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Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Contents

Original Investigations

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Evaluation of School-age Hearing Screening Applications: The Tele-audiological Perspective

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ABSTRACT

Objective: Hearing health is one of the areas that should be considered especially in childhood. School-age hearing screening (SAHS) is important for the detection and prevention of hearing loss. The aim of our study is to compare the use of teleaudiological applications for SAHS with standard SAHS applications and to determine possible similarities or differences between the methods.

Methods: The study was carried out with a total of 224 students who were first-year students in the same primary school within the borders of Istanbul. The study was completed in two phases with a test session at 15-day intervals. In the first stage, video-otoscope images of all individuals who would be subjected to standard SAHS were recorded and tympanometry test was performed. In the second stage, SAHS results were recorded with the tele-audiological method.

Results: According to the tympanometry results obtained from the participants, it was determined that the rate of abnormal hearing was 4.5%. According to the video-otoscope results, which were evaluated as asynchronous, the number of students suspected of dense earwax plug and membrane pathology was 6.7% in the left ear and 5.8 in the right ear. According to the SAHS method results, the average rate of passing and failing the test in the standard method was 12.9% in the right ear, and 12.9% in the left ear. According to the results of the tele-audiological method of the same student group, the rate of failing the test was 16.1% in the right ear and 15.2 in the left ear.

Conclusion: Measuring tele-audiologically or using the standard method did not affect the test results. Accordingly, the test result is independent of whether the test is performed with the tele-audiological or standard method.

Keywords: Hearing screening, telehealth, tele-audiology, school-age hearing screening, tympanometry video-otoscopy

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INTRODUCTION

Hearing loss has a detrimental effect on an individual's speech production, language development, and academic performance. Hearing loss may develop after birth in babies without any problems detected in newborn hearing screening and may be diagnosed during childhood; thus, childhood is an important period that needs special attention in the evaluation of hearing health. Hearing loss in children has also been reported to cause decreased social skills, emotional problems, and executive dysfunctions (1). While the rate of hearing loss in newborns is around 1-3/1000 worldwide, this rate rises to 2-4% in newborns who need intensive care (2). However, the prevalence rates of childhood hearing loss also differ. Studies have shown that the prevalence rates of childhood hearing loss vary greatly between 1.4% and 17.5% (3-5). School-age hearing screening (SAHS) is as important as newborn hearing screening in terms of detecting and preventing hearing loss. Therefore, SAHS becomes as important as newborn hearing screening in terms of detecting and intervening in hearing loss. Several studies suggest that SAHS may allow timely detection of childhood hearing loss and provide favorable financial conditions to address the burden of undiagnosed hearing loss in school-aged children (6-8). However, hearing screening at school-age may also cause some additional problems. The studies have reported that the increase in the number of students, the reliability of the results, and the adequacy of the staff to participate in the screening poses great challenges in the practice of hearing screening (9,10). Tele-audiological applications should be considered as an alternative to traditional applications for the solution of existing problems in screening programs. To use telehealth systems, two basic modeling systems have been accepted according to the interaction between health professionals and health service providers. The first model is called the "store and forward" or "asynchronous" telehealth model, which involves transferring pre-recorded information from one location to another. The second model is the "real-time" or "synchronous" telehealth application (11).

Our study aims to compare the use of tele-audiological applications for SAHS with standard (traditional) SAHS applications and to determine possible similarities or differences between the methods.

METHODS

The Clinical Research Local Ethical Committee with the registration number 83045809-604-01.02-A01 (İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ethical Committee) approved our study (approval no: 52131, date: 06.09.2018). Written consent was obtained after all participants were informed about the study.

Subjects

The research was carried out with a total of 224 children, 97 (43.3%) girls, and 127 (56.7%) boys, who were first-grade primary school students in İstanbul. The mean age was 73.56±2.21 (70-77) months. The results are shown in Table 1.

Procedure

In our study, hearing screening application at 15-day intervals took place. Those screenings were completed in individuals in the same primary school and classes in two stages. In the first stage, a tympanometry test was completed by an audiologist for all individuals who would undergo standard SAHS. A pressure range of 300 dPa to +200 dPa at 85 dB SPL with a probe tone of 226 Hz was used for tympanometry evaluation. The static admittance range of 0.3-1.5 mmho and pressure range of +100/-120 dPa were considered normal. Tympanograms that did not meet the criteria were considered abnormal and classified into appropriate categories (for instance, B or C). In addition to the tympanometry examination, video-otoscope images of all participants who would undergo SAHS were recorded. The obtained images were evaluated asynchronously by the otolaryngologist. Individuals with normal external auditory canal opening and membrane appearance on the video otoscope image were considered normal. Visualization of pathological findings on the tympanic membrane surface or the presence of intense ear wax were considered suspicious pathology. After the video-otoscope evaluation, all participants were subjected to the hearing screening test's Hughson & Westlake threshold measurement procedure. The participants were switched from 20 dB HL in 5 dB increments until the threshold level was determined (12). As a passing criterion, the 20 dB HL threshold was determined at 0.5 Hz, 1 kHz, 2 kHz, and 4 kHz frequency. Responses below the threshold level were considered abnormal. Standard SAHS was completed.

Before the second test session, a teacher selected from the school was given tele-audiology training and was appointed as a test assistant. In addition, the school's internet network and system requirements were actively checked for the smooth progress of the tele-audiological SAHS. In the second stage, the same audiologist who performed the standard hearing screening completed the Hughson & Westlake hearing threshold measurement procedure with the trained assistant by connecting to the test environment via video method over the internet connection at the study center. At this stage, as a passing criterion, the 20 dB HL threshold level was determined at 0.5 Hz, 1 kHz, 2 kHz, and 4 kHz frequencies. Responses obtained at the threshold level below this were considered abnormal (Figure 1).

Equipment

Equipment used in SAHS with standard and tele-audiological methods included two portable computers (Lenovo ThinkPad

Table 1. Gender distribution by age

Gender	Female n=97 (43.3%)	Male n=127 (56.7%)	t value	Sig. (p-value)
	Mean ± SD	Mean ± SD		
Age (month)	73.28±2.17	73.78±2.21	-1.693	0.092

n: frequency, %: percent, SD: standard deviation, t: statistical significance of t-test value, sig: statistically significant

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T480 14" HD Business Laptop Intel 8th Gen Quad-Core i5-8250U, 16GB DDR4 RAM, China), software to provide a remote connection between the computers (teamwiver-version13), portable audiometer device that could be connected to a computer (Oscilla Peltor H7A, Italy), Otometrics Madsen Otoflex 100 Diagnostic Tympanometry Device (USA), Video-otoscope device (Otocam-300, USA), a webcam device (4 TECH, HD 1080p, China), and two loudspeakers (Genius SP S110, China).

Statistical Analysis

The analysis of the data included in the research was carried out with the SPSS (Statistical Program in Social Sciences) 25 program. The Kolmogorov-Smirnov test was used to check whether the data included in the study complied with the normal distribution (13). Comparisons between measures were performed with the paired t-test. The Pearson correlation coefficient was also calculated. Values frequently used in the evaluation of the findings were as follows; 0.00-0.19 no relationship (negligible low relationship), 0.20-0.39 weak relationship, 0.40-0.69 moderate relationship, 0.70-0.89 strong relationship, and 0.90-1.00 very strong relationship (13). Interrater reliability was used to show variability between 2 or more raters measuring the same group of participants (14). Intraclass correlation coefficients (ICC) were used to assess interobserver reliability. Since the subjects were evaluated by the same observer, the ICC (1,1) model was used. ICC values below 0.40 showed weak, 0.41-0.70 acceptable, 0.71-0.90 good, and above 0.91 excellent reliability (15). The McNemar chi-square (χ^2) test was used to analyze dependent categorical variables. All participants included in the study were provided with similar test setups and conditions, and the measurement values of the tests were recorded.

RESULTS

In our study, according to the tympanometry evaluation results applied to all participants, type B, and type C results were considered abnormal. Accordingly, it was determined that the abnormal response rate in right and left ears was 4.5%. In addition to the results of the tympanometry evaluation, the number of students with intense suspicion of earwax and membrane pathology was determined according to the video-otoscope image results evaluated by the otolaryngologist with the asynchronous tele-audiology method. Accordingly, it was 6.7% in the left ear and 5.8 in the right ear. According to these results, according to the video otoscope image evaluation of the right ear, 3.6% had earwax density and 2.2% had a suspicion of eardrum pathology (eg, otitis media). And in the left ear, earwax density was observed at the rate of 4%, and suspicion of membrane pathology was observed at the rate of 2.7% (Table 2).

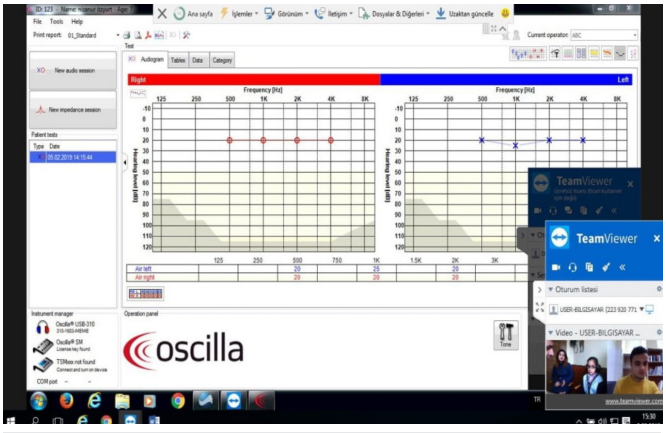

Figure 1. Screenshot of test recording screen (including the images of the remote audiologist and the assistant personnel with the student being screened)

The tympanometric and video-otoscopic evaluation results of the students participating in the study were compared. Accordingly, there was a statistically significant relationship between right ear video-otoscopic examination and right ear tympanometry finding (p=0.023). There was a statistically significant correlation between left ear video-otoscopic examination and left ear tympanometry finding (p=0.039) (Table 3).

The passing and failing rates were evaluated according to the SAHS method results of the students participating in the study. Accordingly, the average rate of referral in the right ear of individuals who underwent SAHS with the standard method was 12.9%, and the rate of referral in the left ear was 12.9%. According to the tele-audiological method results of the same student group, the rate of failing the screening test in the right ear was 16.1%, and 15.2% in the left ear (Table 4). There was no statistically significant difference between the results of standard and tele-audiological methods according to left and right 0.5 Hz, 1 kHz, 2 kHz, 4 kHz and mean measurements (p>0.05) (Table 5).

Using tele-audiological or standard methods did not affect the test results. Accordingly, the test result was independent of

Table 2. Demographic information and ear findings

Variable	Groups	Frequency	Percent
Gender	Female	97	43.3
	Male	127	56.7
Right ear tympanometry	Normal	214	95.5
	Pathological	10	4.5
Left ear tympanometry	Normal	214	95.5
	Pathological	10	4.5
Video-otoscopic left ear	Open external ear canal	209	93.3
	Dense ear wax	9	4.0
	Membrane pathology	6	2.7
Video-otoscopic right ear	Open external ear canal	211	94.2
	Dense ear wax	8	3.6
	Membrane pathology	5	2.2

whether the test was performed with the tele-audiological or standard method. All results are shown in Table 6.

Our study used the ICC (1,1) model to evaluate the reliability between measurements. Accordingly, the ICC between the standard and tele-measurements of the right 0.5 kHz value was calculated as 0.411 [95% confidence interval (CI); 0.234-0.547]. The ICC between the standard and tele-measurements of the right 1 kHz value was calculated as 0.431 (95% CI; 0.259-0.562). The ICC between the standard and tele-measurements of the right 2 kHz value was calculated as 0.371 (95% CI; 0.182-0.517). The ICC between the standard and tele-measurements of the right 4 kHz value was calculated as 0.331 (95% CI; 0.158-0.257) Accordingly, the ICC between the standard and tele-measurements of the right ear mean value was calculated as 0.334 (95% CI; 0.133-0.488). The ICC between the standard and tele-measurements of the left 0.5 kHz value was calculated as 0.497 (95% CI; 0.345-0.613). The ICC between the standard and tele-measurements of the left 1 kHz value was calculated as 0.547 (95% CI; 0.411-0.652). The ICC between the standard and tele-measurements of the left 2 kHz value was calculated as 0.226 (95% CI; 0.017-0.405). The ICC between standard and tele-measurements of the left 4 kHz value was calculated as 0.256 (95% CI; 0.168-0.219). The ICC between the standard and tele-measurements of the left mean value was calculated as 0.312 (95% CI; 0.105-0.471) (Table 7). The calculated ICC values show that the agreement between the measurements is acceptable (13).

DISCUSSION

The World Health Organization estimates that 466.46 million people have hearing loss worldwide, of whom 34 million are children (5). In children under 15 years of age, 60% of hearing impairment results from preventable causes, 31% of which are related to infections such as mumps, measles, rubella, meningitis, cytomegalovirus infections, and chronic otitis media (6). Investing in early detection, diagnosis, and rehabilitation of hearing impairment is essential for creating hearing health promotion programs for schoolchildren (7,16). Community-based hearing programs have been proposed to improve access to ear and hearing care (17). Complete evaluation of patients with ear disease requires direct imaging of the ear canal, tympanic membrane, and middle ear structures to make an accurate diagnosis and initiate appropriate treatment. Tele-audiology applications have the potential to be important tools for accessibility to community-based hearing programs. Using telehealth systems in school-age hearing screening is advantageous in reaching more students for hearing assessment, reducing the number of personnel required, and evaluating results by field experts. In addition, by training healthcare providers in tele-audiological applications, hearing assessment, diagnosis of hearing loss and intervention services can be provided relatively easily (18).

The gold standard for hearing screening of schoolchildren is pure tone audiometry. Either acoustic immittance or otoscopy performed by otorhinolaryngologists is usually recommended to detect middle ear alterations in schoolchildren (19).

Tympanometry has been suggested as a very useful test in many studies for the evaluation of middle ear pathologies in SAHS. In addition, otoscopic evaluation has been suggested to identify outer and middle ear problems (9,20,21). However, it has been reported that the Video Otoscope application facilitates remote consultations in patients in whom the examination is required and otoscopic evaluation cannot be performed. In a study that evaluated pure tone audiometry and tympanometry findings

Table 3. Comparison of tympanometry and video-otoscopic examination situations

Variable	Groups	n/%	Tympanometry		Total	χ^2	p-value (Sig.)
Right			**Right normal**	**Right pathological**			
Video-otoscopic right	Open external ear canal	n	204	7	211	7.521	0.023*
		%	95.3%	70.0%	94.2%		
	Dense ear wax	n	7	1	8		
		%	3.3%	10.0%	3.6%		
	Membrane pathology	n	3	2	5		
		%	1.4%	20.0%	2.2%		
Left			**Left normal**	**Left pathological**	**Total**	**χ^2**	**p-value (Sig.)**
Video-otoscopic left	Open external ear canal	n	202	7	209	6.498	0.039*
		%	94.4%	70.0%	93.3%		
	Dense ear wax	n	8	1	9		
		%	3.7%	10.0%	4.0%		
	Membrane pathology	n	4	2	6		
		%	1.9%	20.0%	2.7%		
Total		n	214	10	224		
		%	100.0%	100.0%	100.0%		

n: frequency, %: percent, sig; *p<0.05, there is a statistically significant difference between the two tests

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of 141 preschool and primary school students, it was reported that there were 12 children with abnormal tympanometry responses (22). Again, in a study conducted in 2016, a total of 1,181 children from kindergarten to ninth grade were evaluated. Accordingly, the tests were repeated two years later, and 862 children were re-evaluated. Four percent of children screened in 2016 (n=27, 4%) and three percent of children screened in 2018 (n=23, 3%) had abnormal otoscopy and tympanometry findings (23). In a study in which 155 children were screened for hearing, it was reported that in children in whom the face-to-face examination was required and otoscopic evaluation could not be performed, results were obtained with remote consultation applications and according to the results of the study, a pathology was detected in 13 ears (4.2%) with the video-otoscopy application (24).

