are presented in Table 2. A statistically significant difference was found in the subglottal pressure estimate (p<0.05). However, there were no statistically significant differences between pre- and post-warm-up for the sound pressure level and average airflow rate variables (p>0.05).

Table 1: Mean values and standard deviations of acoustic measurements before and after vocal Warm-up

	Pre		Post		
	Mean	**SD**	**Mean**	**SD**	**P value**
F0 (Hz)	180.09	60.03	180.28	60.76	0.894
Jit (%)	0.964	0.72	0.583	0.432	0.000*
Shim (%)	3.099	0.857	2.402	0.637	0.000*
NHR (dB)	0.124	0.013	0.124	0.014	0.865

SD: Standart Deviation; F0: Fundamental Frequency; Jit: Jitter; Shim: Shimmer; NHR: Noise to Harmonic Ratio, *: Significance level <0.05.

Table 2: Mean values and standard deviations of aerodynamic measurements before and after vocal Warm-up

	Pre		Post		
	Mean	**SD**	**Mean**	**SD**	**P value**
SPL (dB)	92.78	3.80	93.65	4.14	0.207
Airflow (Lit/Sec)	0.165	0.83	0.159	0.074	0.799
Psub (cmH2O)	5.66	1.24	7.00	2.00	0.000*

SD: Standart Deviation; SPL: Sound Pressure Level; P_{sub}: Subglottal Pressure Estimate
* Significance level <0.05.

DISCUSSION

In the present investigation, the authors attempted to determine the immediate effects of vocal warm-up on acoustic and aerodynamic parameters in speech and language pathology students. Significant changes across parameters were determined (decrease in jitter and shimmer values, increase in subglottal pressure estimate) under the postwarm-up condition, indicating that vocal warm-up alters the physiology of the vocal mechanism.

According to Bishop, warming up muscles improves sport performance, resulting in physiological changes, such as increased blood flow to muscles, decreased muscle viscosity, increased oxygen delivery, acceleration of metabolic reactions, and increased speed of nervous impulses. In addition, warm-ups have been proposed to decrease the risk of sports injury (44). As voice production is a complex biomechanical phenomenon, mostly controlled by laryngeal muscle activation, warm-up is thought to improve the vocal mechanism in a similar way as that of other muscles of the human body. Furthermore, a vocal warm-up may help reduce potential risk factors of voice disorders in professional voice users, such as speech language pathologists. Despite their heavy voice use and elevated vocal risk given their occupational demands, voice issues among SLPs and SLP students have received little attention from researchers (45).

Acoustic analysis showed positive effects of vocal warm-up in two parameters. Jitter, which is related to frequency perturbation, is defined as the amount of cycle-to-cycle variability of frequency. The other perturbation measure, shimmer, assesses cycle-to-cycle variations in the period amplitude. These parameters are frequently used as baseline measures to capture changes between pre- and post-intervention measures in voice research. High jitter and shimmer values are associated with dysphonia, which is an indication of the vibrational irregularity of vocal folds (6, 25, 46). The results of this study revealed a significant decrease in jitter and shimmer after a 20-minute vocal warm-up. This suggests that vocal fold vibration can be controlled more effectively via vocal warm-ups (47). Improvements in the jitter and shimmer parameters following vocal warm-up were in line with previous research (12-14). A recent study designed to assess the impact of vocal warm-up exercises consisting of tongue trills, lip trills, and humming at a steady tone and then with pitch variations revealed similar positive results for jitter and shimmer values in singing students (14). Amir, Amir, and Michaeli's work also confirmed that performing a vocal warm-up based on vocal exercises at different pitches, as well as breathing, posture, and relaxation exercises, which is also a similar protocol to that of our study, significantly decreased jitter and shimmer values and improved vocal stability in 20 singers (13).

Regarding aerodynamic analysis, an increased subglottic pressure was observed in the post-warm-up condition. The subglottal air pressure is estimated from the intraoral air pressure produced during lip occlusion for a series of /pVpV/ syllables. The same task

performed at the minimum loudness level was used to estimate the phonation threshold pressure, another frequently used aerodynamic variable (6, 25). The aforementioned literature on the aerodynamic effects of vocal warm-up is still scarce and has conflicting findings, especially concerning the two parameters (7, 19, 21, 28-32). Contrary to our findings, a study comparing the effects of OVTE and SOVTE found a significant decrease in subglottal air pressure post-warm-up under both conditions. It was suggested that this decrease might be related to vocal fatigue as Titze stated that reduced subglottal pressure could be a consequence of respiratory muscle fatigue, promoting the early phase of vocal fatigue (48).

The warm-up protocol used in this study was heavily based on SOVTE (lip trills, tongue trill, humming and nasal consonants). In an integrative review by Apfelbach and Guzman, studies investigating the effects of SOVTE on subglottal pressure have not produced consistent results. SOVTE has been reported to increase or decrease subglottic pressure or result in no change. The authors explained this discrepancy because of different baseline measures. In other words, SOVTE normalise subglottal pressure level by either increasing or decreasing, depending on the pre-intervention amount of pressure (34). Although increased subglottal pressure generally indicates hyperfunctional voice use, which is undesirable for optimum vocal quality, the findings can be interpreted from this perspective (6). The mean subglottal pressure increased from 5.66 cm H2O to 7.00 cm H2O following vocal warm-up in our research. According to the normative data for phonatory aerodynamic measures obtained with PAS among healthy Turkish speakers, the norm value for subglottal pressure parameter within the corresponding age group was 7.67 cm H2O in voicing efficacy protocol (49). Thus, the increase in subglottal pressure levels in our study generated an improvement towards normal values in a healthy Turkish-speaking population. It is worth noting that normative data for air pressure measurements in a Turkish-speaking population are higher than the data of an adult normative study on PAS by Zraick et al. This difference has been interpreted as a result of the participants' native language (49, 50).

Schaeffer conducted pre- and post-stimulation research to measure aerodynamic parameters on PAS in 20 participants with vocal complaints (26). Stimulation training targeted coordination of respiration and phonation in addition to control of abdominal muscles during phonation. After the stimulation training, 17 out of 20 participants approximated their subglottal pressure level to the normal range, which was in line with our study findings.

In summary, data from the current study revealed positive effects of vocal warm-up on the acoustic and aerodynamic parameters of the voice. Specifically, the jitter and shimmer perturbation measures significantly decreased, indicating better acoustic quality. In addition, the subglottal pressure estimate improved to the normal range.

It may be interesting to conduct further research in real-life settings where it is possible to observe the vocal demands of professional voice users during an ordinary day. Future research on vocal warm-up should include a larger number of participants and different warm-up protocols with varying durations. A fully experimental research can also be conducted by including a control group, which is lacking in this study.

The current study has some methodological limitations related to research design and sample size. Using a quasi-experimental approach, the study lacks equivalent control group and randomisation. The sample size is relatively small. Further studies should attempt to recruit more participants and control threats to internal validity in order to generalise the findings to a broader population.

CONCLUSION

Vocal warm-up is critically important for obtaining the optimum vocal quality in both speaking and singing voices. Although professional voice users are advised to perform a vocal warm-up before intensive voice use, the physiological mechanism of warm-up remains unclear. This study highlights the positive influence of a vocal warm-up on objective voice quality. The instrumental analysis of voice using MDVP and PAS demonstrated a significant decrease in perturbation parameters and improvement in the subglottal pressure estimate. Professional voice users, such as speech-language pathologists, should implement vocal warm-up strategies in their routines to improve the quality of their voice and attenuate the adverse effects of vocal load.