In our study, according to the ear results of 224 students who underwent tympanometry evaluation, abnormal tympanometric

Table 4. Distribution of passing states according to test methods

Scale	Result	Standard method		Tele-audiological method	
		Frequency	Percent	Frequency	Percent
Right 0.5 Hz	Passed	206	92.0	204	91.1
	Failed	18	8.0	20	8.9
Right 1 kHz	Passed	213	95.1	206	92.0
	Failed	11	4.9	18	8.0
Right 2 kHz	Passed	215	96.0	213	95.1
	Failed	9	4.0	11	4.9
Right 4 kHz	Passed	217	96.9	214	95.5
	Failed	7	3.1	10	4.5
Right average	Passed	195	87.1	188	83.9
	Failed	29	12.9	36	16.1
Left 0.5 Hz	Passed	202	90.2	198	88.4
	Failed	22	9.8	26	11.6
Left 1 kHz	Passed	214	95.5	208	92.9
	Failed	10	4.5	16	7.1
Left 2 kHz	Passed	217	96.9	214	95.5
	Failed	7	3.1	10	4.5
Left 4 kHz	Passed	216	96.4	212	94.6
	Failed	8	3.6	12	5.4
Left average	Passed	195	87.1	190	84.8
	Failed	29	12.9	34	15.2

Table 5. Results according to test procedures and descriptive statistical findings of tests

Group	Tele-audiological method	Standard method	t value	Sig. (p-value)	Pearson r	Sig. (p-value)
	Mean ± SD	Mean ± SD				
Right 0.5 Hz	20.8±3.11	20.67±2.64	0.571	0.568	0.262	0.001*
Right 1 kHz	20.67±3.07	20.42±2.21	1.141	0.255	0.289	0.001*
Right 2 kHz	20.6±3.34	20.47±2.82	0.521	0.603	0.231	0.001*
Right 4 kHz	20.58±3.62	20.45±3.04	0.428	0.669	0.017	0.799
Right average	20.69±2.98	20.55±2.73	0.573	0.567	0.201	0.003*
Left 0.5 Hz	20.89±3.05	20.65±2.2	1.194	0.234	0.348	0.001*
Left 1 kHz	20.63±2.77	20.31±1.61	1.848	0.066	0.433	0.001*
Left 2 kHz	20.49±2.68	20.27±1.75	1.119	0.264	0.139	0.037*
Left 4 kHz	20.58±3.26	20.29±1.96	1.137	0.257	-0.009	0.894
Left average	20.59±2.43	20.38±1.62	1.240	0.216	0.200	0.003*

SD: standard deviation, t: statistical significance of paired t-test value, sig: statistically significant, r: between two observation correlation coefficient, sig; *p<0.05, There is a statistically significant difference between the two tests

Table 6. Evaluation of pass and fail situations

Variable	Groups	n/%	Standard method right ear		Total	McNemar χ^2 test p-value	Standard method left ear		Total	McNemar χ^2 test p-value
			Passed	Failed			Passed	Failed		
Tele-audiological method 0.5 Hz	Passed	n	190	14	204	0.856	183	15	198	0.608
		%	92.2%	77.8%	91.1%		90.6%	68.2%	88.4%	
	Failed	n	16	4	20		19	7	26	
		%	7.8%	22.2%	8.9%		9.4%	31.8%	11.6%	
Tele-audiological method 1 kHz	Passed	n	198	8	206	0.21	201	7	208	0.263
		%	93.0%	72.7%	92.0%		93.9%	70.0%	92.9%	
	Failed	n	15	3	18		13	3	16	
		%	7.0%	27.3%	8.0%		6.1%	30.0%	7.1%	
Tele-audiological method 2 kHz	Passed	n	207	6	213	0.791	210	4	214	0.549
		%	96.3%	66.7%	95.1%		96.8%	57.1%	95.5%	
	Failed	n	8	3	11		7	3	10	
		%	3.7%	33.3%	4.9%		3.2%	42.9%	4.5%	
Tele-audiological method 4 kHz	Passed	n	208	6	214	0.607	205	7	212	0.481
		%	95.9%	85.7%	95.5%		94.9%	87.5%	94.6%	
	Failed	n	9	1	10		11	1	12	
		%	4.1%	14.3%	4.5%		5.1%	12.5%	5.4%	
Tele-audiological method average	Passed	n	170	18	188	0.361	173	17	190	0.522
		%	87.2%	62.1%	83.9%		88.7%	58.6%	84.8%	
	Failed	n	25	11	36		22	12	34	
		%	12.8%	37.9%	16.1%		11.3%	41.4%	15.2%	
Total		n	195	29	224		195	29	224	
		%	100.0%	100.0%	100.0%		100.0%	100.0%	100.0%	

n: frequency, %: percent, McNemar ki-kare test (χ^2) p-value

Table 7. ICC value for all measurement

Measurement	ICC (1,1)	95% CI	
		Lower bound	Upper bound
Right 0.5 Hz	0.411	0.234	0.547
Right 1 kHz	0.431	0.259	0.562
Right 2 kHz	0.371	0.182	0.517
Right 4 kHz	0.331	0.158	0.257
Right average	0.334	0.133	0.488
Left 0.5 Hz	0.497	0.345	0.613
Left 1 kHz	0.547	0.411	0.652
Left 2 kHz	0.226	0.017	0.405
Left 4 kHz	0.256	0.168	0.219
Left average	0.312	0.105	0.471

ICC: intraclass correlation coefficient, CI: confidence interval, SEM: standard error of measurement, SD: smallest detectable difference

pressure findings were observed in both ears (types B and C) at a level of 4.5%. In addition, the differences, and similarities between the results of the tympanometric evaluation obtained from the standard SAHS and the results of the video-otoscopic evaluation were evaluated in our study. According to our study, when the right ear was evaluated as asynchronous with a video-otoscopic examination by an otolaryngologist, an abnormal image was obtained at a rate of 5.8% in the right ear of the participants and at a rate of 6.7% the left ear (ear wax and suspicious membrane pathology). According to our study, there was a statistically significant difference between right ear video-otoscopic examination and right ear tympanometry (p=0.023). There was a statistically significant relationship between left ear video-otoscopic examination and left ear tympanometry (p=0.039).

In the literature, many studies evaluate the prevalence of school-age hearing loss. Different prevalence rates have been reported in studies in different countries. While it was 0.9% in Taiwan (25), this rate rose to 34% in Brazil (26). In studies evaluating SAHS in England, Fonseca et al. (27) reported that 9.1% of 109,505 children from 43 centers were referred to audiology clinics or ENT hospitals in the initial stage and 53.4% of these children were found to have hearing loss. In a study using tele-audiology methods, it was reported that abnormal results were obtained at a rate of 14.8% in the hearing screening test in 218 children (28). Mahomed-Asmail et al. (29) compared the results of SAHS with tele-audiological method and traditional screening method. Accordingly, it was

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reported that there was a high level of agreement between both methods.

Considering the 0.5 kHz and 4 kHz averages in our study, the referral rate was 12.9% according to the standard audiological screening method in the right ear, while the referral rate was %16.1 in the evaluation performed with the tele-audiological method. While the referral rate was 12.9% according to the results of the standard method in the left ear, this rate was 15.2% according to the results of the tele-audiological method. When the results of 0.5 kHz, 1 kHz, 2 kHz, 4 kHz, and mean value measurements of each ear were evaluated with the standard or tele-audiological methods, the differences between the rates of individuals who passed and failed the hearing screening test were not statistically significant ($p>0.05$).

In a study, tablet-based screening results were compared with gold-standard pure-tone audiometry. Diagnostic values varied among the different hearing screening approaches that were evaluated: sensitivities ranged from 60% to 95%, specificities ranged from 44% to 91%, positive predictive values ranged from 15% to 44%, negative predictive values ranged from 95% to 99%, accuracy values ranged from 49% to 88%, and area under curve values ranged from 0.690 to 0.883. Regarding diagnostic values, the highest results were found for the tablet-based screening method and the series approach (30). A study of children aged 5-8 years showed that face-to-face screening showed 87-97% compliance compared to videoconferencing in a school setting. This supports the applicability of teleaudiological methods for hearing screenings.

In our study, we used the ICC (1,1) model to evaluate the reliability between measures. According to the results of our study, it was observed that tele-audiological or standard measurement methods did not affect the test results. The results obtained support the literature and the test result are independent of whether the test is performed with tele-audiological or standardized method. The ICC values obtained according to our study results show that the agreement between the measurements is at an acceptable level.

It is thought that the asynchronous video-otoscope application used in the study can contribute to the consultation skills of otolaryngologists by providing image quality. In addition, the use of the tele-audiological method, especially in hearing screenings, will facilitate access to field experts (for example, an audiologist or an otolaryngologist).

Depending on the rapid change and development in the field of technology; it is inevitable for telehealth systems to be a dynamic and rapidly changing health service delivery tool. It is envisaged that telehealth systems can contribute to the applicable principles of audiology/otolaryngology.

Study Limitations

The sample size in our study was limited to only 224 children. Therefore, care should be taken when generalizing the results to a common population (external validity). Additional studies with larger sample sizes and the development of current practices are needed to support these findings.

CONCLUSION

Depending on the rapid change and development in the field of technology; it is inevitable for telehealth systems to be a dynamic and rapidly changing healthcare delivery tool. The findings of our study support the use of tele-audiology applications in SAHS programs in schools with appropriate information-communication equipment and with adequate training of volunteering personnel. There will be significant advances in all areas of tele-audiology, including hearing screening, as it allows experts to evaluate the findings.

Ethics Committee Approval: The Clinical Research Local Ethical Committee with the registration number 83045809-604-01.02-A01 (İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ethical Committee) approved our study (approval no: 52131, date: 06.09.2018).

Informed Consent: Written consent was obtained after all participants were informed about the study.

Peer-review: Externally and internally peer-reviewed.

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Evaluation of Factors Affecting Morbidity in Patients with Osteogenesis Imperfecta

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ABSTRACT

Objective: Osteogenesis imperfecta (OI) is a rare genetic disease characterized by osteoporosis and fragility of the bones. These patients often require anesthesia for orthopaedic surgery because of recurrent bone fractures. Our primary goal in this study was to evaluate the patients operated for OI to determine the factors that are associated with perioperative and postoperative morbidity.

Methods: The patient files were retrospectively evaluated between 2008 and 2018. Demographic data, number and type of operations, the duration of the last operation, type of anesthesia, perioperative position, perioperative and postoperative fracture formation, and amount of bleeding were recorded. Additionally, the need for intensive care, if any, length of intensive care unit stays, and length of hospital stay were determined, and the effect of these factors on morbidity and mortality was investigated.

Results: In this study, 44 patients with OI, who had undergone 105 operations, were included with a mean age of 11.07±7.70 years. We demonstrated that the presence of scoliosis (p=0.001), body mass index measurements (p=0.008), and higher number of operations (p=0.014) were significantly associated with morbidity. However, when we made the regression model, we reported that only the presence of scoliosis, appeared to be a significant model (p=0.002; odds ratio: 9.082). Scoliosis increased the risk of morbidity 9.082-fold, which was an independent risk factor.

Conclusion: In our study, we demonstrated that the scoliosis had an effect that increases the risk of morbidity 9-fold, and that scoliosis is an independent risk factor. Considering these data, we suggest that all OI patients undergoing orthopaedic surgery should be radiologically screened for the presence of scoliosis before the operation.

Keywords: Osteogenesis imperfecta, anesthesia, scoliosis, orthopaedic procedures

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INTRODUCTION

Osteogenesis imperfecta (OI) is a disease with a prevalence of about 6-7:100,000 births (1). OI is a rare connective tissue disease that develops secondary to the structural or synthesis disorder of collagen and the manifests in children with diffuse osteoporosis, fragility of the bones, fractures and deformities (2). Although the main defect in these patients is in bone tissue, many systems such as skin, ligaments, tendons, sclera, nose and ear can also be affected (3).

Patients diagnosed with OI often require anesthesia for surgical interventions due to recurrent bone fractures. Accurate identification of risk factors and optimization of general medical conditions before surgery is essential for a smooth course of anesthesia (4). Pulmonary complications secondary to kyphoscoliosis have been suggested to be quite common in severe OI patients (5). Skeletal anomalies causing anatomical deformation of the airway may complicate tracheal intubation (6). Neck and mandible fractures may be seen during laryngoscopy, and the clinical picture may result in posterior brain herniation by causing basilar invagination, resulting in disruption of blood and cerebrospinal fluid flow (7). Increased bone fragility is an important consideration for the anesthesiologist. In these patients, there is a 10-30% incidence of bleeding diathesis. Studies have reported that blood loss increases with increased duration of operation and the increased number of osteotomies (8). Aortic root dilatation and left-sided valve failure are the most reported cardiac pathologies in the literature (9). A closer follow-up may be necessary when severe perioperative complications such as bleeding, fracture, and pulmonary symptoms are present (10).

The cause of mortality in milder types (types I and IV) may be due to conditions such as myocardial infarction and malignancy, which are not associated with the components of the disease, for more severe types, such as type III, respiratory and neurological problems or cardiac failure due to kyphoscoliosis have been reported in the literature to cause death in a considerable extent (11).

Although it is an important challenge in anesthesia, the number of studies in the literature for patients with OI is limited. Therefore, we intended to clarify the factors associated with morbidity and mortality to have a deeper understanding of patients with OI patients. Our primary goal in this study was to retrospectively evaluate the OI-diagnosed patients operated for orthopaedic surgery and to determine the factors associated with morbidity. The secondary aim of this study was to report factors associated with mortality.

METHODS

This retrospective study was performed following the approval of the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 12, date: 29.06.2018). Patients who were operated at the Orthopedics and Traumatology Clinic of İstanbul University, İstanbul Faculty of Medicine between the years of 2008-2018 with complete medical records and ≤18 years of age and who did not have missing follow-ups were included to the study. Adults, patients with missing files, non-orthopaedic surgery patients, and patients who refused the operation were excluded from the study. Archived files, perioperative anesthesia forms, discharge information in the hospital registry system, and radiological imaging were used to obtain the data. Long-term follow-up information was obtained from the patients themselves and their relatives through the contact information of the patients. Age and comorbidities of the patients and preoperative hemogram, coagulation parameters, and biochemical results were recorded. The incidence of comorbidities was determined. The degrees of Cobb angle of all patients were also recorded. Scoliosis was defined as the frontal plane curve of >10° measured by the Cobb angle. Demographic data, number and type of operations, the duration of the last operation, type of anesthesia, perioperative position, perioperative and postoperative fracture formation, and amount of bleeding were recorded. Additionally, factors such as the presence of the need for intensive care stay, length of intensive care unit (ICU) stay, and hospital stay were determined. The effects of all these data on morbidity and mortality were subjected to statistical analyses.

We defined morbidity as perioperative and postoperative complications, post-operative respiratory distress, musculoskeletal (walking disorder or assisted walking due to muscle and joint deformities, peripheral nerve symptoms), and neurological (central nerve injury) complications.

Patients who had general anesthesia for OI in this study undergo tracheal intubation by administration of 2-3 mg/kg propofol, 1-2 μg/kg fentanyl and 0.6 mg/kg rocuronium and maintenance was provided by 1-MAC sevoflurane.

Statistical Analysis

The NCSS 2007 software was used for the statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, ratios, minimum and maximum) were used in the analysis of the data in addition to Student t-test and Mann-Whitney U tests for the two-group comparisons of the qualitative data with and without normal distribution, respectively. Enter logistic regression analysis was used to determine the effective risk factors for morbidity and mortality. Pearson chi-square test, Fisher-Freeman-Halton test, and Fisher's Exact test were used in the comparison of qualitative data. The level of significance was accepted as $p<0.05$.

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RESULTS

Data of 51 patients who had undergone 113 operations were evaluated, and their eligibility for the study was investigated. Among these, 44 patients and 105 operations were included in the study. Six patients were excluded due to rejection of the operation and one patient due to missing file. Descriptive and preoperative clinical characteristics of the patients are given in Table 1. It was found that administration of general anesthesia was generally preferred by the staff in this hospital when anesthesia is needed in patients with OI. General anesthesia was applied to all patients except one who preferred spinal anesthesia.