Data Availability Statement: Raw data were generated at the voice analysis laboratory of Anadolu University Research for Speech and Language Disorders. Derived data supporting the findings of this study are available from the corresponding author M. A. on request.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Anadolu University (Date: 15.12.2015, No: 27441).

Informed Consent: Informed consent was obtained in writing from all the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- M.A., E.T.Ö.; Data Acquisition- M.A.; Data Analysis/Interpretation- M.A., E.T.Ö.; Drafting Manuscript- M.A.; Critical Revision of Manuscript- M.A., E.T.Ö.; Final Approval and Accountability- M.A., E.T.Ö.

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Impact of Parkinson's Disease-Related Dysphagia Severity on Quality of Life: Comparison Between Self-Reports and Videofluoroscopic Swallowing Study Results

Serkan Bengisu[1], Merve Savaş[1], Demet Aygün[2], Senanur Kahraman Beğen[1], Tutku Altıntaş[1], Burak Manay[1]

[1]İstanbul Atlas University, Faculty of Health Sciences, Department of Speech and Language Therapy, İstanbul, Türkiye
[2]İstanbul Atlas University, Faculty of Medicine, Department of Neurology, İstanbul, Türkiye

ORCID ID: S.B. 0000-0002-6580-1189; M.S. 0000-0002-7138-2603; D.A. 0000-0002-1828-1811; S.K.B. 0000-0001-6938-301X; T.A. 0009-0001-2729-741X; B.M. 0009-0000-9509-4633

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ABSTRACT

Objective: The aim of this study was to evaluate the impact of dysphagia due to Parkinson's disease (PD) on quality of life and to compare the results of the objective assessment with those of patient self-reports.
Materials and Methods: The study included 28 participants with PD. Patients were assessed clinically using the Eating Assessment Tool (EAT-10) and objectively via video-fluoroscopy (VFSS). The data obtained with VFSS were scored using the Penetration Aspiration Scale (PAS) and Functional Oral Intake Scale (FOIS) by an SLP blinded to patient information and clinical assessment methods. Swallowing disorder-related quality of life was assessed using the Swallowing Quality of Life Questionnaire (SWAL-QOL).
Results: It was found that as PD severity and duration increase, the severity of swallowing impairment also increases, leading to a negative effect on quality of life being affected negatively accordingly ($p<0.05$). According to the SWAL-QOL questionnaire results, dysphagic patients had lower SWAL-QOL scores, particularly in terms of burden, eating desire, duration, symptom frequency, food selection, and mental health domains. In addition, a statistically significant difference was found between the groups with and without dysphagia in all EAT-10, PAS, and FOIS scores ($p=0.000$, $p=0.20$, $p= 011$). There was no statistically significant difference between self-reports on the presence of swallowing disorders and the results of the objective assessment using the VFSS ($p=0.298$).
Conclusion: In patients with PD, swallowing impairment becomes more pronounced as the duration and severity of the disease increase, and quality of life is negatively affected. The results of this study suggest that the results between objective assessments and patient reports are inconsistent and therefore emphasise the importance of objective measurement methods in dysphagia assessment.
Keywords: Parkinson disease, dysphagia, quality of life, videofluoroscopy, self reports

INTRODUCTION

Parkinson's Disease (PD) is one of the most common neurodegenerative diseases, affecting the nervous system and causing motor and non-motor symptoms due to extrapyramidal involvement (1). More than 80% of patients develop dysphagia during the disease (2). The prevalence of PD in individuals older than 80 years is 1903 per 100,000 people worldwide and increases with age (3). In Turkey, a study reported a prevalence of 202 per 100,000 individuals with PD (4, 5). Severe dysphagia is subjectively reported to occur approximately 10 years after the onset of motor symptoms, often in the advanced stages of PD (5-7). The reported prevalence of dysphagia in patients undergoing PD varies widely, from 18.5% to 100%, due to differences in methods of assessing swallowing function.

Dysphagia, which is defined as difficulty swallowing, is a disorder of the sensorimotor system required for swallowing. It is estimated that approximately 600,000 individuals develop neurogenic dysphagia annually. Accurate and early diagnosis can improve quality of life and prevent death (8). Dysphagia is strongly associated with aspiration pneumonia in elderly

Corresponding Author: Serkan Bengisu **E-mail:** serkan.bengisu@atlas.edu.tr
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individuals, leading to hospitalisation, morbidity, and death. Therefore, understanding the prevalence of dysphagia in fragile individuals can facilitate early diagnosis and treatment (9).

Assessment techniques used in swallowing examinations are both objective and subjective. Physical examination, instrumental examination, and medical history are all part of the neurogenic dysphagia assessment process. In our country, subjective evaluation tools, such as the Swallowing Quality of Life Questionnaire (SWAL-QOL), Gugging Swallowing Screening Test (GUSS), and Eating Assessment Tool (EAT-10), have completed reliability and validity studies. In objective evaluation, instrumental imaging methods, such as the Fiberoptic Endoscopic Swallowing Study (FEES) and Videofluoroscopic Swallowing Study (VFSS), are used (10-13). These tools have various advantages over one another (14). In evaluating patients with swallowing disorders, an integrated clinical assessment should include as many elements as possible from both non-instrumental and instrumental assessments (15). Despite the effectiveness of subjective tools in identifying patients at risk for swallowing disorders, objective assessment tools should also be used to evaluate swallowing dysfunction in detail and to detect silent aspiration (16). Differences in the severity of dysphagia based on subjective patient reports and instrumental assessments may be observed in patients with dysphagic complaints. The use of both objective and subjective assessments provides a clear and comprehensive presentation of the nature of the problem (17).

Studies employing instrumental assessments, such as FEES or VFSS, have shown that more than 50% of patients with PD who do not self-report dysphagia actually have it. This discrepancy underscores the necessity of utilising objective evaluations like FEES or VFSS to accurately diagnose dysphagia in PD (5, 18, 19). There was a substantial disparity between the prevalence of dysphagia reported by patients themselves (35%) and the cases confirmed through objective assessments (82%) (20). Pneumonia is the primary cause of death in PD, affecting 4%–30% of patients (6). Surprisingly, a significant proportion of individuals with PD (20-40%) are unaware of their swallowing issues, with less than 10% acknowledging dysphagia symptoms (5,21,22). In the advanced stages of PD, many patients experience severe dysphagia, which is often accompanied by weight loss, hypersalivation, and cognitive decline. Clinical indicators of dysphagia in PD include Hoehn and Yahr stages 4 and 5, body mass index below 20 kg/m2, and symptoms like hypersalivation, sialorrhea, and dementia. Weight loss and the presence of silent aspiration may cause dysphagia-related complications, such as aspiration pneumonia (23). Moreover, impaired cough reflexes among patients undergoing PD contribute to an increased risk of aspiration pneumonia (24). Therefore, it is crucial for patients to recognise and report symptoms indicating swallowing difficulties, including silent aspiration, especially in the early and mid-early stages of the disease to facilitate timely intervention and management by healthcare professionals.