The mean number of previous operations was 7.40±7.33. Among the postoperative patients, 6.7% were admitted to the ICU. The distribution of the operative and postoperative characteristics is given in Table 2. The mean Cobb angle in patients with scoliosis was 35.40±24.93.

The distribution of factors associated with postoperative morbidity and mortality is given in Table 3, and morbidity was detected in 37 operations.

When the effect of demographic data on morbidity was evaluated, no difference was observed between the groups in terms of age. Body mass index (BMI) measurements were statistically significantly lower in patients with morbidity. Additionally, morbidity was found to be statistically significantly higher in patients with scoliosis. When we investigated the effect of preoperative clinical features on morbidity; no statistically significant difference was found between the groups according to the results of international normalized ratio, number of platelets, and results of preoperative pulmonary function tests (PFTs) and position (Table 4).

No statistically significant effect of the type of operation, the type of anesthesia, duration of the last operation, presence of fracture, and presence of bleeding were found on morbidity. The number of operations the cases with morbidity (+) underwent was found to be statistically significantly higher compared with morbidity (-) cases (p=0.014). There was no statistically significant difference in morbidity according to the length of postoperative ICU stay and hospital stay (p>0.05) (Table 5).

Factors that were found to have a significant effect on morbidity such as BMI, presence of scoliosis, and the number of previous operations were evaluated by Enter logistic regression analysis (Table 6).

The variables included in the study were evaluated by Enter logistic regression analysis. The presence of scoliosis, one of the risk factors affecting the morbidity status, appears to form a significant model. The explanatory coefficient of the model was 69.6%. According to the model, the presence of scoliosis affected morbidity by increasing the risk by 9.082-fold. Scoliosis was an independent risk factor.

Table 1. Distribution of demographic data

Age (years)		11.07±7.70
BMI (kg/m²)		20.71±4.96
Coexisting disease n (%)	No	57 (54)
	Yes	48 (45.7)
	Scoliosis	14 (13.3)
	ASD	5 (4.7)
	Diabetes	4 (3.8)
	Meningomyelocele	4 (3.8)
	Cerebral palsy	3 (2.8)
	Epilepsy	3 (2.8)
	Hyperthyroidism	3 (2.8)
	Chronic bronchitis	2 (1.9)
	Others	10 (9.4)
INR		1.03±0.07
Platelets		371036.54±90486.26
Respiratory function tests	Normal	94 (89.5%)
	Abnormal	11 (10.4%)

BMI: body mass index, ASD: autism spectrum disorders, INR: international normalized ratio

Table 2. Perioperative variables

Number of previous operations		7.40±7.33
Duration of the last operation (minutes)		139.66±74.49
Type of anaesthesia	General	104 (99.0%)
	Spinal	1 (1.0%)
Presence of fracture	No	103 (98.1%)
	Yes	2 (1.9%)
Presence of bleeding	No	69 (65.7%)
	Yes	36 (34.3%)
Amount of bleeding (mL)		313.06±203.24
Admittance to the intensive care unit	No	98 (93.3%)
	Yes	7 (6.7%)
Length of stay in the intensive care unit (days)		2.14±0.69
Length of hospital stay (days)		10.26±9.94
Cobb angle for patients with scoliosis		35.40±24.93
Procedures classified by anatomical region	Femur	66 (62.9%)
	Tibia	19 (18.1%)
	Knee	10 (9.5%)
	Forearm	5 (4.7%)
	Others	5 (4.7%)

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DISCUSSION

In this study, we found that low BMI, presence of scoliosis, and recurrent operations in severe OI types affect morbidity and pose a high risk. Particularly scoliosis was an independent risk factor for morbidity. Therefore, we suggest that a detailed perioperative preparation can reduce these risks. In the present study, we reported that 45.7% of the patients had additional diseases. There were no complications except perioperative fractures in two cases. We found that 35.2% of the cases had postoperative respiratory, neurological, psychiatric, and musculoskeletal complications and growth retardation. Similar to our findings, Tripković et al. (12) in their retrospective study between 1980-2012 evaluating the preoperative features, comorbidities, types of anesthesia and complications associated with anesthesia in 26 patients diagnosed with OI and who had undergone a total of 103 operations at an orthopaedic clinic reported that 89 patients received general anesthesia and 14 patients received regional anesthesia; 14 had intraoperative complications (mostly difficult intubation) and six had postoperative cardiovascular instability. However, different from our results Bojanić et al. (13) reported no perioperative anesthetic complications in their cohort, including 180 operations in 49 patients with OI. We think that the difference between the studies originates from the methods of two studies. They included only perioperative anesthesia-related complications, but we included all perioperative and postoperative complications, including both anesthesia and orthopaedic related. Engel Espinosa et al. (14), in another retrospective study, screened the perioperative complications of 29 patients with OI and who were operated on 105 times between 1991 and 2009. They detected a latex allergy as a co-morbidity for 2 patients. Among the interventions, they had complications occurring in 38% cases, whereas perioperative complications included non-malignant hyperthermia and a femoral fracture. This result is very similar to our complication rate. We demonstrated that the presence of scoliosis influenced morbidity. Pulmonary complications are important causes of morbidity and mortality in patients with OI. Pulmonary problems are multifactorial in these patients, but few studies are present that systematically assess the pulmonary function in individuals with OI (15). In our study, when we examined the patients with abnormal preoperative PFT results, it was found that this surprisingly had no effect on morbidity. We believe that this is due to the small number of patients included with abnormal PFT in our study. Wekre et al. (16) In their prospective study, evaluated the association of spinal deformities and pulmonary dysfunction in an adult patient group with OI and suggested that spinal deformities affect the height and lung function of these patients. Additionally, the spirometry measurements of patients with OI were analysed in a multicentre observational study by Tam et al. (15). Forced vital capacity and forced vital capacity in 1 second values were found to be extremely low in patients with type III OI compared with the normal population; however, the spirometry analysis revealed that pulmonary involvement was low. There are several case reports reporting similar cases managed under general anesthesia. Karabiyik et al. (17) Reported that they used laryngeal mask airway safely together with total intravenous anaesthesia. Therefore, studies on regional anesthesia have come to the forefront (18). These patients should be kept under close clinical observation both during the hospitalization and after discharge in terms of

Table 3. Distribution of factors associated with morbidity and mortality

		n (%)
Postoperative morbidity	No	68 (64.8)
	Yes	37 (35.2)
	Musculoskeletal complication	26 (70.2)
	Neurological complication	6 (13.6)
	Perioperative fracture	1 (2.7)
	Postoperative respiratory distress	1 (2.7)
	Others	4 (10.6)
Mortality	No	103 (98.1)
	Yes	2 (1.9)

Table 4. Morbidity assessment according to descriptive characteristics and preoperative clinical features

		Morbidity (-) (n=66)	Morbidity (+) (n=39)	p-value
Age (years)		10.07±5.78	12.77±10.02	[a]0.289
BMI (kg/m^2)		21.16±3.94	19.94±6.31	[a]0.008**
Scoliosis	No	63 (69.2)	28 (30.8)	[b]0.001**
	Yes	3 (21.4)	11 (78.6)	
INR		1.04±0.07	1.02±0.06	[a]0.123
Platelets		369453.03±92916.19	373786.84±87257.71	[c]0.815
Respiratory function tests	Normal	59 (62.8)	35 (37.2)	[d]0.519
	Abnormal	7 (63.6)	4 (36.3)	

BMI: body mass index, INR: international normalized ratio, [a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Student t-test, [d]Fisher-Freeman-Halton test, **p<0.01

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Table 5. Evaluation of morbidity by operation characteristics

		Morbidity (-) (n=66)	Morbidity (+) (n=39)	p-value
Number of previous operations		5.49±6.26	8.53±7.72	[a]0.014*
Area of operation	Femur	46 (69.7)	20 (30.3)	[d]0.134
	Tibia	12 (63.2)	7 (36.8)	
	Knee	4 (40.0)	6 (60.0)	
	Arm	3 (60.0)	2 (40.0)	
	Others	1 (20.0)	4 (80.0)	
Duration of the last operation		135.45±61.79	146.47±92.04	[c]0.540
Type of anaesthesia	General	66 (63.5)	38 (36.5)	[e]0.371
	Spinal	0 (0)	1 (100)	
Presence of fracture	No	0 (0)	1 (100)	[e]0.136
	Yes	0 (0)	2 (100)	
Presence of bleeding	No	41 (59.4)	28 (40.6)	[b]0.313
	Yes	25 (69.4)	11 (30.6)	
Amount of bleeding (mL)		334.80±233.33	263.64±100.23	[a]0.536
Admittance to the intensive care unit	No	60 (61.2)	38 (38.8)	[e]0.254
	Yes	6 (85.7)	1 (14.3)	
Length of stay in the intensive care unit (days)		2.33±0.52	1.00±0	[e]0.130
Length of hospital stay (days)		10.38±9.33	10.05±11.07	[a]0.274

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Student t-test, [d]Fisher-Freeman-Halton test, [e]Fisher's Exact test, *p<0.05

Table 6. Logistic regression analysis of risk factors affecting the status of morbidity

	p-value	OR	95% CI	
			Lower	Upper
BMI (kg/m^2)	0.405	1.039	0.950	1.136
Presence of scoliosis	0.002**	9.082	2.226	37.062
Number of previous operations	0.094	1.063	0.990	1.140

CI: confidence interval, OR: odds ratio, BMI: body mass index, **p<0.01

increased risk for postoperative long-term complications that were established in the present study.

Because of the bleeding tendency of patients with OI, studies investigating this relationship have been conducted. For example, Persiani et al. (8) retrospectively evaluated 23 patients with type III OI between 6-13 years of age and who were treated for femoral fractures, and the relationship between age, BMI, duration of operation and blood loss was analysed. In that study, no significant association was found between the duration of surgery and blood loss. The age of the patient was found to be inversely proportional to the amount of blood loss, and children older than 10 years were found to have a statistically lesser amount of average blood loss (8). It has been suggested that the risk of intraoperative and postoperative bleeding is lower in children with higher body weights. As a result, blood loss per kilogram was higher in patients with a low BMI. In our study, we found that the rate of morbidity was significantly higher in patients with a low BMI. However, we could not find any relationship between blood loss and morbidity. We think that this increased morbidity is due to malnutrition and poor care of patients. Pichard et al. (19) Reported that there was no relationship between the duration of operation and mean blood loss and that the blood loss decreased with increasing age.

There are no studies that investigated the relationship between ICU stay and morbidity in patients with OI. Transfer to the postoperative ICU may be necessary when patients have ongoing conditions such as severe intraoperative complications, disorders of haemorrhagic diathesis, or restrictive respiratory symptoms. In our study, 6.7% of the patients were admitted to the ICU. Two cases resulted in mortality (1.9%) in the present study. There are few studies have investigating perioperative morbidity and mortality in orthopaedic operations of patients with OI. Among the studies in which other surgical procedures were examined, Lamanna et al. (20) In their cardiac case series in patients diagnosed to have OI, reported that valvular surgery in these patients might be complicated by bleeding, arrhythmia, cardiac rupture, valve detachment, and delayed wound healing, although they are technically feasible. Additionally, the morbidity and mortality of those cases were found to be higher. In this study, perioperative mortality and long-term mortality rates were reported as 18% and 8%, respectively (20). On the other hand, McAllion and Paterson (21) in a retrospective report,

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investigated the causes of death of 68 patients with OI and who died between 1980-1995. They especially emphasized the importance of respiratory complications in severe disease form (type III). It was reported that chest deformity and scoliosis contribute to the limitation of pulmonary functions in these patients. It has been reported that most of the deaths are the results of intracranial hemorrhage and bacillary invagination or restrictive heart failure due to kyphoscoliosis. It is also emphasized that minor traumatic events may be complicated causing death (21). In this present study, it was seen that scoliotic deformity among the risk factors for morbidity had a highly significant association with morbidity. According to the model, the presence of scoliosis affected morbidity by increasing the risk by 9.082-fold. The presence of scoliosis is an independent risk factor. In a survey study examining the observations of 121 patients treated with 51 fusion surgery in 14 countries to document the orthopaedic surgical outcomes of OI-related scoliosis; reported similar results and documented that the increased size of the Cobb angle before spinal fusion and the presence of kyphosis were associated with a high complication rate, and that in the absence of pseudoarthrosis and kyphosis, the spinal curvature appeared in the late period (22). Scoliosis is more common in patients with severe OI and especially in advanced age. Since many systems, especially the cardiopulmonary system, are affected in these patients, morbidity is expected to be higher (23).

Study Limitations

Finally, we should also mention the limitations of our study. Because of the relatively low incidence and prevalence of OI, as with many rare diseases, there is a difficulty in designing a prospective study that can examine target parameters. For this reason, many studies such as the present study were designed retrospectively; OI patients with multiple operations were included in the study as individual cases. On the other hand, surgical indications and techniques used for treating OI are relatively new. Another limitation of our study was the lesser number of cases included in the study, which can contravene the causal relationship of the statistical results. To avoid this limitation, we believe that the data of the cases of OI can be optimized by increasing the number of cases with multicentre studies.

CONCLUSION

In this present study, the presence of scoliosis was found to be an independent risk factor that has an effect that increases the risk of morbidity 9-fold. Considering these data, we believe that medical personnel should be aware of the potential complications associated with OI. We suggest that all patients with OI undergoing orthopaedic surgery should be preoperatively screened for the presence of scoliosis. We recommend more randomized controlled studies to approve our results should be warranted.

Ethics Committee Approval: This retrospective study was performed following the approval of the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (decision no: 12, date: 29.06.2018).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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Cryopreservation of Deciduous Teeth Originated Mesenchymal Stem Cells with Different Techniques

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ABSTRACT

Objective: Mesenchymal stem cells (MSCs) are not used immediately after isolation in experimental and clinical studies. Traditional freezing and thawing processes may affect the cell viability or immunological properties of MSCs. In this study, the effect of different freezing methods on the viability, differentiation potential, and immunological properties of MSCs from human exfoliated deciduous teeth (SHED) was investigated.

Methods: SHED was isolated from SHED from healthy subjects aged between 8-12 years. The third passage cells were frozen with three different freezing solutions containing distinct concentrations of dimethyl sulfoxide, trehalose, ethylene glycol, or PVP40. After thawing, cells were analyzed for cell viability, co-cultured with mononuclear cells, and analyzed for lymphocyte proliferation rate, and cell viability for evaluating immunological properties.

Results: Compared to conventional cell freezing methods, the lymphocyte proliferation rate was suppressed, and cell viability ratios were increased with cryoprotectant solutions containing trehalose and ethylene glycol ($p<0.05$).

Conclusion: Cryoprotectant solutions containing trehalose, ethylene glycol, or PVP40 are more suitable for cell freezing.

Keywords: Mesenchymal stem cells, cryopreservation, cryoprotective agents

INTRODUCTION

Mesenchymal stem cells (MSCs) can differentiate into multiple lineages under suitable conditions, adhere to plastic surfaces and have a fibroblast-like morphology (1). Studies showed that MSCs play a regulatory role in the immune system by suppressing T and B -cell inflammatory responses (2).

Stem cells from human exfoliated deciduous teeth (SHED) are defined as cells that have a high proliferation capacity, can colonize, and differentiate into various cell types (e.g. neural cells, adipocytes, odontoblasts). It has been shown that SHED is better in terms of proliferation and differentiation ability compared to other oral cavity-derived MSCs (3).

Stem cells are not used immediately after isolation in experimental and clinical studies. It was frozen under laboratory conditions and then thawed again. Additionally, the cold chain route is used to transfer stem cells from one place to another. In this way, it is also appropriate to use the MSCs after special freezing procedures (4). A wide variety of methods are used in the cryopreservation of cells. Particularly significant studies have been conducted on

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sperm and embryo freezing (5). Fetal development is monitored by thawing frozen embryos and placing them in the uterus of experimental animals (6). In this project, the effect of different freezing methods on the viability, differentiation potential, and immunological properties of SHED was investigated.