Research indicates that dysphagia considerably affects the quality of life of individuals with PD (25). Using a questionnaire to assess the effect of dysphagia on quality of life has become a standard procedure. Integrating patient perception with traditional instrumental assessment is crucial for comprehensive swallowing evaluation. This approach can identify specific symptoms of swallowing difficulties that patients may struggle to identify, such as challenges in chewing and retention of certain food textures (26). Limited time during clinical or instrumental assessments may overlook these observations. Early detection of dysphagia using a dedicated questionnaire can decrease the risk of complications like aspiration, malnutrition, and pneumonia. Among dysphagia-specific questionnaires, the SWAL-QOL questionnaire developed by McHorney et al. is one of the most frequently preferred questionnaires (27). Because of its generic structure, SWAL-QOL is adaptable to a range of dysphagia reasons. It makes it possible to distinguish between patients who have dysphagia and those who do not, as well as to grade the condition according to a patient's tolerance for various food textures and liquid consistencies (26). By assessing self-reported symptoms and their influence on quality of life related to swallowing, the SWAL-QOL is a useful tool for assessing therapy effectiveness from the patient's perspective. Clinicians who address dysphagia in patients with PD can benefit from an understanding of how the condition affects swallowing-related quality of life (28).

Although dysphagia is prevalent among patients undergoing PD, recognition of swallowing difficulties is often lacking. Given that certain swallowing disorders in PD may not present symptoms and awareness of this issue is limited, both clinical and instrumental assessments along with dedicated questionnaires should be utilised in clinical settings (29). Factors influencing awareness levels regarding dysphagic symptoms in patients undergoing PD have not been fully elucidated. Potential causes of this condition include disruptions in airway somatosensory function. It has been suggested that disease severity may lead to impairments in swallowing and airway sensory function, preventing the basal ganglia and related nervous system structures from integrating sensory inputs for controlling swallowing-related motor functions (30).

In this study, subjective and objective evaluations of swallowing disorders in Parkinson's patients were made, and the level of disease and awareness levels were examined. This was a descriptive study to determine the effect of dysphagia on quality of life in patients undergoing PD. This study aimed to evaluate the effect of dysphagia due to Parkinson's disease on quality of life and to compare the self-reports of patients with the results of objective evaluation using video-fluoroscopy.

MATERIAL and METHODS

Subjects

This research involved 28 patients diagnosed with PD at Atlas University Medicine Hospital between June 1, 2023 and March 1, 2024. Among the participants, 15 (53.6%) were male and 13

(46.4%) were female, with a mean age of 68.6 years (range: 48–92, SD: 10.11). The inclusion criteria required patients to have: (i) no barium allergy; (ii) no tracheotomy or mechanical ventilation; (iii) no diaphragmatic pacer; (iv) no significant concurrent respiratory disease; and (v) no other neurological disorder. Disease staging was performed using the Hoehn–Yahr scale (31). Throughout the study period, all patients continued their anti-Parkinsonian medication. The study was approved by the Ethics Boards and Commissions of İstanbul Atlas University and was conducted in accordance with the Declaration of Helsinki (Date:22.05.2023, No: 27225). All patients met the specified inclusion criteria.

Assessment procedure

Eating status assessment

Following the VFSS examination, the patients' current food habits were categorised using the Functional Oral Intake Scale (FOIS). FOIS, which has a 7-point ordinal scale, is the most frequently used scale for evaluating functional oral intake in dysphagia patients (32). Levels 1 to 3 correspond to differing degrees of non-oral feeding, whereas levels 4 to 7 correspond to varying degrees of oral feeding without a feeding tube (33).

Swallowing function assessment

a. Clinical assessment

The clinical evaluation of the patients for dysphagia was determined by The Eating Assessment Tool 10 (EAT-10). The EAT-10 is a symptom-specific dysphagia outcome tool that is self-administered, validated, and validated in Turkey (34). The EAT-10 measures the severity of swallowing disorder, quality of life, and treatment effectiveness. The scale consists of 10 questions that are scored between 0 and 4 (0=no problem, 4=severe problem). A total score of 3 or above indicates a risk of swallowing disorder.

b. Instrumental assessment

Videofluoroscopic Swallowing Study (VFSS) was used to objectively analyse the swallowing process (35). The VFSS assessment was performed using a General Electric Precision RXi fluoroscopy device. Patients were positioned in the X-ray tube in a straight standing position with their head in a lateral position. The VFSS images were recorded at 30 frames per second. Patient positioning ensured the visibility of specific imaging boundaries, including the anterior lips, posterior pharyngeal wall, inferior cervical oesophagus, and superior nasopharynx.

Standardised VFSS protocols were followed, with each patient undergoing three swallowing trials for liquid and semisolid consistency. Liquid trials began with controlled volumes (3 x 5 ml teaspoons) followed by self-modulated sips in a free-volume setting. Semi-solid consistencies were administered in three portions, each consisting of a controlled single teaspoon with 5 ml per mouthful. Additionally, patients were instructed to take a single bite of solid bread. For statistical analysis, liquid consistencies adhered to IDDSI Level 0; semi-solid consistencies adhered to IDDSI Level 4; and solid consistencies adhered to IDDSI Level 7 per the International Dysphagia Diet Standardisation Initiative.

Recorded VFSS image was assessed by a Speech-Language Pathologist (SLP) blinded to clinical assessments and patient details using the Functional Oral Intake Scale (FOIS) and Penetration Aspiration Scale (PAS). The PAS assesses the degree of penetration and aspiration and whether the substance entering the airway has been removed using an 8-point clinical scale. A score of 8 represents the worst airway protection (36). The validity and reliability of the PAS scale in the Turkish population was assessed by Karaduman et al. (37).

c. Quality of life assessment

The SWAL-QOL was developed to measure patient-reported dysphagia-specific parameters. SWAL-QOL is composed of 44 questions that evaluate 11 sub-domains of QOL, including general burden, eating duration, eating desire, frequency of symptoms, food selection, communication, fear, mental health, social functioning, sleep, and fatigue (27). A 5-point Likert scale was used to provide scores for each parameter. Higher scores on any subscale, ranging from 0 to 100, suggest better quality of life in terms of dysphagia (38). Each domain can have a score ranging from 0 (worst) to 100 (highest). Research on the Turkish population has demonstrated the validity and reliability of SWAL-QOL (38). The questionnaire was given out in an examination room, and each participant took 20 minutes on average. The investigator read aloud the questionnaire items and answer options to each patient to guarantee accurate replies and reduce the possibility of misinterpretations resulting from poor education levels or visual impairments. The objective of this methodology was to enhance comprehension of the survey and minimise the probability of deceptive answers. By administering questionnaires in the same manner to each participant, consistency was preserved, and biases in the data collection process were avoided.

Statistical analysis

All analyses were conducted using the SPSS programme (version 26.0 for Windows; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to present patient demographic information and clinical characteristics. All demographic data were analysed and presented as numbers (N) or percentages (%). The analysis's main goal was to determine the relationship between disease stage, disease duration, swallowing function, and quality of life of patients undergoing PD. To assess the distribution of scores across all scales, the Shapiro-Wilk test was utilised. Because the scores were not normally distributed, Spearman's correlation analysis was used for relationship analysis. Correlation coefficients were interpreted as follows: 0.0 to 0.3 indicated low correlation, 0.3 to 0.5 indicated low to moderate correlation, 0.5 to 0.7 indicated moderate correlation, 0.7 to 0.9 indicated high correlation, and 0.9 to 1.0 indicated excellent correlation (49). For comparisons between groups, the Mann–Whitney U test was applied. The fact that the $p<0.05$ being accepted as statistically significant.

RESULTS

Participants

The study included 28 participants. Participants were categorised into two groups according to their EAT-10 scores: those with and without dysphagia. Sixteen (57.2%) patients had dysphagia, whereas 12 (42.8%) did not. The mean age of patients in the dysphagic group was 69.25±10.38 years with a disease duration of 6.87±4.84 years, and the mean age of patients in the non-dysphagic group was 67.75±10.13 years with a disease duration of 3.45±2.6 years. Among the patients with dysphagia, 5 (31.3%) were in the early stage, 5 (31.3%) in the intermediate stage, and 6 (37.5%) in the advanced stage. In the non-dysphagic group, 8 (66.7%) patients were in the early stage and 4 (33.3%) were in the intermediate stage. No patient in this group was in the advanced stage. There were no statistically significant differences between the two groups in terms of gender, education level, H&Y stage, MMSE score, or disease duration. The demographic and clinical characteristics of the participants are presented in Table 1.

The study involved an analysis of disease duration, disease stage, swallowing-related quality of life, and swallowing scores in patients diagnosed with Parkinson's disease. The findings (Table 2) revealed a noteworthy moderate negative correlation between disease duration and swallowing-related quality of life in all patients with Parkinson's disease. It was observed that swallowing-related quality of life decreased with an increase in the duration of the disease (r=-0.504; p=0.006). Additionally, a negative correlation between disease stage and swallowing-related quality of life was identified, although this relationship did not reach statistical significance (r=-0.342; p=0.75). Moreover, a significant correlation was noted between disease duration, disease stage, and swallowing impairment in all patients with Parkinson's disease. The EAT-10 scores of the patients increased with both the duration and stage of the disease (r=0.556; p=0.001, r=0.533; p=0.004). Furthermore, the results obtained through videofluoroscopy indicated a positive association between disease duration and disease stage, and the patients' scores on the PAS scale (r=0.720; p=0.000, r=0.564; p=0.002), along with a negative correlation with the FOIS scores (r=-0.699; p=0.000, r=-0.508; p=0.006) as both disease duration and disease stage increased (Table 2).

Swallowing-specific quality of life was compared among three groups: general, dysphagic, and nondysphagic. The SWAL-QOL data are presented in Table 3.

Overall, the swallowing-specific quality of life was significantly impacted. The mean SWAL-QOL domain scores ranged from 57.4 to 100. The findings revealed that swallowing dysfunction had a negative impact on patient-reported quality of life. There was a significant difference in the total SWAL-QOL score between the non-dysphagic group (94.58±4.44) and the dysphagic group (84.14±13.41) (p=0.029). All SWAL-QOL domains had lower scores in the dysphagic group. Significant differences were found between the dysphagic and non-dysphagic groups in the sub-domains of general complaints, food desire, eating duration, frequency of symptoms, food choice, and mental health (Table 3).

The scores for swallowing disorders obtained through clinical and instrumental assessments were analysed for general,

Table 1: Comparison of demographic and clinical characteristics between PD patients with and without dysphagia.

	Overall (n=28) x̄ ±SD	Dysphagic (n=16) x̄ ±SD	Non-Dysphagic (n=12) x̄ ±SD	p
Age	68.6±10.11	69.25±10.38	67.75±10.13	0.871
Gender (F/M)	13 (46.4%) / 15 (53.6%)	7 (43.8%) / 9 (56.3%)	8 (55.6%) of 4 (44.4%)	0.237
Disease duration (years)	5.41±4.44	6.87±4.84	3.45±2.6	
⩽ 1	2/ (7.1%)	1/ (6.3%)	1/ (%8.3)	0.081
2–4	15/ (53.6%)	6/ (37.5%)	9/ (75%)	
⩾ 5	11/ (39.3%)	9/ (56.4%)	2/ (16.6%)	
Education				
Primary school	23/ (82.1%)	12/ (75%)	11/ (91.7%)	0.227
High school	3/ (10.7%)	2/ (12.5%)	1/ (8.3%)	
University	2/ (7.1%)	2/ (12.5%)	0	
Hoehn-Yahr stage	1.21±0.56	2.06±0.85	1.33±0.49	
H-Y Mild (1-2)	13/ (46.4%)	5/ (31.3%)	8/ (66.7%)	0.067
H-Y Moderate (2.5-3)	9/ (32.1%)	5/ (31.3%)	4/ (33.3%)	
H-Y Advanced (4-5)	6/ (21.4%)	6/ (37.5%)	0	
MMSE	21.76±6.95	20.62±7.5	23.3±6.09	0.294

MMSE: Mini-Mental State Examination, x̄: Mean, SD: Standard Deviation.

Table 2: Relationship between Swallowing Impairment and SWAL QOL according to Disease Duration and H-Y Stage in Patients undergoing PD

		EAT-10	PAS (IDDSI-0)	FOIS	Total SWAL-QOL
H&Y Stage	r	.533	.564	-.508	-0.342
	p	**0.004****	**0.002****	**0.006****	0.075
Disease Duration	r	.596	.720	-.699	-.504
	p	**0.001****	**0.000****	**0.000****	**0.006****

H&Y: Hoehn and Yahr, EAT-10: Eating Assessment Tool, PAS: Penetration Aspiration Scale, IDDSI: International Dysphagia Diet Standardisation Initiative, FOIS: Functional Oral Intake Scale, SWAL-QOL: Swallowing Quality of Life Questionnaire. *p<0.05, **p<0.01 is considered statistically significant.

Table 3: Comparison of SWAL-QOL Scores between PD patients with and without dysphagia.

	Overall				Dysphagic				Non-Dysphagic				
SWAL-QOL	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**p**
Burden	62.50	100.00	93.30	12.95	62.50	100.00	88.28	15.46	100.00	100.00	100.00	0.00	**0.010****
Eating duration	50.00	100.00	92.98	12.28	50.00	100.00	88.77	14.82	91.60	100.00	98.60	3.27	**0.012***
Eating desire	62.50	100.00	92.65	10.36	62.50	100.00	88.70	11.70	87.50	100.00	97.92	4.87	**0.015***
Symptom freq	59.60	100.00	89.26	12.21	65.30	100.00	86.49	11.27	59.60	100.00	92.96	12.92	**0.027***
Food selection	0.00	100.00	90.63	20.87	0.00	100.00	83.59	25.71	100.00	100.00	100.00	0.00	**0.005****
Communication	0.00	100.00	87.50	23.57	0.00	100.00	83.59	28.77	62.50	100.00	92.71	13.55	0.449
Fear	25.00	100.00	92.18	15.93	25.00	100.00	88.66	19.93	81.25	100.00	96.87	6.25	0.178
Mental health	40.00	100.00	94.46	15.30	40.00	100.00	90.31	19.45	100.00	100.00	100.00	0.00	**0.020***
Social	35.00	100.00	95.71	14.12	35.00	100.00	92.81	18.35	95.00	100.00	99.58	1.44	0.237
Fatigue	25.00	100.00	72.89	22.06	25.00	100.00	67.16	23.85	58.30	100.00	80.53	17.54	0.181
Sleep	0.00	100.00	73.21	25.39	0.00	100.00	67.19	27.34	50.00	100.00	81.25	20.98	0.164
Total	57.40	100.00	84.14	13.41	57.40	96.90	84.14	13.41	87.90	100.00	94.58	4.44	**0.026***

Min: Minimum, Max: Maximum, SD: Standard Deviation, *p<0.05, **p<0.01 is considered statistically significant.

dysphagic, and non-dysphagic groups, and the results are shown in Table 4. The data from the groups indicated a statistically significant difference between the dysphagic and non-dysphagic groups in terms of patient-reported swallowing disorders and the results obtained from instrumental assessments (Table 4).

The scores for swallowing disorders obtained from clinical and instrumental evaluations, and the swallowing-related quality of life scores of patients with Parkinson's disease, were analysed. The results are presented in Table 5.