METHODS

Isolation and Culture of SHED

SHED was isolated as described before (7). Briefly, human exfoliated deciduous teeth without abscesses were collected from healthy subjects aged 8-12 years. The clinical ethical approval was provided from the Marmara University Faculty of Medicine Clinical Ethical Committee with the protocol number 09.2014.0003 (date: 26.01.2023). Tissues were cut into 1x1 mm pieces and enzymatically digested with 3 mg/mL collagenase type I (Thermofisher, US) in phosphate-buffered saline (PBS) (Sigma-Aldrich, Germany) at 37 °C for 45 minutes. After the incubation period cell pellet was washed twice with Dulbecco' Modified Eagles Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin, hereafter complete DMEM (cDMEM). Cells were cultured with cDMEM in T25 culture flasks at 37 °C in 5% CO_2 for 7-10 days until they reached 80-90% confluence. The isolated cells were trypsinized with 0.25% Trypsin EDTA solution and cultured until the third passage.

Peripheral Blood Mononuclear Cell (PBMC) Isolation From Healthy Individuals

10 mL of venous blood was collected from the healthy subjects into heparinized tubes and the blood was transferred to a 15 mL sterile falcon for PBMCs isolation. Blood samples were diluted with PBS in a 1:1 (v/v) ratio. The samples were centrifuged at 2000 rpm for 20 minutes. After centrifugation, the buffy-coat collected in the middle of the tubes was transferred into sterile Falcon tubes and washed twice with 5 mL PBS.

Co-cultures of SHED with PBMC

After the SHED was thawed, it was resuspended in culture media and spread at $5x10^4$ cells per well of 48-well plates. Plates were incubated at 37 °C for 2 days for confluence. PBMC were labeled with carboxyfluorescein succinimidyl ester (CFSE) and cultured with SHED in a 1:10 ratio (SHED: PBMC). PBMC was stimulated with anti-CD3 and anti-CD28 (CDmix) for specific T lymphocyte stimulation. Lymphocytes were analyzed via flow cytometry after 72 h of the incubation period. The lymphocytes were analyzed for proliferation and CD4 + CD25 + FoxP3 + T regulatory cell frequency to determine the immunomodulatory effect of SHED after the thawing process.

Flow Cytometry Analysis

Analyses were performed after each subculture and using the FACS Calibur flow cytometer. After cells were removed, cells were counted and approximately $1x10^6$ cells were homogenized in PBS, incubated by adding 10 µL of fluorescent isothiocyanate (FITC) and phycoerythrin (PE)-conjugated monoclonal antibodies specific to the identified cell surface markers and appropriate isotype controls in the dark for 15 min. Wash buffer (PBS containing 0.1% sodium azide) was added after incubation and centrifuged at 1200 rpm for 5 min. The prepared cell suspension was analyzed via a flow cytometer (FACS Calibur, BD Biosciences, US). The isolated cells were stained with positive cell surface markers for MSCs as follows: CD146 FITC, CD29 APC, CD105 PE, CD90 PE, and CD73 PE. Apart from these, the cells were stained with CD14 PE, CD34 FITC, CD45APC, and HLA-DR as negative markers. Cell proliferation analysis was performed by staining cells with CFSE. Apoptosis was analyzed by staining cells with Annexin-V (FITC) and propidium iodide (PI). CD4 + CD25 + FoxP3 + T regulatory cell frequency was analyzed by staining cells with a human-FoxP3 detection kit (BD Biosciences, US).

Analysis of the Differentiation Potential of SHED

Adipogenic differentiation: The third passage cells were seeded on type I collagen-coated coverslips and allowed to differentiate into adipogenic lineage with the stimulation of the adipogenic medium [0.5-mM isobutyl-methylxanthine (IBMX-Sigma-Aldich), adipogenic medium MEM (Invitrogen/GIBCO)], 10% FBS (Invitrogen/GIBCO), 0.5 mM isobutyl-methylxanthine (IBMX-Sigma-Aldich), 10 M dexamethasone (Sigma-Aldich, Fluka Chemie AG, Buchs, Switzerland), 10 ug/mL insulin (Invitrogen/GIBCO), 200 µM indomethacin (Sigma-Aldich), and 1% antibiotic/antimycotic (Invitrogen/GIBCO) for 28 days at 37 °C 5% CO_2 chamber. The medium was changed twice a week. The adipocytes and oil droplets were evaluated by staining the cells with hematoxylin-eosin and 0.5% oil red O in methanol.

Osteogenic differentiation: The third passage cells were seeded on type I collagen-coated coverslips and allowed to differentiate into osteogenic lineages with the stimulation of an osteogenic differentiation medium (StemPro™, Thermofisher, US). Cells were incubated for 21 days in a 37 °C, 5% CO_2 chamber. The medium was changed twice a week. The osteocytes and intercellular calcium deposits were evaluated by staining the cells with Alizarin Red.

Freezing of SHED by Traditional Slow Freezing and Vitrification Methods

In the vitrification technique used for freezing SHED, a freezing solution containing dimethyl sulfoxide (DMSO) was prepared using 2M DMSO, 1M acetamide, 3M propylene glycol, and 15% human albumin serum. Twenty one million cells/mL were transferred into 1.2 mL cryovials with 200 microliters of vitrification solution. Cryotubes and straws were dipped directly into liquid nitrogen immediately after loading with cryoprotectant and cell suspension. In the dissolution process, the cryovials and straws were dipped directly into the 37 °C water bath and the contents were poured into the washing solution containing 0.5 molar sucrose. The cells were pelleted by centrifugation at 1,200 rpm for 10 minutes, the supernatant was isolated, distributed to flasks

with fresh culture medium, and cultured at 37 °C in a 5% CO_2 atmosphere.

In the second method, 3 different freezing solutions were prepared. Solution A; solution containing 600 µDMEM +300 µL FBS +50 µL DMSO was used for $5x10^5$ SHED. Solution B: RPMI medium containing 31.5% ethylene glycol + 4% PVP40 + 0.36 M trehalose + 10% FBS + 1% PSA was used for $5x10^5$ SHED. Solution C: RPMI medium containing 20% ethylene glycol + 10% glycerol + 10% FBS + 1% PSA was used for $5x10^5$ SHED. The cryopreserved cells were kept at -80 °C for 3 weeks.

Thawing of SHED

The cryovials were removed from the liquid nitrogen tank, slowly shaken horizontally in the air, and immersed in a 37 °C water bath for 1-2 minutes until the solution was completely dissolved in the cryovials. The cryovial content was transferred into a DMEM thawing solution containing 0.1-M trehalose and 10% FBS and left for 3-4 min. Cells were isolated from the thawing solution and transferred to culture wells for co-culture studies with lymphocytes.

Venous Blood Collection from Healthy Individuals and Peripheral Blood Mononuclear Cell Isolation

10 mL of venous blood was collected from the subjects into heparinized tubes and the blood was transferred to 15 mL sterile falcons for mononuclear cells isolation and diluted 1/1 (v/v) with PBS. Tubes were centrifuged at 2000 rpm for 20 min for the isolation of mononuclear cells. The buffy-coat remaining in the middle of the tubes after centrifugation was collected. Cells ($5x10^5$) were suspended in 1 mL cell culture medium and included in the co-culture study.

Labeling of PBMCs with CFSE

18 mM CFSE was used for the proliferation assay of PBMC. CFSE-labeled cells were kept at +4 °C for 6 minutes. Cells were suspended in cRPMI (RPMI 1640 + 10% FBS + 1% penicillin streptomycin) medium and centrifuged at 2000 rpm for 5 min. After the washing steps, cells were suspended in 1 mL cRPMI.

SHED and PBMC Co-culture

After thawing, SHEDs were resuspended in culture media and transferred to $5x10^4$ cells per well of 48-well plates. Plates were cultured for 2 days at 37 °C in a 5% CO_2 incubator for cell adhesion.

At the end of 2 days, PBMCs isolated from the venous blood of healthy individuals and labeled with CFSE were transferred to the wells as $5x10^5$ cells in each well. Unstimulated and anti-CD2 + anti-CD3 + anti-CD28 (CDmix)-stimulated cultures of mononuclear cells in each group were performed. After the culture period, the proliferation analysis of lymphocytes was analyzed via flow cytometry.

Cells Viability Analysis of Lymphocytes

To investigate the effects of cryopreserved SHEDs on the apoptosis of lymphocyte cells in healthy individuals, total viable cells were analyzed via flow cytometry. Cultured cells were stained with Annexin V (5 µL) and PI (5 µL) for 15 min. Staining procedures were performed according to the manufacturer's protocol (BD Biosciences, USA).

The lower left quadrants were analyzed via flow cytometry for viable cell ratios.

Statistical Analysis

The statistical analysis was performed using the GraphPad Prism 8.0 version (GraphPad Software, Inc., CA, USA). Data were given as mean ± standard deviation (minimum-maximum). Comparison of more than two groups was done by One-Way ANOVA test. $P<0.05$ values were considered statistically significant.

RESULTS

Characterization of SHED

The third -passage SHED showed fibroblast-like colonies (Figure 1), and showed MSC characteristics in the third passage with the high expression of positive markers (CD90, CD73, CD29, CD105, CD146), and lack the expression of negative markers (Figure 2). SHED was differentiated into osteogenic, chondrogenic, and adipogenic lineages (Figure 3).

SHEDs Frozen with Cryoprotectant Solutions Increased Cell Viability Ratio of PBMC

The apoptosis ratio of PBMC was analyzed in the presence and absence of SHEDs, which were frozen and thawed with different cryoprotectant solutions. At the end of the culture period, mononuclear cells were stained with Annexin V/PI and analyzed via flow cytometry for the cell survival ratio.

In the presence of SHEDs that were frozen and thawed with solution A, the cell viability ratio (72±5.6%) increased significantly compared to the culture group without SHED (22±4.7%) ($p<0.001$). In the presence of SHEDs that were frozen and thawed with solution B, the viability ratio (68±3.9%) increased significantly compared to the culture group without SHED (22±4.7%) ($p<0.001$). In the presence of SHEDs frozen and thawed with solution C, the viability ratio (71±4.4%) increased significantly compared to the culture group without SHED (22±4.7%) ($p<0.001$) (Figure 4).

SHEDs Frozen with Cryoprotectant Solutions Suppressed Lymphocyte Proliferation

Cell proliferation assays were performed with PBMCs isolated from peripheral venous blood from healthy individuals in the presence and absence of cryopreserved SHEDs. PBMC was co-cultured in the presence and absence of frozen and thawed SHED using three different techniques, and cell proliferation was analyzed on the 3rd day after culture. In the presence of SHEDs that were frozen and thawed with solution A, the proliferation rate (18±4.1%) was significantly reduced compared to the PBMC cultures alone (48±7%) ($p<0.005$). In the presence of SHED cells that were frozen and thawed with solution B, the proliferation rate (23±3.2%) was

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significantly reduced compared to the PBMC cultures alone (48±7%) ($p<0.005$). In the presence of SHEDs that were frozen and thawed with solution C, the proliferation rate (21±3.5%) was significantly reduced compared to the PBMC cultures alone (48±7%) ($p<0.005$). The suppression of the proliferation ratio of SHEDs frozen with three cryoprotectant solutions was similar, and there was no significant difference between the groups ($p>0.05$) (Figure 5).

DISCUSSION

The routine procedure used in cell freezing usually involves slow cooling in the presence of a cryoprotectant to prevent the

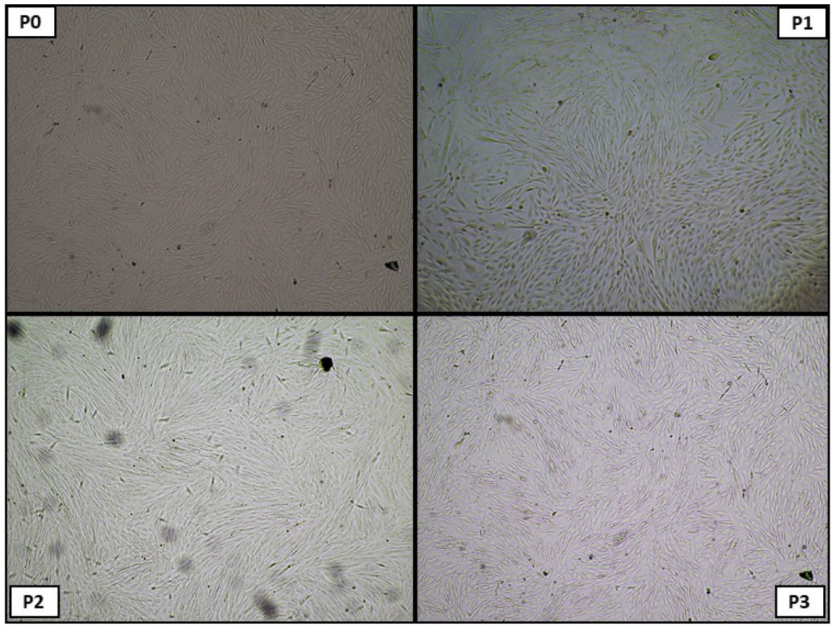

Figure 1. Morphology of SHEDs viewed under an inverted microscope. Fibroblast-like colonies appear in P0, P1, P2, and P3. P0; passage 0, P1; passage 1, P2; passage 2, and P3; passage 3
SHED: stem cells from human exfoliated deciduous teeth

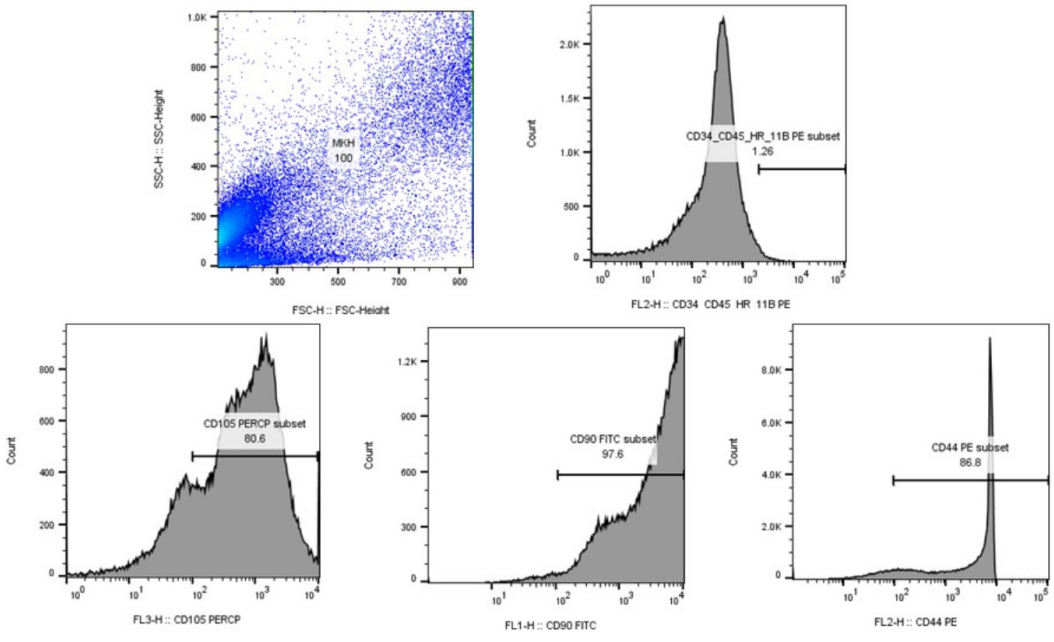

Figure 2. Immunophenotypic characterization of SHEDs. SHEDs in the third passage express positive markers CD105 (80.6%), CD90 (97.6%), CD44 (86.8%) specific to MSCs, and lack the expression of negative markers (CD45, CD34, CD11b, CD19, HLA-DR)
SHED: stem cells from human exfoliated deciduous teeth, MSCs: mesenchymal stem cells

damaging effects of intracellular ice formation. The use of the most cryoprotectant is DMSO and includes a controlled freezing technique at 1 to 2 °C/min and rapid thawing are considered standard (6). While current cryopreservation protocols are clinically effective, there are still about whether to whether they are optimal. DMSO is toxic to tissues and cells, toxicity depends on time, temperature, and concentration. Toxicity varies with cell type and accepted practice is to use the cryoprotectant for a short time at low temperatures (+4 °C) in practical.

MSCs obtained from bone marrow and cord blood can be frozen by the methods used for cryopreservation of hematopoietic analogs and by slow freezing protocols using DMSO used in many studies (8,9). 10% DMSO and slow cooling/rapid heating do not affect the viability or differentiation potential of adipose tissue-derived MSCs (10). Adult MSCs from human dental pulp also showed high post-dissolution viability and three lineage differentiation after slow cooling in 1-1.5 mol/L DMSO (~7.5-10%), and it is superior to propylene glycol (11).

It is known that DMSO affects the epigenetic profile and differentiation induction of mouse stem cells (12). However, since it has side effects in its use as a cryoprotectant in hematopoietic cell therapy, in addition to cell toxicity, it has led to the use of freezing

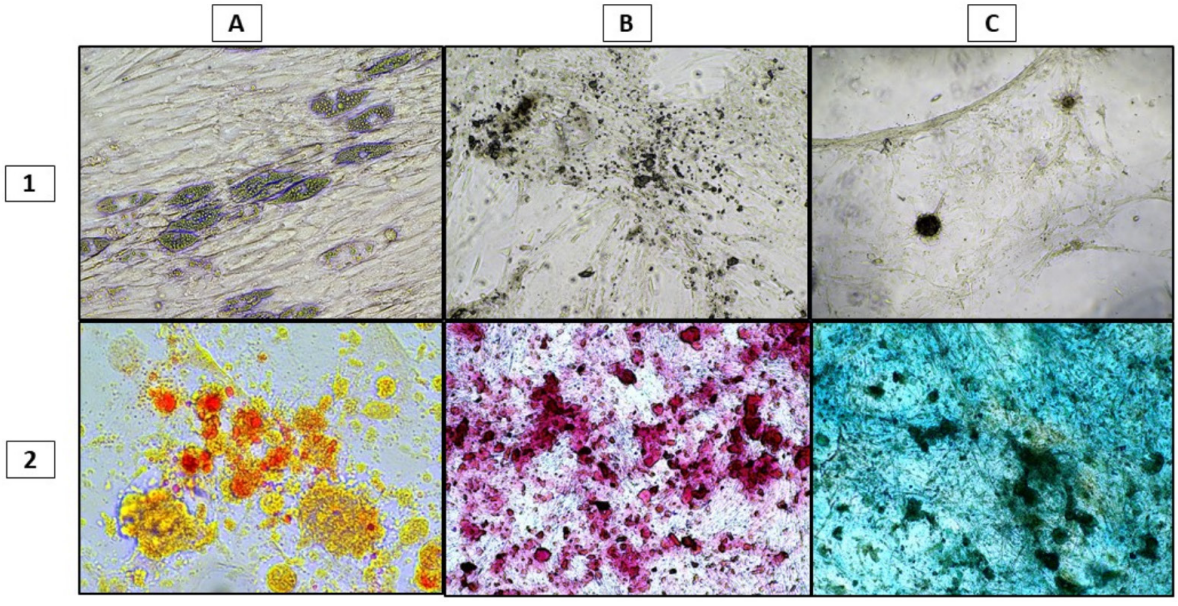

Figure 3. Adipogenic, osteogenic, and chondrogenic differentiation potential of SHEDs. The light microscope images of SHEDs in the third passage. **A)** Adipogenic differentiation of SHEDs. A1 shows inverted microscope image for colony morphology after adipogenic differentiation culture period. Oil droplets are stained orange with Oil red O stain in A2. **B)** Osteogenic differentiation of SHEDs. Osteocyte like colonies are shown in B1 under an inverted microscope. Calcium deposits are stained as red with Alizarin red stain in the intracellular matrix in B2. **C)** Chondrogenic differentiation of SHEDs. Condrocytes and cartilage formation was shown in C1 with a light microscope. Proteoglycans are stained blue with Alcian blue stain in C2

SHED: stem cells from human exfoliated deciduous teeth

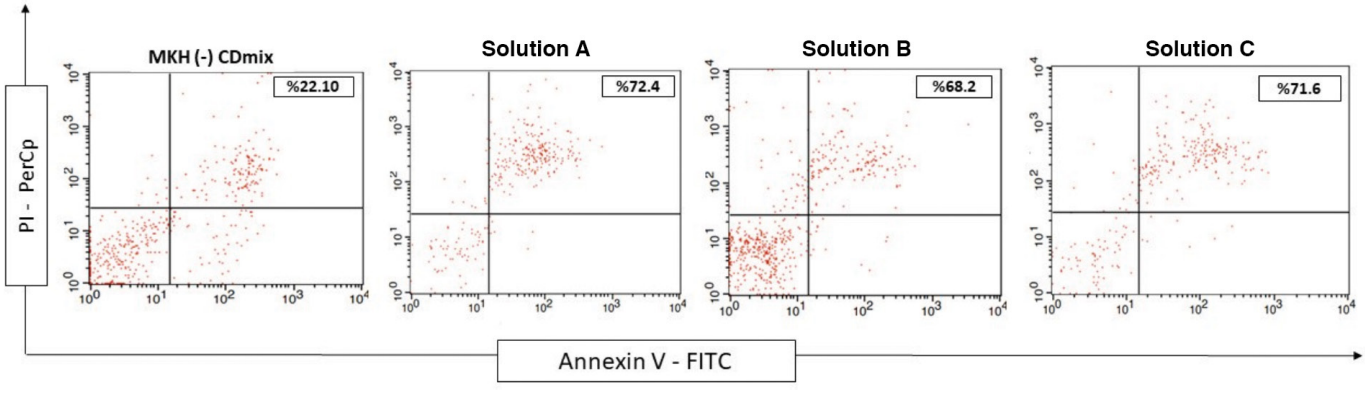

Figure 4. Cell viability analysis of SHEDs. The viability ratio of SHEDs is high after freezing and thawing with cryoprotectant solutions

SHED: stem cells from human exfoliated deciduous teeth

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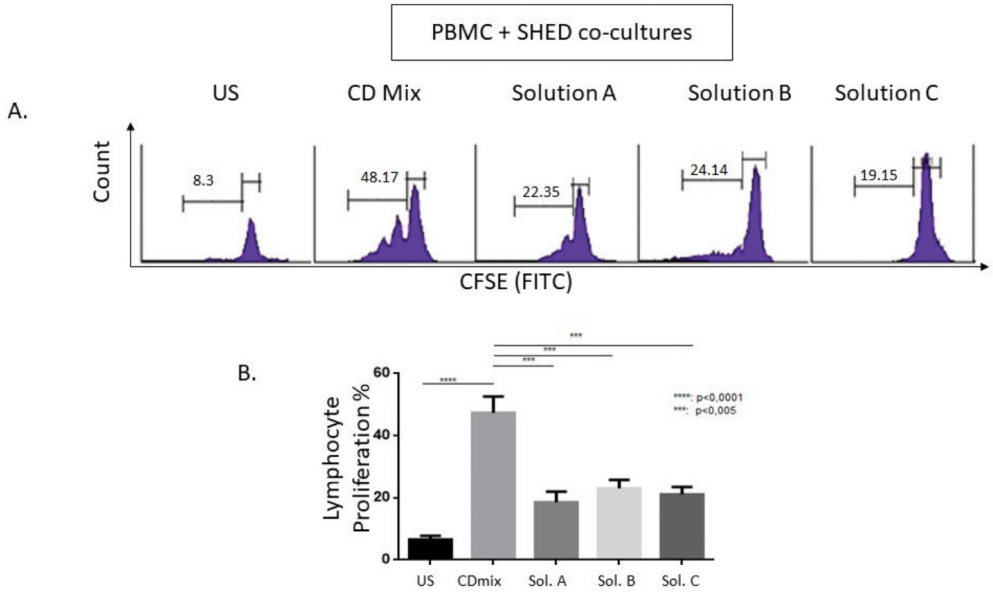

Figure 5. Flow cytometry analysis for lymphocyte proliferation rate. After the co-culture of SHEDs with PBMC, PBMC was analyzed for proliferative responses. **A)** Flow cytometry analysis of lymphocytes after co-culture with cryopreserved SHEDs. **B)** Statistical analysis of lymphocyte proliferation rate after co-culture of lymphocytes with cryopreserved SHEDs. The data showed that cryoprotectant solutions (solution A, solution B, and solution C) can protect the immunologic properties of SHEDs. US; unstimulated PBMC, CDmix; stimulated lymphocytes

SHED: stem cells from human exfoliated deciduous teeth, PBMC: peripheral blood mononuclear cell

applications of MSCs with or without other cryoprotectants (13). Many alternative cryoprotectant formulations have been developed to eliminate animal serum from cryoprotectant solution, which are both cost-effective and suitable for clinical use, and for situations where the terminal sterilization is impossible. However, this is also expensive and poses a potential danger in transmitting human pathogens (14).

Polyvinylpyrrolidone (PVP) is an extracellular cryoprotectant, investigated as an alternative to cryopreservation with DMSO and FBS. The recovery and differentiation capacity of cells were studied after equilibration in a number of different cryopreservation media, 'dump' freezing to -80 °C and storage in liquid nitrogen. The recovery of cells cryopreserved in 10% PVP with human serum may be better than cells stored frozen in DMSO, although lower with animal serum. A similar study used methylcellulose alone or in conjunction with reduced DMSO levels and demonstrated that human serum can alter FBS in standard DMSO mixtures without affecting cell healing, with 1% methylcellulose yielding as low as 2% compared to DMSO concentrations (15). In a previous study, Annexin V was used to analyze cells 24 h after thawing for apoptosis analysis, and it was observed that adipogenic and osteogenic differentiation of these cells were preserved (16). Liu et al. (17) approved the use of reduced DMSO for good quality and non-differential (xeno-free) cryopreservation medium for bone marrow stem cells used in cellular therapy. They used polyethylene glycol (PEG) and trehalose with DMSO concentrations between 2.5% and 7.5% instead of FBS. Standard slow cooling with DMSO and 10% FBS methods were compared by measuring cellular viability, proliferative capacity, and differentiation potential. The results showed that the use of PEG with reduced DMSO concentrations instead of FBS was comparable, but only when 2% bovine serum albumin was used. Besides, 10% DMSO and 90% FBS gave better results than other combinations in cryopreservation. In contrast to cord blood, bone marrow, or peripheral blood-derived hematopoietic cell studies, trehalose is ineffective, but effective along with DMSO at a reduced rate (17).

In this study, we demonstrated that three different cryoprotectant solutions are ideal for freezing MSCs. It has been shown that these cryoprotectant solutions are non-toxic on SHED cells and are also suitable for long-term storage in the freezer without changing the immunological properties of SHEDs.

With regard to the review of the literature on cryoprotective agents' biological response to human dental pulp stem cells, this study contributes to the knowledge regarding how these agents affect this process as part of the literature. A comparison of the use of PEG with reduced DMSO concentrations instead of FBS revealed that the results were comparable, but only when 2% bovine serum albumin was used instead of FBS. It has also been found that 10% DMSO and 90% FBS have been more effective in cryopreservation than other cryoprotectant combinations, compared with cord blood, bone marrow, or peripheral blood-derived hematopoietic cell studies, trehalose was shown to be ineffective. However, it was shown to be effective in a cryoprotectant combination with DMSO at a reduced rate, when used along with DMSO.

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Study Limitations

The limitation of our study is the absence of a control group follow-up. Due to the limited number of cells that could be obtained from donor patients, no further experimental groups were formed as a result. Cells were not stored for more than a year in frozen form It was not possible to eliminate genetic variations since the dental stem cells were obtained from different patients.

CONCLUSION

To conclude, we have found that three different cryoprotectant solutions are ideal for freezing MSCs, among them liquid nitrogen. It has been shown that these cryoprotectant solutions are non-toxic on SHED cells and are also suitable for long-term storage in the freezer without changing the immunological properties of SHEDs.

Ethics Committee Approval: The clinical ethical approval was provided from the Marmara University Faculty of Medicine Clinical Ethical Committee with the protocol number 09.2014.0003 (date: 26.01.2023).

Informed Consent: Patient consent is not required for this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.A., Tu.A.; Design - T.A., D.G., Tu.A.; Data Collection and/or Processing - T.A., D.G., Tu.A.; Analysis and/or Interpretation - T.A., Tu.A.; Literature Search - T.A., D.G., Tu.A.; Writing - T.A., D.G., Tu.A.

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

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Analysis of Body Composition and Dynamic and Static Balance in Individuals Previously Infected with COVID-19

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ABSTRACT

Objective: This study examines body composition and the parameters of dynamic and statistic balance in individuals previously infected with coronavirus disease-2019 (COVID-19) and to compare these individuals with the control group.

Methods: A total of 112 volunteering individuals, 56 individuals previously diagnosed with COVID-19 via polymerase chain reaction test (COVID-19 group), and 56 healthy individuals (control group), between the ages of 18 and 26 participated in the study. Sociodemographic characteristics of the individuals in both groups and their COVID-19 related information were recorded. While Tanita BC 418 (Tokyo, Japan, 2015) operating with bioelectrical impedance was used for body composition measurement, the flamingo balance test and Y balance test were used respectively for static and dynamic balance measurements.

Results: Because of the statistical analysis conducted, it was found that the COVID-19 group had a statistically significant lower balance level than the control group according to the Y balance test anterior, posterolateral, posteromedial, total reach values and flamingo balance test values in terms of balance performance ($p<0.05$).

Conclusion: Because of the study, no significant difference was found in the body composition of individuals aged 18-26 previously infected with COVID-19 compared with healthy individuals of the same age. In terms of static and dynamic balance parameters, it was found that those who were previously infected with COVID-19 were more negatively affected than the control group. We think that determining these balance disorders seen after the COVID-19 infection will be a guide in planning rehabilitation programs for actual needs.

Keywords: COVID-19, dynamic balance, static balance, body composition

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is defined as the clinical condition caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from the coronavirus family, which causes a large number of deaths worldwide (1). The disease can be transmitted from person to person in a variety ways most commonly combined-droplet transmission (2). Studies conducted have reported that the symptoms of coronavirus differ from person to person and symptoms commonly include fever, cough, shortness of breath, muscle aches, loss of sense of smell and taste and gastrointestinal findings (1,3). While these symptoms have commonly appeared 2-14 days later, reportedly some symptoms continued after the resolution of the acute illness (4-6).

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Balance is defined as an individual's ability to maintain the line of gravity within the base of support. It is central to taking the necessary position of the body in the formation of movement (7). Somatosensorial/proprioceptive, vestibular system, and visual system provide balance-related input to the central nervous system (CNS). Notifications sent to the CNS about balance orientation are integrated by these three systems. Balance is then achieved by selectively activating the muscles to maintain balance, producing a corrective, stabilizing torque (7).

It is thought that the effect of SARS-CoV-2 infection on balance systems may be due to the virus's access to the CNS through the olfactory bulb (8). This may cause neurological problems such as headache, facial paralysis, loss of consciousness, dizziness, vestibular disorders, and even paralysis (9). Some studies even concluded that SARS-CoV-2 may damage the auditory-vestibular system through direct infection or vascular damage, and balance problems such as sensorineural hearing, tinnitus, and vertigo may occur during or after infection (10). According to another study conducted simultaneously, dizziness appears to be one of the main balance problems in almost one-third of the patients. Despite these reports, balance has been evaluated in COVID-19 patients by using surveys rather than objective measurements. In other words, a comprehensive assessment that guarantees an objective assessment of balance-related systems is still limited (11).