In the conducted study, a statistically significant, negative, and moderate correlation was found between the EAT-10 and PAS IDDSI 0 scores, as well as the SWAL-QOL scores of all participants (r=-0.685; p=0.000, r=-0.579; p=0.001). These results suggest that as the EAT-10 and PAS IDDSI 0 scores of the participants decreased, their SWAL-QOL scores increased. Additionally, a statistically significant, positive, moderate correlation was established between the FOIS and SWAL-QOL total scores of the participants (r=0.546; p=0.03), indicating that as the FOIS total scores increased, the SWAL-QOL scores also increased.

Table 4: Comparison of Swallowing Impairment Scores between PD patients with and without dysphagia.

	Overall				Dysphagic				Non-Dysphagic				
	Min	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**p**
EAT-10	0.00	18.00	4.60	4.90	2.00	18.00	7.18	5.10	0.00	2.00	1.16	0.93	**0.000***
PAS-IDDSI 0	1.00	8.00	2.25	2.04	1.00	8.00	3.00	2.42	1.00	3.00	1.25	0.62	**0.020***
FOIS	5.00	7.00	6.03	0.83	5.00	7.00	5.68	0.79	5.00	7.00	6.50	0.67	**0.011***

Min: Minimum, Max: Maximum, SD: Standard Deviation, *p<0.05, **p<0.01 is considered statistically significant.

Table 5: Relationship between Swallowing Disorders and SWAL QOL among patients undergoing PD.

		EAT-10	PAS IDDSI 0	FOIS
Total SWAL-QOL	r	-.685	-.579	.546
	p	**0.000****	**0.001****	**0,003****

*p<0.05, **p<0.01 is considered statistically significant.

Table 6: Comparison between self-reported swallowing and videofluoroscopic studies

	Negative	Positive	Total	χ^2	p
Self-Reported	12 (42.9%)	16 (57.1%)	28 (100%)	6.082	0.298
VFSS	19 (67.9%)	9 (32.1%)	28 (100%)		

*p<0.05, **p<0.01 is considered statistically significant.

Furthermore, a comparison was made between Parkinson's self-reports's patients regarding swallowing disorders obtained using the EAT-10 and the results of objective evaluation using videofluoroscopy. The analysis revealed no statistically significant difference between self-reports and VFSS results (p=0.298). The results are presented in Table 6.

DISCUSSION

The aim of this study was to evaluate the effect of dysphagia due to Parkinson's disease on quality of life and to compare the self-reports of patients with the results of objective assessments using video-fluoroscopy. According to the results of our study, as the duration and severity of the disease increase, swallowing disorders among patients increase, and their quality of life is affected more accordingly. In addition, when the results of the evaluation via video-fluoroscopy were examined, it was observed that the aspiration risks of patients increased with increasing disease duration and severity, negatively affecting their oral food intake processes. These results are generally consistent with the literature.

Based on their EAT-10 scores, the participants were classified into two groups: dysphagic and non-dysphagic. Dividing the subjects into groups according to whether they had dysphagia or not, the different effects of dysphagia on swallowing-related quality of life domains became more obvious. As a result of our study, statistically significant differences were found between the dysphagic and non-dysphagic groups in the sub-domains of general burden, eating desire, eating duration, symptom frequency, food choice, and mental health. The most affected areas were general burden, fatigue, eating time, and sleep, according to the literature on quality of life in individuals with dysphagia caused by PD (39-41). The general burden and eating time sub-domain were also affected in our study.

According to research examining the psychological and social effects of dysphagia, around one-third of patients avoided eating with others, resulting in the loss of socialisation-related function (42). In their study of individuals with dysphagic and non-dysphagic Parkinson's disease, Ploughman-Prine et al. found that the dysphagic group had lower SWAL-QOL scores in all areas; however, the differences were statistically significant only for the subdomains of mental health, social functioning, and general complaints (43). This implies that dysphagia has an adverse effect on the swallowing quality of life of patients undergoing PD, but only in specific domains.

In our study, a significant difference was found between the dysphagic and non-dysphagic groups in the sub-domains of eating time and eating desire. Prolonged eating time is a common and significant complaint in patients with PD. Consistent with this finding, Coriolano et al. reported that patients with PD required more time than age-matched normal controls to consume a given volume of water. It has been stated that the general bradykinesia seen in PD may be a possible reason for this (44).

The SWAL-QOL, which was originally designed to assess quality of life, has been utilised in some studies to evaluate swallowing function. To identify individuals with swallowing dysfunction, Rinkel et al. (45) proposed a clinical cut-off score of 14 from a total score of 100 on the SWAL-QOL. In this study, only 6 (21.4%) patients with Parkinson's disease exhibited a total score 86, indicating clinically significant dysphagia. Based on the results of this study, the SWAL-QOL score may not be an adequate screening tool for identifying patients with Parkinson's disease who require further evaluation of swallowing according to this cut-off score.

Discrepancies may arise between subjective patient reports and instrumental evaluations in individuals with dysphagic complaints. A previous study noted that PD participants tended to downplay swallowing difficulties in subjective questioning (20). Some elderly patients with Parkinson's disease might overlook that dysphagic symptoms could stem from impaired cognitive function, leading to underreporting or lack of awareness in subjective assessments like the SWAL-QOL. This emphasises the value of using instrumental assessments, such as the VFSS and FEES, and proactive education for patients undergoing PD. Alongside patient-rated questionnaires, clinician-rated measures are recommended to accurately define dysphagia in patients undergoing PD (46). Employing both objective and subjective assessments provides a comprehensive understanding of the issue (2).

In this study, in addition to the patients' self-reports regarding swallowing and swallowing-related QOL, instrumental evaluations using the VFSS were conducted, and the relationship between these two conditions was compared. The VFSS is accepted as the gold standard for the evaluation of dysphagia (47). The VFSS can be used to measure the degree of dysphagia, evaluate the effectiveness of treatment, and assess swallowing function. Penetration or aspiration is one possible dysphagia problem. In particular, when diagnosing

occult aspiration, VFSS can precisely identify both the aetiology and existence of aspiration. 9 (32.1%) patients in our study were diagnosed with dysphagia based on VFSS penetration/aspiration findings, despite not having overt symptoms. Kalf et al. reported large differences in the prevalence of dysphagia between subjectively reported and objectively confirmed cases in their meta-analysis published in 2012 (20). The results of our study are consistent with those of this previous study.

Although dysphagia is observed in most patients with Parkinson's disease, it has been demonstrated that these patients have low awareness of swallowing difficulties (29). Factors affecting the level of awareness of dysphagic findings in patients with Parkinson's disease have not yet been sufficiently elucidated. Possible causes include impairment of laryngeal structure and somatosensory function of the airway. It has been suggested that the structures involved in the oral and pharyngeal swallowing processes and the somatosensory function of the airway may be impaired because of disease severity. Therefore, the basal ganglia and related nervous system structures cannot integrate sensory inputs for swallowing-related motor control (30).

Our study has several limitations. Primarily, patients with PD in our sample were predominantly in the early stages of the disease and exhibited mild dysphagia symptoms. The limited representation of patients with advanced-stage PD might have restricted the comprehensiveness of our findings regarding severe dysphagia symptoms and advanced PD stages. Furthermore, only some patients with PD were included in our study. These limitations should be considered in future research.

CONCLUSION

This study revealed a significant negative correlation between dysphagia symptom severity and swallowing-related quality of life. Increasing disease duration and severity increases the severity of swallowing disorders, and quality of life is negatively affected. Another finding of the study was that inconsistency was observed between the results obtained from scales including self-assessment of swallowing disorders and objective assessment methods. These results emphasise the need for clinicians to use objective measurements and patient-reported questionnaires when evaluating dysphagia in patients with Parkinson's disease.