Body composition is defined as the proportional amount of muscle, bone, fat, and other important parts of the body (12). The important point in the evaluation of body composition is calculating the body fat percentage by finding the body density. For a healthy life, a certain amount of fat is required because too low a or too high body fat may cause some serious health problems (13).

Considering the relationship between body composition and COVID-19, it has been shown that obesity defined by high body mass index (BMI) in patients with COVID-19 may be associated with poor outcomes such as intensive care unit admission, severe COVID-19, use of mechanical ventilation, and even death (14,15). The fact that the prevalence of obesity being approximately one-third of the world population causes COVID-19 infection to have a higher effect on society. Here, it is stated that creating a healthy lifestyle and especially reaching the ideal body weight is a critical approach in preventing and reducing some bad consequences, including death, in case of getting infected with COVID-19 (14).

When the literature is reviewed, it can be seen that there are few studies evaluating the balance and body composition of individuals previously infected with COVID-19. Although there is a statistically significant relationship between balance and body composition (16), no studies were found evaluating these parameters together in individuals previously infected with COVID-19. Considering this information, our study aimed to examine the body composition, static, and dynamic balance levels of individuals previously infected with COVID-19 and to compare these with the healthy control group in terms of these parameters.

METHODS

This study was designed as a descriptive and cross-sectional study examining the balance and body composition parameters of individuals previously infected with COVID-19. The study was conducted at Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Anatomy, Anatomy Practice Laboratory between January 2022 and May 2022. Before the study, necessary permission (decision no: 2022/06, date: 23.03.2022) was obtained from Zonguldak Bülent Ecevit University Non-interventional Clinical Research Ethics Committee.

The population of the study consisted of 112 students (56 females and 56 males) who continued their undergraduate education at Zonguldak Bülent Ecevit University Faculty of Medicine and Faculty of Dentistry, who met the inclusion criteria and who signed the informed consent form. Two groups were included in the study as a patient group of 56 individuals previously infected with COVID-19 and a control group of 56 individuals. Inclusion criteria for the patient group were being between the ages of 18 and 30, having been diagnosed with COVID-19 in the last +12 months, having a negative polymerase chain reaction (PCR) test, or having completed an isolation period of 14 days. Inclusion criteria for the control group were 18-30 years of age, not having been diagnosed with COVID-19 (+), diagnosed as COVID-19 (-) by PCR test, and not having any symptoms of COVID-19 infection. Exclusion criteria were having any orthopedic or neurological problems that may cause especially balance problems, the presence of chronic pain that has been continuing at least for 4 months, having a positive Romberg and Fuduka Step test, using sleeping pills or psychiatric drugs. The demographic information form prepared by the researchers was filled in and static balance was evaluated with the flamingo balance test (FBT), dynamic balance was evaluated with the Y balance test (YBT), and body composition was evaluated with the Bioelectrical Impedance Method.

Demographic Information Form

Demographic information form prepared by the researchers included questions about the individuals' gender, age, height, the data of having been diagnosed with COVID-19 (+), PCR test results (via E-nabız), the ending date of the isolation period and the symptoms that occurred in this process, cigarette and alcohol use, history of surgery, presence of chronic disease, presence of pain, and drugs used.

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Flamingo Balance Test

FBT, the validity and reliability of which was found to be 0.71 (intraclass correlation coefficient) by Tsigilis et al. (17), was used to evaluate static balance. The participants were asked to stand on a 50 cm long, 4 cm high, and 3 cm-wide wooden flamingo balance board. They were asked to hold their free leg by bending back with their hand on the same side after getting on the balance board, and they were told that they could use their free arm to keep their balance. They were then asked to stand on the balance board for a minute. The test was conducted on both the right and left legs. The total number of times when the balance was disturbed in 1 min was noted (18).

Y Balance Test

The reliability of the test was conducted by Türkeri et al. (19) in 2020. While preparing the test environment, a fixed point was determined and 3 different tape measures with 120° in-between were fixed to the ground in a Y shape with one end coming to a fixed point. Before starting the test, the leg length of each participant was recorded in cm by measuring the distance from the anterior superior point of the iliac spine to the medial distal part of the medial malleolus from both sides. The participants were placed on the centre of the test setup with bare feet and were asked to reach the anterior, posterolateral, and posteromedial directions with both feet and touch lightly to the farthest point with the tip of their toes. These distances they reached were recorded in cm (20). After the data were collected, the best reaching distance in each direction was divided by length and multiplied by 100 and the scores obtained were normalized to rule out the leg advantage (21).

Bioelectrical Impedance Analysis

Tanita BC 418 (Tokyo, Japan, 2015) operating with the bioelectrical impedance method was used to determine the body composition of the participants. Before the measurement, the students were asked to have spent at least 2 h after having a meal, not to have consumed alcohol within the past week, and female students were asked to have measurements outside their menstrual cycle. When the process was completed, the participants body weight, BMI, basal metabolic rate (kJ, kcal), muscle resistance (IMPEDANCE; Ω), body fat ratio (FAT %), body fat mass (FAT MASS; kg), fat free mass in the body (kg), total body fluid (TBW; kg), arm fat ratio (AFAT; %), leg fat ratio (LFAT; %), and total muscle ratio (%) values measured by the device were reported (22).

Statistical Analysis

Before starting the study, the sample size was calculated with the G Power Version 3.1.9.2 program. While calculating the sample size, since the researcher did not have any predictions about the parameters to be used in the study and because there were no reference studies in the literature that could be used to obtain the parameters, "medium effect size" described by Cohen was used during the calculations (23). The required sample size for the study was found as minimum 82, with an effect size of 0.30 for independent samples t-test to meet 80% of the test power at a confidence interval of 95%.

SPSS 20.0 (Statistical Package for Social Science) was used for the statistical analysis of the study. The normality distribution of the data was examined with the Shapiro-Wilk test. Mann-Whitney U test and chi-square test continuity correction were used respectively to analyse the quantitative and qualitative variables. While the quantitative variables were expressed as mean, standard deviation, median, minimum, and maximum values, qualitative variables were expressed as number-percentage (n %). The Mann-Whitney U test was used to compare the groups. $P<0.05$ was considered a significant level because of statistical analysis. The data were taken from the thesis entitled "Analysis of balance, reaction time, and concentration parameters of individuals previously infected with COVID-19" and they were analysed again for this study.

RESULTS

Out study was completed with 112 individuals, 56 (28 female, 28 male) individuals previously infected with COVID-19 and 56 (28 female, 28 male) individuals who were not previously infected with COVID-19, attending Zonguldak Bülent Ecevit University between January 2022 and May 2022. Table 1 shows the age, gender, height, cigarette-alcohol use, and chronic disease data of the COVID-19 group and control groups. No statistically significant difference was found between the groups in terms of these data according to the results of Mann-Whitney U test and chi-square test ($p<0.05$) (Table 1).

Table 2 shows the static and dynamic balance results of the participants. According to Mann-Whitney U test results, a statistically significant difference was found between the static and dynamic balance scores of the groups ($p<0.05$). Dynamic balance values of the groups are shown in Figure 1 with a radar graph, while static balance values are shown in Figure 2 with a bar graph.

Table 3 shows the body composition results of the participants. According to Mann-Whitney U test results, no statistically significant difference was found between the groups in terms of body composition parameters ($p>0.05$).

DISCUSSION

Although respiratory symptoms disappear after COVID-19 infection, significant deficiencies in daily living activities are observed in patients who are discharged. This condition is not only specific to elderly patients; it may also affect young individuals (24). Especially in patients with a chronic disease, there are long-term major sequelae called "post-intensive

care syndrome", which cause many physical disorders such as balance problems and muscle weakness (25). Many studies resulting from this condition emphasize the importance of rehabilitation problems to improve the quality of life after COVID-19 infection, to return to daily activities, and to eliminate post COVID-19 sequelae (26). In this study, when individuals previously infected with COVID-19 were compared with healthy controls, while no difference was found in terms of body composition values, it was found that individuals previously infected with COVID-19 had worse balance in terms of dynamic and static balance. In a study by Doğan (27) on 59 individuals between the ages of 20 and 30 who had been infected with COVID-19 at least three months ago and who had received home isolation and medication therapy, dynamic and static balance was evaluated with functional reach test and a single-leg standing test. According to the results of the evaluation, it was found that eyes open dynamic and static balance was affected significantly negatively in individuals previously infected with COVID-19, compared with the control group (27). Our study was conducted in the same age group, and although different balance evaluation methods were used, the same conclusions were reached. In this respect, it can be seen that our study supports this study.

In a study by Giardini et al. (26), which included 25 individuals with COVID-19 infection, 25 patients with acute exacerbation of chronic obstructive pulmonary disease, and 25 healthy individuals, static balance was evaluated with a stabilometric

Table 1. Sociodemographic characteristics of the participants and statistical analysis results between groups

Sociodemographic characteristics	COVID-19 group n=56	Control group n=56	p-value
Age (years) $\bar{x}$ ± s min-max	20.50±1.695 18-26	20.54±1.501 18-26	0.898**
Body weight (kg) $\bar{x}$ ± s min-max	68.59±14.56 47.60-111	65.32±13.91 44-107.20	0.259**
Height (cm) $\bar{x}$ ± s min-max	171.38±9.65 153-191	170.82±10.12 155-193	0.612**
Gender n (%) female/male	28 (50%)/28 (50%)	28 (50%)/28 (50%)	1.000*
Cigarette use, n (%) yes/no	12 (21.4%)/44 (78.6%)	9 (16.1%)/47(83.9%)	0.628*
Alcohol use, n (%) yes/no	15 (26.8%)/41 (73.2%)	10 (17.9%)/46 (82.1%)	0.364*
Chronic disease, n (%) yes/no	5 (8.9%)/51 (91.1%)	4 (7.2%)/52 (92.8%)	1.000*

*chi-square test continuity correction, **Mann-Whitney U test, $\bar{x}$ ± s: mean ± standard deviation, n: number, %: percentage, min: minimum value, max: maximum value, COVID-19: coronavirus disease-2019, p<0.05

Table 2. Static and dynamic balance results of the participants and statistical analysis results between the groups

	COVID-19 group (n=56) median (min-max)	Control group (n=56) median (min-max)	p-value
YBT-A (%) Reaching with the right foot Reaching with the left foot	 82.91 (58.82-106.94) 80.96 (52.32-111.11)	 86.97 (86.97-62.06) 86.09 (60-114.73)	 0.012* 0.032*
YBT-PL (%) Reaching with the right foot Reaching with the left foot	 91.29 (65.38-119.84) 87.82 (65.38-124.41)	 102.41 (65.85-134.95) 100.55 (68.29-136.84)	 0.001* 0.001*
YBT-PM (%) Reaching with the right foot Reaching with the left foot	 73.73 (46.05-102.38) 71.64 (51.31-97.75)	 84.36 (11.87-113.75) 81.25 (52.63-114.28)	 0.022* 0.001*
YBT total (%) Reaching with the right foot Reaching with the left foot	 79.95 (64.95-107.48) 80.42 (62.39-104.48)	 90.68 (64.63-115.80) 88.59 (65.44-121.40)	 0.025* 0.001*
FBT (score) Reaching with the right foot Reaching with the left foot	 7 (2-15) 8 (2-20)	 4 (0-9) 4 (0-11)	 <0.001* <0.001*

YBT: Y balance test, A: anterior, PL: posterolateral, PM: posteromedial, FBT: flamingo balance test, n: number, min: minimum value, max: maximum value, COVID-19: coronavirus disease-2019, p<0.05, *Mann-Whitney U test

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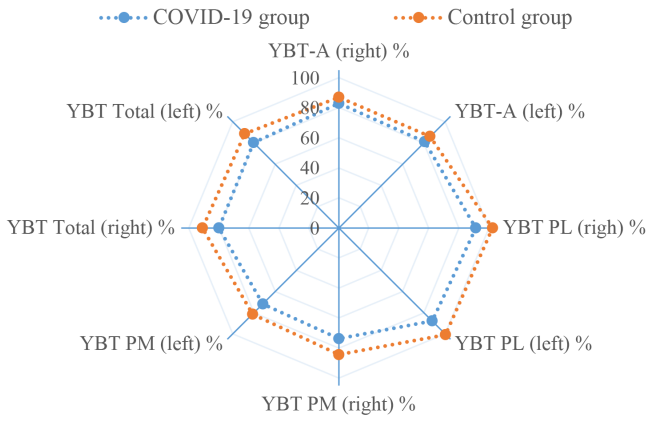

Figure 1. Comparison of Y balance test results of COVID-19 and control group with radar graph

YBT: Y balance test, A: anterior, PL: posterolateral, PM: posteromedial, COVID-19: coronavirus disease-2019

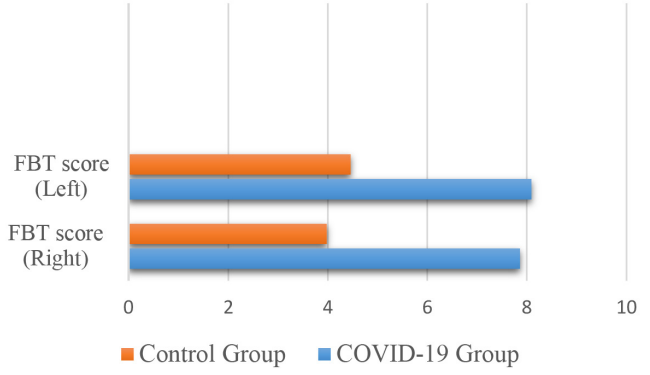

Figure 2. Comparison of flamingo balance test results of COVID-19 and control group with bar graph

FBT: flamingo balance test, COVID-19: coronavirus disease-2019

platform, while dynamic balance was evaluated with Mini-BESTest and Timed Up and Go test. Because of the study, it was found that both the static balance and dynamic balance performance of the group with previous COVID-19 infection were significantly worse compared with the other groups (26). Unlike our study, static and dynamic balance values were measured in individuals approximately 69.5 years old with a mean of 25.4 BMI. Additionally, although different evaluation methods were used, the results were found to be parallel to the results of our study.

In a study they evaluated whether there was a difference in post-COVID-19 syndrome-related balance and proprioception, Gervasoni et al. (28) analyzed the data of 66 post-COVID-19 patients prospectively. The dynamic balance of the participants was evaluated both eyes open and eyes closed with the innovative robotic device Hunova. Because of the study, it was stated that when vision, somatosensorial information, and vestibular information were integrated, post-COVID syndrome affected dynamic balance test performance negatively, regardless of the disease severity (28). In another study conducted, Sharpendromberg and Time Up and Go tests were used to evaluate static and dynamic balance and knee joint position sense in 15 women infected with COVID-19 and 15 healthy women. Because of the tests conducted, a significant difference was found between the static and dynamic balances of the two groups (COVID-19 and healthy group) ($p<0.05$) (29). In our study, dynamic and static balance levels of 56 individuals previously infected with COVID-19 were evaluated using the YBT and the FBT. Because of the evaluations, it was found that the COVID-19 group had worse static and dynamic balance performance compared with the control group. Although our methods for evaluating balance were different

Table 3. Body composition results of the participants and statistical analysis results between the groups

	COVID-19 group (n=56) median (min-max)	Control group (n=56) median (min-max)	p-value
BMR (kcal)	1474 (1156-2660)	1508 (1150-2312)	0.275*
BMI (kg/m²)	22.70 (16.70-31.90)	21.85 (17.20-30.30)	0.101*
IMPD (Ω)	655.50 (469-875)	640 (459-894)	0.272*
FAT (%)	22.20 (6.60-36.60)	18.85 (2.70-37)	0.268*
FFM (kg)	48.15 (35.40-86.70)	48.40 (36.50-76.70)	0.263*
TBW (kg)	35.25 (25.90-63.50)	35.45 (26.70-56.10)	0.256*
AFAT (%)	24.27 (9.50-40.20)	23.02 (8.60-40.95)	0.412*
LFAT (%)	25.75 (3.15-61)	22.20 (4.60-65.80)	0.330*
Trunk FAT (%)	20.15 (4.50-36.70)	18.85 (3-36.30)	0.222*
Muscle rate (%)	74.32 (60.17-89.26)	77.41 (59.97-92.79)	0.256*

BMR: basal metabolism rate, IMP: muscle resistance, FAT: body fat ratio, FFM: fat free mass in the body, TBW: total body fluid, AFAT: arm fat ratio, LFAT: leg fat ratio, n: number, min: minimum value, max: maximum value, COVID-19: coronavirus disease-2019, p<0,05, *Mann-Whitney U test

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from studies in the literature, results similar to those in the literature were obtained.

Measures such as quarantine, isolation and social distance caused decreased physical activity, deterioration in muscle mass and function and increase in body fat. These changes in the body composition are associated with a series of chronic conditions, including cardiovascular disease, diabetes, vulnerability, cognitive decline, and balance problems (30). Therefore, we think that the evaluation of body composition is an important issue to identify possible risk factors before and after COVID-19 infection.

When the literature was reviewed, it was found that a limited number of studies examining body composition in individuals previously infected with COVID-19 and studies were mostly conducted during the COVID-19 pandemic. In a study by Lemos et al. (31), the body composition of 171 volunteering individuals between the ages of 19 and 65 were measured with the bioelectrical method. The participants were grouped into three according to the severity of COVID-19 symptoms as non-hospitalized individuals with mild symptoms (n=61), those hospitalized (n=58) and those hospitalized in the intensive care (n=52). Because of the study, it was found that individuals who were hospitalized had significantly higher fat mass and body fat percentage values compared with individuals who were not hospitalized (31). In our study, when individuals previously infected with COVID-19 were compared with healthy controls in terms of body composition, no statistical difference was found. We believe that this difference may be because the participants were young and the fact that the individuals previously infected with COVID-19 had mild or moderate disease according to the guide prepared by the Turkish Republic Ministry of Health.

Study Limitations

Since the YBT ignores parameters such as sensor organization, motor adaptation, and rhythmic weight shifting, balance evaluations of the participants could be made in more detail by using technology-supported systems. While this situation was a limitation of our study, technology -assisted balance systems could not be used due to their high cost. Another limitation of our study is that the body composition gave indirect information about the physical activity levels of the participants, and the physical activity levels of the participants were not evaluated.

CONCLUSION

We found that although approximately 7-8 months had passed since the infection, young adults who had mild or moderate level of COVID-19 infection had worse static and dynamic balance levels than healthy individuals in the same age group. No significant difference was found between the groups in terms of body composition parameters. In line with these results, the fact that post - COVID-19 balance disorders were found even in individuals who had mild-moderate level of COVID-19 infection shows that providing balance training to individuals to prevent injuries and complications that may occur due to post-COVID-19 falls is an important topic in rehabilitation programs.

Ethics Committee Approval: Before the study, necessary permission (decision no: 2022/06, date: 23.03.2022) was obtained from Zonguldak Bülent Ecevit University Non-interventional Clinical Research Ethics Committee.

Informed Consent: Informed consent form was obtained from the participants.

Peer-review: Externally and internally peer-reviewed.

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The Effects of the COVID-19 Pandemic on Patients with Trauma Presented to the Emergency Department: A Multicentre Experience in İstanbul

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ABSTRACT

Objective: This study examines the characteristics of patients with trauma who presented to the emergency department before and after the novel coronavirus disease-2019 (COVID-19) pandemic and analyze the effects on the traumatic injuries.

Methods: In this study, medical records of patients who presented to the emergency departments of seven hospitals operating as tertiary level hospitals in İstanbul between March-June 2018, March-June 2019, and March-June 2020 are due to trauma were retrospectively analyzed. The clinical and demographic characteristics of traumatic injuries before and after the pandemic were compared.

Results: In our study, 4088 trauma patients' data were reviewed: 1279 in March-June 2018, 1684 in March-June 2019, and 1125 in March-June 2020. When the total number of patients was examined, it was noticed that the number of patients decreased significantly during the COVID-19 pandemic. No significant difference was found between the periods regarding the sex and trauma mechanisms of the patients. The mean age was higher in patients admitted in 2020 compared to previous years. In our study, incidences of intracranial hemorrhage, femur fracture, lung injuries, and mortality rates were higher in March-June 2020 compared to previous years.

Conclusion: In March-June 2020, compared to the previous year, there was a 34% decrease in trauma cases admitted to the emergency department. Albeit no difference was found between the periods regarding trauma mechanisms, the higher mortality in the March-June 2020 period indicates that trauma continues to be one of the major causes of death despite the pandemic.

Keywords: COVID-19, emergency, injuries, trauma

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INTRODUCTION

Despite increased trauma prevention measures and advances in post-trauma care, trauma-related deaths remain one of the main causes of mortality worldwide (1). Likewise, it has been reported that roughly 3% of all deaths in our country are due to trauma, and the most common cause of these deaths is motor vehicle accidents (2).

The coronavirus disease-2019 (COVID-19) pandemic, which broke out in December 2019 and spread worldwide in a short time, still continues to affect millions of people. Morbidity and mortality are attempted to be prevented through treatment strategies and widespread vaccination. Upon the declaration of COVID-19 as a pandemic by the World Health Organization, measures, such as lockdown, social isolation, or restriction of crowded organizations, were taken in many countries. Although the measures were reduced from time to time, these measures were repeated at the peak times of the outbreak. Social restrictions also decreased hospital admissions due to non-COVID-19 causes (3,4). In the literature, it has been reported that there is a decrease in acute coronary syndrome (5), stroke (6), orthopedic (7,8), and pediatric trauma (9) cases during the pandemic.

Similarly, in our country, it was seen that outpatient clinic applications other than COVID-19 decreased, and elective surgeries were postponed due to social isolation measures (3,10). However, the patient profile of the emergency departments diversified with the addition of COVID-19 cases. Although studies for certain disease prevalence have been revealed in the literature in this process, our study compares the demographic characteristics of patients with trauma who presented to seven different hospitals before and after the COVID-19 pandemic.

METHODS

This was a retrospective, multicenter, cross-sectional study, including 4088 patients with trauma who were admitted to University of Health Sciences Turkey, İstanbul Gaziosmanpaşa Training and Research Hospital, Haydarpaşa Numune Training and Research Hospital, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul Haseki Training and Research Hospital, Şişli Hamidiye Etfal Training and Research Hospital, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, and Kartal Dr. Lütfi Kırdar City Hospital Emergency Department. These seven centers where data was collected were tertiary trauma centers in İstanbul, the most populous city of Turkey, to which all age groups applied. Before conducting this study, ethical approval was obtained from the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (decision no: 133, date: 08.07.2020).

In our study, the period before and during the pandemic was divided into three periods as March-June 2018, March-June 2019, and March-June 2020. March-June 2018 and 2019 were the period when COVID-19 cases were not yet identified worldwide, while March-June 2020 was the period when a pandemic was declared worldwide and our country went into total closure. The medical records of the patients admitted to the above-mentioned centers due to trauma on these dates were reviewed retrospectively. Our inclusion criterion was to applied to the emergency department after having acute trauma in any age group. If the same patient presented to the emergency department more than once in the specified date range, only the first admission was taken into consideration. Patients who were transferred from another hospital to surgery, orthopedics, or another branch due to trauma were excluded from this study.

Age, sex, trauma mechanism, discharge, or hospitalization, and traumatic injuries of the patients were noted down from the hospital records, and the changes in trauma admissions during the pandemic were analyzed.

The primary outcome of our study was to analyze the effects of the COVID-19 pandemic on patients with trauma presented to the emergency department and its effects on trauma-related injuries. Our secondary outcome was to investigate the effects of the pandemic on traumatic deaths and discharges.

Statistical Analysis

Continuous data were presented with mean ± standard deviation and with frequency (n) and percentage (%) for the categorical data. The normality assumptions were controlled by the Shapiro-Wilk test. The association between categorical data was determined by Pearson chi-square and Fisher's Exact test. One-Way ANOVA was used to compare age among study groups, and the Tukey' s HSD (honestly significant difference) test was used as a post-hoc test for significant cases. Statistical analysis was conducted using the software of IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). A two-sided p-value less than 0.05 was considered statistically significant.

RESULTS

In our study, the data of 4088 patients with trauma, 2963 in the pre-COVID-19 period and 1125 in the March-June 2020 period, were analyzed. The mean age of patients who presented in March-June 2018 was 42.6±25.9 years, while it was 41.4±25.7 years for those in March-June 2019, and 44.1±25.1 years for those who applied in March-June 2020. The mean age of the patients who presented in 2020 was significantly higher than in 2019 (p=0.021) (Table 1). When we examined the number of trauma patients in the March-June periods of 2018, 2019, and 2020, it was noticed that the number of cases during the pandemic decreased by 34% compared to 2019. No significant difference was determined regarding the sex distribution of the patients by years (p=0.282). When we examined the trauma mechanisms according to 2018, 2019, and 2020, no significant difference was found between the trauma mechanisms of the patients who were admitted to the hospital in the same months before and during the pandemic (Table 2).

The incidence of finger amputation in 2020 (1.2%) was higher than in 2019 (0.4%) (p=0.034), whereas the incidence of shoulder

dislocation in 2020 (0.5%) was higher than in 2018 (0%) (p=0.022), and the incidence of other joint dislocations in 2018 (0.6%) was significantly higher than in 2020 (0%) (p=0.014). Motor accident (p=0.056), occupational accidents (p=0.095), and foot sprain (p=0.073) incidences were higher in 2020, and the incidences of falling off a bicycle (p=0.072) in 2019 were higher, yet the difference was not significant.

In our study, the incidence of intracranial hemorrhage in 2020 (13%) was higher than in 2018 (9.7%) (p=0.021), whereas the incidence of lumbar vertebral fracture in 2019 (2.8%) was higher than in 2020 (1.4%) (p=0.049). The incidence of hemothorax in 2020 (3.1%) was higher than that in 2018 (1.6%) and 2019 (1.8%) (p=0.026). The lung contusion incidence in 2020 was 5.6%, which was higher than in 2018 (1.3%) and 2019 (2.6%) (p<0.001). The incidence of intestinal perforation (1.3%) was significantly higher in 2018 than 2019 (0.1%) and 2020 (0.4%) (p<0.001). While the incidence of urinary bladder injury in 2020 (0.7%) was higher than in 2018 (0.1%) (p=0.033), the incidence of intra-abdominal fluid in 2020 (4.1%) was higher than in 2018 (2.1%) and 2019 (2%) (p=0.001), the soft tissue injury rate in 2018 (15.8%) was higher (p=0.021) than in 2019 (12.4%), and the incidence of simple cuts or abrasions (17.9%) in 2020 was higher than in 2018 (12.2%) and 2019 (12.5%) (p<0.001). When the distribution of fracture types by years was analyzed, the incidence of costal fracture (3.6%) in 2019 and 2020 was higher (p<0.001) than in 2018 (p<0.001), whereas the rate of radius fracture and hand phalanx fracture (8.6% and 3.6%) in 2019 were higher (p=0.005 and p=0.030, respectively) than in 2020 (5.5% and 2%). The incidence of femoral fractures in 2020 (22%) was higher than in 2019 (17.5%) (p=0.009). The incidence of muscle tears in 2019 (3.1%) was significantly higher than in 2018 (1.6%), whereas the rate of other tears in 2018 (9.4%) was significantly higher than in 2019 (5.5%) and 2020 (6%) (p=0.011 and p<0.001) (Table 3). The rate of patients who died in 2020 (4.3%) was significantly higher than in 2018 (2.1%) and 2019 (2.4%) (p=0.003). In 4052 patients who were negative for COVID-19, the exitus rate (3.6%) in 2020 was higher than in 2018 (2.1%) (p=0.037). While 72.2% of the 36 patients with COVID-19 polymerase chain reaction (PCR) positive were discharged and 2.8% were referred, 25% were exitus (Table 4).

DISCUSSION

In our study, we determined that there was a 34% decrease in trauma cases admitted to the emergency department in the March-June 2020 period compared to the previous year. Besides, no significant difference was determined between the mentioned periods regarding trauma mechanisms. However, we found a higher post-traumatic death rate during the pandemic.

Table 1. Demographic characteristics

Demographics	2018 (n=1279)	2019 (n=1684)	2020 (n=1125)	p-value
Sex, n (%)				
Female	470 (36.7)	581 (34.5)	381 (33.9)	0.282
Male	809 (63.3)	1103 (65.5)	744 (66.1)	
Age (years), mean ± SD	42.6±25.9[a,b]	41.4±25.7[a]	44.1±25.1[b]	**0.021**

SD: standard deviation, HSD: honestly significant difference
Pearson chi-square test. One-Way ANOVA with post-hoc Tukey HSD test. Same letters in a row denote the lack of statistically significant difference

Table 2. Mechanism of injury

Mechanism, n (%)	2018 (n=1279)	2019 (n=1684)	2020 (n=1125)	p-value
Motor vehicle accident	102 (8)	110 (6.5)	74 (6.6)	0.254
Auto versus pedestrian	190 (14.9)	243 (14.4)	149 (13.2)	0.507
Motorcyle accident	61 (4.8)	106 (6.3)	79 (7)	0.056
Fall from high place	125 (9.8)	178 (10.6)	113 (10)	0.766
Stab wound	48 (3.8)	62 (3.7)	50 (4.4)	0.557
Firearm injuries	32 (2.5)	58 (3.4)	42 (3.7)	0.189
Bicycle accident	23 (1.8)	33 (2)	10 (0.9)	0.072
Burn	8 (0.6)	4 (0.2)	8 (0.7)	0.127
Blunt assault	56 (4.4)	61 (3.6)	45 (4)	0.578
Industrial injury	34 (2.7)	65 (3.9)	47 (4.2)	0.095
Ingress of foreign body	12 (0.9)	17 (1)	14 (1.2)	0.745
Limb impingement	1 (0.1)	2 (0.1)	2 (0.2)	0.863
Suicide	2 (0.2)	0 (0)	0 (0)	0.174

Pearson chi-square test, Fisher's Exact test

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The decrease in trauma cases during the pandemic period may be due to the decrease in traumatic injuries because of the social restrictions and lockdown mandates, or because patients after minor trauma did not apply to hospitals for fear of COVID-19 contamination. Similar to our study, Hartnett et al. (11) compared March 29-April 25, 2020 with March 31-April 27, 2019, and found that there was a 42% decrease in the department of emergency admissions. İlhan et al. (12), in their single-center study, revealed a 60% decrease in trauma admissions during the pandemic. In another study compared before and after lockdown, it was shown that post-traumatic hospitalization decreased by 30.9% during the lockdown period (13). In another study conducted with 618 patients, it was stated that the need for open surgery increased in the pandemic period compared with the pre-pandemic period, although a 25% decrease was detected in the patients who applied to the emergency department for surgical reasons during the pandemic period (10). In the study investigating the injury-related hospitalization of 21 hospitals between March 15-April 30, 2016-2020, it was shown that hospitalization decreased by 26% during the lockdown period (14).