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Characteristics of Primary Hyperparathyroidism in Multiple Endocrine Neoplasia Type 2A

Hülya Hacişahinoğulları[1], Onour Chasan[1], Gamze Bilik Oyman[1], Ümmü Mutlu[1], İsmail Cem Sormaz[2], Gülşah Yenidünya Yalın[1], Nurdan Gül[1], Ayşe Kubat Üzüm[1], Yasemin Giles Şenyürek[2], Özlem Soyluk Selçukbiricik[1]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, İstanbul, Türkiye
[2]İstanbul University, İstanbul Faculty of Medicine, Department of General Surgery, İstanbul, Türkiye

ORCID ID: H.H. 0000-0001-9989-6473; O.C. 0000-0001-5755-3704; G.B.O. 0000-0001-8636-8700; Ü.M. 0000-0002-5259-7326; İ.C.S. 0000-0001-6907-978X; G.Y.Y. 0000-0002-9013-5237; N.G. 0000-0002-1187-944X; A.K.Ü. 0000-0003-0478-1193; Y.G.Ş. 0000-0001-5339-1840; Ö.S.S. 0000-0003-0732-4764

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ABSTRACT

Objective: Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal dominantly inherited tumour syndrome and primary hyperparathyroidism (pHPT) is one of the major components of MEN2A. Our study evaluated the features of MEN2A-related hyperparathyroidism
Material and Methods: Records of 49 patients with MEN2A followed up at Istanbul Faculty of Medicine were retrospectively reviewed.
Results: This study included 25 females and 24 males, and 55% of the patients had *RET* 634 variants. The median follow-up duration was 12 years. Medullary thyroid cancer (MTC) was present in 44 patients, and the mean age at diagnosis was 30.8±14 years. Pheochromocytoma was detected in 61% of patients, and the mean age at diagnosis was 36.4±12.6 years. Twelve patients (F/M=1) had pHPT, and the mean age at diagnosis was 40±15.7 years. The frequency of pHPT was 6% in the ATA moderate-risk category and 33.3% in the high-risk category (*RET* 634 variants). pHPT developed in 3 of 4 patients carrying the *RET* C634R variant. The most common symptoms were nephrolithiasis and osteoporosis, and 67% of patients had normocalcemic pHPT. Selective surgery was performed in 9 patients and subtotal parathyroidectomy in 1 patient. The median follow-up duration after the diagnosis of pHPT was 10.5 years, and persistent disease developed in 1 patient. Recurrent hyperparathyroidism occurred in 1 patient 12 years after the first operation. Five patients developed permanent hypoparathyroidism.
Conclusion: *The RET* mutation at codon 634 is associated with a high frequency of pHPT, usually accompanied by normocalcemia or, less frequently, mild hypercalcemia.
Keywords: Multiple Endocrine Neoplasia type Type 2A, MEN2A, Primary Hyperparathyroidism

INTRODUCTION

Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal dominantly inherited cancer syndrome caused by a pathogenic germline variant in the Rearranged During Transfection (*RET*) proto-oncogene. *The RET* gene encodes a receptor-type tyrosine kinase and plays a role in cell growth, proliferation, and differentiation. Gain-of-function mutations in the *RET* proto-oncogene cause multiple tumours in tissues where *RET* is predominantly expressed, such as C cells of the thyroid gland, adrenal medulla, and enteric autonomic plexus (1). The prevalence of MEN 2A was reported as 13–24 per million (2, 3).

Classical MEN2A is characterised by medullary thyroid carcinoma (MTC), pheochromocytoma, and primary hyperparathyroidism (pHPT). The penetrance of MTC is approximately 100%. The age of development of MTC depends on the specific *RET* mutation (4). Overall, the penetrance of pheochromocytoma is 32%, and its frequency varies between 10% and 50% according to the *RET* mutation. In patients with the *RET* mutations at codon C634, the penetrance is about 50%. MEN2A-related pheochromocytoma usually occurs earlier than sporadic forms; the incidence rate is highest in the 3rd-4th decade (5, 6). The penetrance of pHPT is lower in MEN 2A

Corresponding Author: Hülya Hacışahinoğulları **E-mail:** mercandogru@hotmail.com
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compared with MEN type 1 (MEN1). The prevalence of pHPT varies between 0-35% depending on the *RET* genotype. pHPT typically presents in the fourth decade of life (range, 12 to 70 years) and is asymptomatic in 42% to 84 % of patients (7, 8). The phenotypic expression of pPHT most often occurs in patients with the *RET* mutation at codon 634. pHPT can rarely be the first manifestation of MEN2A (4, 9).

The American Thyroid Association (ATA) guidelines recommend the screening for pHPT in patients with RET mutation to begin by the age of 11 years for patients in the ATA high-risk category and by the age of 16 years for patients in the ATA moderate-risk category (4). Screening for pHPT includes the measurement of albumin-corrected serum calcium or ionised calcium and intact parathyroid hormone (PTH). Multiglandular disease is less frequent in MEN2A than in MEN1. Imaging modalities to localise enlarged parathyroid glands include neck ultrasonography (USG), technetium Tc 99m sestamibi scintigraphy, ^{18}F-fluorocholine positron emission tomography/computed tomography (PET/CT), and 4-dimensional computed tomography (4D-CT) (10).

The criteria for surgical treatment are the same as those for the sporadic form of pHPT. Surgery options for patients with no history of previous neck surgery are as follows: resection of enlarged glands with intraoperative PTH monitoring, subtotal parathyroidectomy (removal of 3+1⁄2 glands), and total parathyroidectomy with heterotopic autotransplantation. The optimal surgical procedure for managing pHPT remains controversial. However, the guidelines recommend subtotal or total parathyroidectomy with autotransplantation if all glands are enlarged. If there is a history of previous neck surgery (for pPHT or MTC), imaging studies should be performed for localisation in patients who are considered for reoperation (4).

Due to the low penetrance of pHPT in MEN2A syndrome, studies examining the characteristics of pHPT are limited. We evaluated the frequency, clinical and laboratory features, treatment modalities, and long-term follow-up outcomes in patients with MEN2A-associated pHPT.

MATERIAL AND METHODS

This retrospective study included patients who were diagnosed with MEN2A and followed up in the Endocrinology and Metabolic Diseases Clinic of Istanbul Faculty of Medicine between 1992 and 2024. Demographic and clinical characteristics, laboratory results, radiological imaging methods, treatment modalities, surgical procedures, and long-term outcomes were reviewed. The data of the subgroup diagnosed with pHPT were evaluated in detail.

The development of hypercalcemia within 6 months after the operation for pHPT was defined as a persistent disease, and the occurrence of hypercalcemia following a normocalcemic interval after 6 months postoperatively was considered as a recurrent disease. The cure was deemed as normalisation of calcium homeostasis for at least six months after surgery.

The study protocol was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Date: 26.07.2024- No: 14). Informed consent was not obtained due to the retrospective design of the study.

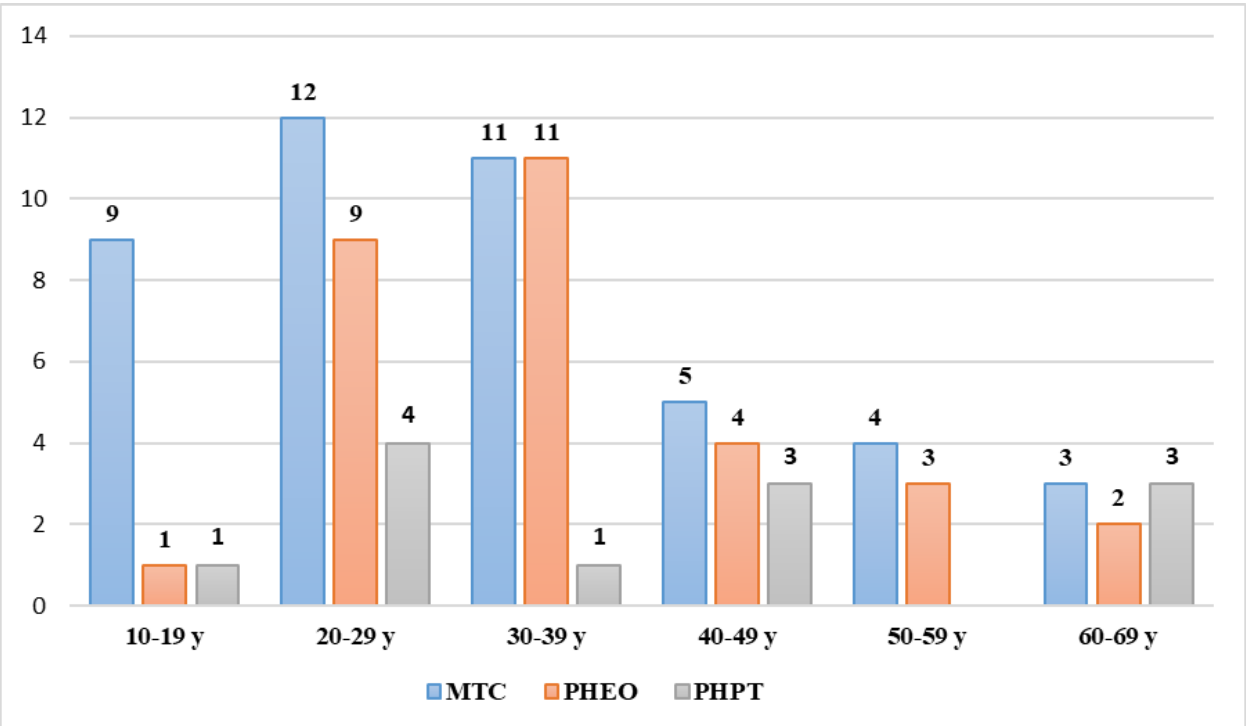

Figure 1: Age-adjusted distributions of the diseases
MTC: Medullary thyroid cancer, PHEO: Pheochromocytoma, PHPT: Primary hyperparathyroidism

Statistical analysis

Statistical analyses were performed using the SPSS software (version 21.0). Categorical variables were presented as the frequency and percentage of occurrence, whereas numerical variables were displayed as the median, mean, and standard deviation (SD).

RESULTS

A total of 49 patients with MEN2A were included in the study, and 25 were female (51%) and 24 were male (49%). The mean age of the patients was 44.8 ± 15 years. The median duration of follow-up was 12 years (range 2 to 36). In 43 of the 49 patients, genetic analysis results were available. The distribution of *RET* variants was as follows: C618A (5/43, 11.5 %), C618R (2/43, 5%), C618S (2/43, 5%), C634A (7/43, 16%), C634G (1/43, 2%), C634R (4/43, 9%), C634S (8/43, 18.5%), C634T (4/43, 9%), C634Y (3/43, 7%), L790F (5/43, 12%), and V804M (2/43, 5%).

All patients underwent total thyroidectomy. Central lymph node dissection was performed in 61% (n=30), and lateral lymph node dissection was performed in 36.7% (n=18) of the patients. Pathological examination was compatible with only C-cell hyperplasia in 5 of the 49 patients and medullary thyroid cancer in the remaining 44 patients. The mean age at diagnosis of MTC was 30.8±14 years (range, 12 to 61) (Figure 1). Sixteen patients underwent multiple surgeries (2 operations in 10 patients, 3 operations in 5 patients, and 4 operations in 1 patient) and 1 patient underwent radiotherapy. Remission was not achieved in 21 patients. Pheochromocytoma was detected in 30 patients (61%). The mean age at diagnosis of pheochromocytoma was 36.4±12.6 years (Figure 1). Bilateral pheochromocytoma was present in 15 patients (50%) at diagnosis. In 3 of 15 patients who underwent unilateral adrenalectomy, pheochromocytoma developed in the other adrenal gland between 7 and 16 years after the first surgery. Recurrence occurred in 4 patients between 5 and 17 years after the first surgery. In 12 patients (11 MTC, 1 patient with C cell hyperplasia), pheochromocytoma was detected before the thyroid operation, and the pheochromocytoma operation was performed primarily followed by the thyroidectomy. In the remaining patients, the interval between the thyroidectomy operation and the diagnosis of pheochromocytoma ranged from 1 to 23 years.

Of the 49 patients, 12 had developed pHPT. The mean age at diagnosis of pHPT was 40±15.7 years (range, 19 to 61) (Figure 1). Seven patients were symptomatic, and the most common symptoms were nephrolithiasis (n=4) and osteoporosis (n=4). Case 12 developed nephrocalcinosis and chronic kidney disease. In 11 patients, the laboratory results at the time of diagnosis were available. The mean albumin-corrected serum calcium level was 10.2±1 mg/dL (normal range 8.5-10.5) and the mean PTH level was 78 pg/ml (normal range 15-65).

USG was performed for preoperative localisation in 10 patients and Tc 99 m sestamibi scintigraphy was performed in 6 of them. Parathyroid lesions were localised in 7 patients. Details are summarised in Table 1. Ten patients underwent parathyroidectomy. One patient did not accept surgical treatment, and parenteral bisphosphonate therapy was applied for osteoporosis. Selective surgery was performed in 9 patients and subtotal parathyroidectomy in 1 patient. The number of excised glands was 1 in 7 patients, 2 in 2 patients and 3+1/2 in 1 patient.

The median follow-up time from pHPT diagnosis to the last follow-up visit was 10.5 years (range 1 to 24). Case 7 developed persistent disease after parathyroidectomy. He has been followed up for 24 years and has not developed an indication for parathyroidectomy. Case 5 developed recurrent hyperparathyroidism 12 years after the first operation. Five patients developed permanent hypoparathyroidism after surgery. Among all patients, permanent hypoparathyroidism developed in 8 patients (8/49), 5 of whom had previous pHPT. In addition, 3 patients without a diagnosis of pHPT developed permanent hypoparathyroidism after thyroidectomy due to MTC.

DISCUSSION

In this study, we retrospectively evaluated 49 patients diagnosed with MEN2A. In particular, we reviewed the clinical and laboratory characteristics, treatment modalities, and long-term outcomes of patients with primary hyperparathyroidism.

In a study conducted in Denmark, it was reported that the female/male ratio was 0.89 and the most common *RET* variant was C611Y (68%) in their study population (3). In our study, the female-to-male ratio was 1.04 and 63% (27/43) of the patients carried the *RET* 634 variant. The ATA guideline categorises the *RET* mutation according to the risk of aggressive MTC. Pathogenic variants at codon 634 are in the high-risk category. While 63% of our patients were in the high-risk category, the remaining 37% were in the moderate-risk category. ATA guidelines recommend thyroidectomy at or before the age of 5 years in children who belong to the ATA high-risk category (4). Kelebwe et al. showed that disease stage and age at diagnosis are independent prognostic factors for medullary thyroid cancer (11). Most of our patients were diagnosed in the 3rd-4th decade and this may be related to the decreased cure rate.

MEN 2A-associated pheochromocytoma usually occurs in the 3rd-4th decade of life. Siqueira et al. reported that the frequency of pheochromocytoma in MEN 2 patients was 31.4% and the mean age at diagnosis was 35.5±13.4 years (12). Similarly, the mean age at diagnosis of pheochromocytoma was 36.4±12.6 years in our study; however, pheochromocytoma was detected more frequently (67%). In the same study, Siqueira et al. also stated that 92.8% of patients with pheochromocytoma had *a RET* mutation at codon 634. In our study, among 30 patients with pheochromocytoma, there were 26 patients for whom genetic results were available. Of these 26 patients, 19 had *a RET* mutation at codon 634 (73%) and the remaining 7 (27%) had *a RET* mutation at codon 618.

Table 1: Characteristics of Patients with PHPT

Patient No	Gender	Age at diagnosis of pHPT (years)	RET Variant	Symptoms	Plasma PTH Levels	Plasma Ca Level*	Neck USG	Treatment Methods	No. of Removed Glands	Age at diagnosis of MTC (years)	Surgical procedures for MTC	Follow up Status
Case 1	M	29	C634R	Osteoporosis	67	9	Right inferior	Medical**		-	TT	
Case 2	F	49	C634R	Osteopenia	225	10.7	Right inferior	Surgery	3+1/2	49	TT+ CLND	HPT
Case 3	F	60	C634S	Osteoporosis	142	10.4	Negative	Surgery	1	60	TT+CLD+LND	Cure
Case 4	M	49	C634Y	-	712	11.7	Right inferior	Surgery	1	50	TT+CLD+LND	Cure
Case 5	F	19	C634Y	-	249	9.5	Negative	Surgery	2 ***	19	TT+ CLND	Recurrence
Case 6	F	24	C634T	-	185	10	Right inferior	Surgery	1	24	TT+CLD+LND	Cure
Case 7	M	26	NA	Nephrolithiasis	NA	NA		Surgery	1	26	TT+ CLND	Persistence
Case 8	F	60	NA	-	87	9.1	Negative	Follow up		32	TT	
Case 9	F	27	C634T	-	74	9	Right	Surgery	2****	28	TT+CLD+LND	HPT
Case 10	M	30	C634R	Nephrolithiasis	106	10.2	-	Surgery	1	30	TT+ CLND	HPT
Case 11	M	61	C618S	Nephrolithiasis Osteoporosis	115	10.4	Negative	Surgery	1	61	TT+CLD+LND	HPT
Case 12	M	45	C634A	Nephrolithiasis Osteoporosis	1172	12.2	Left inferior	Surgery	1	45	TT+ CLND	HPT

*Plasma albumin-corrected Ca Level **Patient was treated with intravenous zoledronic acid *** Right and left inferior ****Right superior and inferior
NA: Not available, PTH: Parathyroid Hormone, PHPT: Primary Hyperparathyroidism, Ca: Calcium, HPT: Hypoparathyroidism, TT: Total Thyroidectomy, TT + CLND: Total thyroidectomy combined with central lymph node dissection, TT + CLD + LND: Total thyroidectomy combined with central lymph node dissection and lateral neck dissection, albumin-corrected serum calcium level normal range: 8.5-10.5mg/dL, PTH normal range:15-65 pg/mL

MEN2A-related hyperparathyroidism is usually asymptomatic. In the study of Holm et al., it was reported that the median age at the time of diagnosis of pHPT was 45 years, 75% of patients were asymptomatic, and the most common symptoms were osteoporosis and polydipsia (13). Unlike this study, 58% (7/12) of the patients were symptomatic and the most common symptoms were nephrolithiasis and osteoporosis in our study, and the median age at diagnosis of pHPT was 37.4 years. In the study by Raue et al. it was shown that serum calcium was slightly elevated in 69% of the patients with pHPT and normal in 16% (8). In our study, among the 12 patients, 67% (8/12) had normocalcemic primary hyperparathyroidism, 17% (2/12) had mild hypercalcemia, and only one patient (1/12) had moderate hypercalcemia. Rau et al. also reported that pHPT and medullary thyroid carcinoma were diagnosed synchronously in 75% of patients (8). Similarly, in our study, pHPT was found concomitantly with MTC in 83% of patients. Pheochromocytoma was also present in 10 (83%) patients with pHPT. *RET* mutation at codon 634 was present in 9 of these 10 patients in our study.

The RET mutation at codon 634 is reported to be associated with the presence of pheochromocytoma and hyperparathyroidism (14). Mulligan et al. showed that patients with *the RET* C634R variant had a higher risk of developing parathyroid disease than the other 634 variants (15). On the other hand, it was reported that pHPT developed in 32% of patients carrying *the RET* C634R variant in German families, which was not as high as previously reported (16). In our study, pHPT developed in 3 of 4 patients carrying *the RET* C634R variant. In the study of Holm et al, it was found that the frequency of pHPT was 5% in the ATA moderate-risk category and 50% in the high-risk category (13). In our study, the frequency of pHPT was 6% in the ATA moderate-risk category and 33.3% in the high-risk category.

In the study by Herfarth et al, the first surgical procedure performed was selective resection in 62% of patients, subtotal resection in 24%, and total parathyroidectomy with autotransplantation in 14%. They found that 8.6% of patients developed persistent hyperparathyroidism and 14.3% developed recurrent hyperparathyroidism (17). In our study, 10 patients were operated for pHPT, and selective surgery was performed in 9 of these patients. One of the 10 patients developed recurrent disease and one patient developed persistent disease. In the study of Holm et al, it was stated that subtotal parathyroidectomy was performed in 69% of patients

(n=9) and selective surgery in 23% (n=3), and permanent hypoparathyroidism occurred in 46% of patients (n= 6) (13). In our study, permanent hypoparathyroidism occurred in 50% (5/10) of the patients.

CONCLUSION

Consistent with previous studies, in our study, *the RET* mutation at codon 634 was associated with an increased frequency of pHPT, especially in the C634R variant. In contrast, the frequency of pHPT was lower in the ATA moderate-risk category. Calcium levels are mildly elevated and may be associated with uniglandular or multiglandular disease.

Ethics Committee Approval: This study was approved by the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (Date: 26.07.2024- No: 14).

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- H.H., O.C., G.B.O., U.M., İ.C.S., G.Y.Y., N.G., A.K.Ü., Y.G.Ş., Ö.S.S.; Data Acquisition- H.H., O.C., G.B.O., U.M., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Data Analysis/Interpretation- H.H., O.C., G.B.O., U.M., Ö.S.S.; Drafting Manuscript- H.H., O.C., G.B.O., U.M., İ.C.S., G.Y.Y., N.G., A.K.Ü., Y.G.Ş., Ö.S.S.; Critical Revision of Manuscript- H.H., O.C., G.B.O., U.M., Ö.S.S.; Final Approval and Accountability- H.H., O.C., G.B.O., U.M., İ.C.S., G.Y.Y., N.G., A.K.Ü., Y.G.Ş., Ö.S.S.

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

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Editor: İsmet Aslan
Address: Istanbul University, Istanbul Faculty of
Medicine Deanery, Turgut Özal Cad. 34093, Çapa,
Fatih, Istanbul, Turkiye
Phone: +90 212 414 21 61
E-mail: tr-ent@istanbul.edu.tr

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Address: İstanbul Üniversitesi Merkez Kampüsü,
34452 Beyazıt, Fatih / Istanbul, Turkiye
Phone: +90 212 440 00 00