Table 3. Diagnoses per year

Main diagnosis, n (%)	2018 (n=1279)	2019 (n=1684)	2020 (n=1125)	p-value
Cranial fracture	138 (10.8)	204 (12.1)	116 (10.3)	0.283
Intracranial hemorrhage	124 (9.7)[a]	172 (10.2)[a.b]	146 (13)[b]	0.021
Cervical vertebral fracture	11 (0.9)	9 (0.5)	13 (1.2)	0.191
Thoracic vertebral fracture	24 (1.9)	29 (1.7)	18 (1.6)	0.873
Lumbar vertebral fracture	27 (2.1)[a.b]	47 (2.8)[a]	16 (1.4)[b]	0.049
Thoracic injury	39 (3)[a]	82 (4.9)[b]	87 (7.7)[c]	<0.001
Hemothorax	21 (1.6)[a]	31 (1.8)[a]	35 (3.1)[b]	0.026
Pneumothorax	25 (2)	54 (3.2)	31 (2.8)	0.112
Lung contusion	17 (1.3)[a]	43 (2.6)[a]	63 (5.6)[b]	<0.001
Costal fracture	13 (1)[a]	60 (3.6)[b]	41 (3.6)[b]	<0.001
Cardiac injury	5 (0.4)	2 (0.1)	0 (0)	0.064
Great vessel injury	8 (0.6)	11 (0.7)	6 (0.5)	0.936
Internal organ injury	56 (4.4)	61 (3.6)	52 (4.6)	0.371
Liver injury	18 (1.4)	16 (1)	10 (0.9)	0.379
Spleen injury	11 (0.9)	19 (1.1)	9 (0.8)	0.624
Intestinal perforation	16 (1.3)[a]	1 (0.1)[b]	4 (0.4)[b]	<0.001
Kidney injury	8 (0.6)	7 (0.4)	2 (0.2)	0.236
Urinary bladder injury	1 (0.1)[a]	5 (0.3)[a.b]	8 (0.7)[b]	0.033
Intra-abdominal free fluid	27 (2.1)[a]	34 (2)[a]	46 (4.1)[b]	0.001
Simple incisions/graze	156 (12.2)[a]	211 (12.5)[a]	201 (17.9)[b]	<0.001
Orthopedic fracture	910 (71.1)	1231 (73.1)	813 (72.3)	0.502
Humeral fracture	103 (8.1)	162 (9.6)	97 (8.6)	0.314
Ulna fracture	70 (5.5)	76 (4.5)	44 (3.9)	0.182
Radius fracture	83 (6.5)[a.b]	144 (8.6)[a]	62 (5.5)[b]	0.005
Metacarpal bone fracture	28 (2.2)	33 (2)	29 (2.6)	0.549
Hand phalanx fracture	30 (2.3)[a.b]	60 (3.6)[a]	23 (2)[b]	0.030
Pelvic fracture	98 (7.7)	134 (8)	86 (7.6)	0.938
Femur fracture	258 (20.2)[a.b]	294 (17.5)[a]	248 (22)[b]	0.009
Tibia fracture	182 (14.2)	252 (15)	162 (14.4)	0.837
Fibula fracture	71 (5.6)	112 (6.7)	87 (7.7)	0.099
Metatarsal fracture	42 (3.3)	49 (2.9)	45 (4)	0.286
Foot phalanx fracture	20 (1.6)	27 (1.6)	21 (1.9)	0.819
Muscle tears	20 (1.6)[a]	53 (3.1)[b]	22 (2)[a.b]	0.011
Other fractures	120 (9.4)[a]	92 (5.5)[b]	68 (6)[b]	<0.001

Pearson chi-square test, Fisher's Exact test. Same letters in a row denote the lack of statistically significant difference

Regarding the trauma mechanisms, Chiba et al. (15) found a 38.7% reduction in motorcycle accidents, a 42.5% reduction in auto versus pedestrian accidents, and a 28.4% reduction in bicycle accidents. However, they did not report a significant reduction in motor vehicle accidents during the pandemic (15). Besides, DiFazio et al. (16) reported a 75% reduction in motor vehicle accidents and a 28.9% reduction in falls, along with a 44.9% reduction in trauma admissions during the lockdown period of the pandemic. Moreover, İlhan et al. (12) detected a significant decrease in pedestrian injuries during the pandemic. On the other hand, in our study, unlike these studies, the trauma mechanism was similar in the specified periods of all three years. Albeit a significant decrease in traumatic injuries was an expected finding during the pandemic, it was remarkable for us that the trauma mechanism did not change. The reason for this may be that although there are social restrictions and lockdown, a substantial group, such as people with special work permits or motor couriers, is exempt from these bans. Additionally, although the decrease in the number of vehicles on the road relieves Istanbul traffic, the trauma mechanism may not change compared to previous years due to the use of vehicles at higher speeds on relatively empty roads. When we examined the traumatic injuries in our study, the fact that intracranial bleeding, hemothorax, lung contusion, intestinal perforation, urinary system injury, free fluid in the abdomen, soft tissue injury, rib fracture, and femur fracture were detected more frequently in the March-June 2020 period compared to previous years support the exposure to high-energy trauma during the pandemic period. Hence, we consider that the enforcement of traffic rules and raising public awareness about traumas are of considerable importance even during lockdown periods.

Chiba et al. (15) revealed that mortality decreased during the lockdown period compared with the previous year. On the other hand, Yasin et al. (17) showed that mortality was higher during the pandemic period in their study, in which they included 750 road traffic collision patients during the pre-COVID-19 period and 499 road traffic collision patients during the COVID-19 period. Likewise, when we looked at the post-traumatic death rates in our study, there was a significant increase in the death rate in 2020. The reason for this may be the occurrence and mortality of high-energy traumatic injuries at higher speeds in reduced traffic. Furthermore, a more elective approach to the patients due to the pandemic and the waiting for the PCR results for the operation during the pandemic might increase the mortality.

Study Limitations

The current study has some limitations. First, it was a retrospective study and therefore, some data were not available. Trauma scores could not be calculated due to missing data. Although we showed that some injuries were more common in the COVID-19 period in our study, we could not compare the trauma scores with the pre- and post-COVID-19 periods. Second, although we conducted a multicenter study, regional studies with larger participation are needed to analyze the effects of the COVID-19 pandemic and social isolation on trauma.

CONCLUSION

In line with the literature, lockdown and social isolation measures mandated in many countries due to the pandemic resulted in a remarkable decrease in the number of traumas admitted to hospitals in our country. However, when we examined the trauma mechanism during the lockdown, there was no significant change compared with the previous years, but the mortality rate was higher, especially with intracranial hemorrhage, femur fracture, and lung injuries. These findings indicate that trauma remains one of the major causes of death despite the pandemic. Thus, it supports the significance of planning trauma care and necessary

Table 4. Recent outcome of patients by year

Outcome n (%)	2018 (n=1279)	2019 (n=1684)	2020 (n=1125)	p-value
All patients (n=4088)				
Discharge	1238 (96.8)[a]	1633 (97)[a]	1072 (95.3)[a]	0.003
Referral to another hospital	14 (1.1)[a]	10 (0.6)[a]	5 (0.4)[a]	
Exitus	27 (2.1)[a]	41 (2.4)[a]	48 (4.3)[b]	
COVID-19 PCR negative patients (n=4052)				
Discharge	1238 (96.8)[a]	1633 (97)[a]	1046 (96.1)[a]	0.037
Referral to another hospital	14 (1.1)[a]	10 (0.6)[a]	4 (0.4)[a]	
Exitus	27 (2.1)[a]	41 (2.4)[a.b]	39 (3.6)[b]	
COVID-19 PCR positive patients (n=36)				
Discharge	-	-	26 (72.2)	-
Referral to another hospital	-	-	1 (2.8)	
Exitus	-	-	9 (25)	

COVID-19: coronavirus disease-2019, PCR: polymerase chain reaction
Pearson chi-square test, same letters in a row denote the lack of statistically significant difference

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measurements in today's peak day of COVID-19 and a likely new lockdown period to prevent mortality.

Ethics Committee Approval: Before conducting this study, ethical approval was obtained from the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (decision no: 133, date: 08.07.2020).

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Investigation of the Effect of Low-positive HER-2 on Neoadjuvant Chemotherapy Response in Hormone-positive Breast Cancer Patients

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ABSTRACT

Objective: Recently, it has been suggested that low-positive human epidermal growth factor receptor-2 (HER-2) is a separate group of breast cancer. We examined the effect of low-positive HER-2 on neoadjuvant chemotherapy (NACT).

Methods: This retrospective study included female patients aged >18 years who were diagnosed with histologically proven breast cancer between January 1, 2016, and January 1, 2020, and had breast surgery after NACT. Patients with triple-negative, estrogen receptor (<10%) weak positive, HER-2 immunohistochemical (IHC) scores 3+ or 2+/FISH-positive patients, and metastatic patients were excluded. Pathological complete response (pCR) was defined as the no invasive and *in situ* residue in the breast and lymph nodes in surgery after NACT.

Results: One hundred twenty seven patients were included in this study. HER-2 IHC-score "0" patients were 55 (43.3%), "1+" patients were 52 (40.9%), and "2+" patients were 20 (15.7%). Nine (7.1%) patients showed a complete response to NACT. In the univariate analysis with clinicopathological variables of the patients to predict the complete response to NACT; estrogen receptor [odds ratio (OR): 0.97, 95% confidence interval (CI): 0.96-0.99, p=0.012], Ki-67 (OR: 1.12, 95% CI: 1.06-1.18, p<0.001), tumor grade (OR: 0.036, 95% CI: 1.13-30.36, p=0.036), and lymphovascular invasion (OR: 0.11, 95% CI: 0.01-0.93, p=0.043) showed the predictive features. In the multivariate analysis, Ki-67 (OR: 1.10, 95% CI: 0.04-1.17, p=0.001) was found to be an independent predictor of pCR.

Conclusion: We determined that the low-positive-HER2 group has no effect on the treatment response in patients treated with NACT. We found that Ki-67 was an independent predictive for pCR.

Keywords: Breast cancer, neoadjuvant chemotherapy, low-positive HER-2

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer worldwide, excluding skin cancer, and is the leading cause of cancer related mortality in women (1). In developed countries, the majority of newly diagnosed breast cancer patients are diagnosed at an early or locally advanced stage. Early-stage breast cancer patients are usually treated with primary surgery (lumpectomy or mastectomy), whereas some early-stage patients with human epidermal growth factor receptor-2 (HER-2) positive or triple-negative molecular features and locally advanced breast cancer patients are managed with multimodal therapy combining systemic and locoregional therapies (2). Achieving pathological complete response (pCR) with neoadjuvant chemotherapy (NACT) is a strong predictor of treatment response and can be considered a surrogate marker of treatment efficacy. Early identification of features that can predict the pCR may allow a better selection of patients who will benefit from treatment and may protect the patient from potentially ineffective treatments. In many meta-analyses, prognostic improvement in pCR to neoadjuvant therapy has been reported, especially in tumors with aggressive behavior such as HER-2-positive or triple-negative (3-5).

Neoadjuvant therapy for hormone receptor (HR)-positive and HER-2-negative breast cancer is considered for women with larger tumors and/or locally advanced breast cancer. Well-differentiated tumors with low proliferation rate and HR expression are less likely to obtain a pCR after NACT (6). However, in these well-differentiated slowly proliferating tumors, a relatively poor response to treatment was not associated with a poor prognostic response (7). In clinical practice, HER-2 immunohistochemical (IHC) scores 0, 1+, or IHC 2+/ FISH-negative patients are classified as HER-2-negative by IHC staining methods. However, recently Schettini et al. (8) reported that patients with low-positive HER-2 breast cancer (HER-2 1+ by IHC or HER-2 2+/FISH negative) may be a distinct group. In the Destiny-Breast04 study, trastuzumab deruxtecan, an antibody-chemotherapy conjugate, was shown to provide a progression-free survival and the overall survival advantage in hormone-positive and negative subgroups compared with chemotherapy (physician choice) in low-positive HER-2-positive disease who had previously received chemotherapy (9). Future improvements in the prognosis of the HR-positive/HER-2-negative patient group with new treatments, and the identification of predictors that will affect the pCR that can be achieved with currently existing clinicopathological features have gained importance again.

In this study, in hormone-positive patients, we investigated the effect of HER-2 IHC scores 0, 1+, and 2+/FISH-negative breast cancer for pathologic complete response to NACT and we aimed to determine the other clinicopathological features that may predict pCR.

METHODS

In this retrospective study, high-risk female patients (with axillary nodal involvement) over the age of 18 who were diagnosed with histologically proven breast cancer between January 1, 2016, and January 1, 2020, and had breast surgery after NACT were included. Patients with triple-negative, estrogen receptor (<10%) weak positive, HER-2 IHC 3+ or HER-2 IHC 2+/FISH-positive patients, and metastatic patients were excluded. Patients received standard 4 cycles of cyclophosphamide (600 mg/m^2) and epirubicin (90 mg/m^2) every 3 weeks, followed by weekly paclitaxel (80 mg/m^2) for 12 weeks or 4 cycles of docetaxel (75 mg/m^2) every 3 weeks as NACT. Estrogen receptor and progesterone receptor expression and HER-2 status of tumors were obtained from the results of immunohistochemistry or fluorescent *in situ* hybridization in breast cancer tissue obtained by core needle biopsy before NACT. pCR was defined as the no invasive and *in situ* residue in the breast and lymph nodes in surgery after NACT. Patients' clinicopathologic features such as age, HR expression, HER-2 status, histological type, lymphovascular invasion (LVI), grade, and pre-operative tumor diameter were obtained from the hospital medical electronic record system. The study was approved by the Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (protocol no: 2020.238.10.06, date: 27.10.2020).

Statistical Analysis

SPSS version 26.0 (SPSS Inc., Chicago, III) was used for all statistical analyses. Continuous variables are represented with the median and range. Categorical variables were summarized using frequency and percentage. Univariate and multivariate analysis with a logistic regression model were applied to predict pCR. P<0.05 was considered statistically significant.

RESULTS

Clinical Features of the Patients

One hundred twenty seven patients were included in this study. The median age of the patients was 50 (28-73). While 104 patients (81.9%) had invasive ductal histology, 5 patients (3.9%) had invasive lobular histology. The median Ki-67 percentage, estrogen receptor expression rate, and progesterone receptor expression rate were 25%, 95%, and 40%, respectively. HER-2 IHC scores: the number of "0" patients were 55 (43.3%), "1+" patients were 52 (40.9%), and "2+" patients were 20 (15.7%). While 64 patients (50.4) had grade 2 tumors, 33 patients (26%) had grade 3 tumors. The number of LVI-positive patients was 62 (48.8%). Nine (7.1%) patients showed a complete response to NACT (Table 1).

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Univariate and Multivariate Analysis

In the univariate analysis with clinicopathological variables of the patients to predict the complete response to NACT; estrogen receptor expression [odds ratio (OR): 0.97, 95% confidence interval (CI): 0.96-0.99, p=0.012], Ki-67 (OR: 1.12, 95% CI: 1.06-1.18, p<0.001), tumor grade (OR: 0.036, 95% CI: 1.13-30.36, p=0.036), and LVI (OR: 0.11, 95% CI: 0.01-0.93, p=0.043) showed the predictive feature (Table 2).

In the multivariate analysis with variables found to be significant in the univariate analysis, Ki-67 (OR: 1.10, 95% CI: 0.04-1.17, p=0.001) was found to be an independent predictor of pCR (Table 3).

DISCUSSION

In this study, we investigated the effect of low-positive HER-2 in predicting a complete response to NACT in patients with hormone-positive breast cancer. We found that patients with HER-2 scores "0", "1+" and "2+" had no effect on complete response to NACT. In univariate analysis with other clinicopathological factors: estrogen receptor, Ki-67, tumor grade and LVI were found to be predictive for pCR. In the multivariate analysis, Ki-67 was determined as an independent predictor of pCR.

Table 1. Clinical-pathological characteristics

	n	%
Age		
>50	56	44.4
≤50	71	55.6
Histological type		
Invasive ductal	104	81.9%
Invasive lobular	5	3.9%
Others	18	14.2%
Estrogen receptor	95*	10-100**
Progesterone receptor	40*	1-100**
Ki-67	25*	1-80
HER-2		
0	55	43.3
1+	52	40.9
2+	20	15.7
Grade		
Grade 1	8	7.6
Grade 2	64	50.4
Grade 3	33	26
LVI	16.0%	21
Positive	62	48.8
Negative	63	48.9
Clinical tumor diameter		
T1	26	20.5
T2	91	71.7
T3	8	6.3
T4	2	1.5
Pathological complete response	9	7.1

HER-2: human epidermal growth factor-2, LVI: lymphovascular invasion, *median, **range

Denkert et al. (10), in the pooled data analysis of 4 different prospective studies, suggested that low-positive HER-2-positive breast cancer is a separate subgroup from the HER-2 IHC score "0" tumors with clinicopathological features such as hormone positivity and complete response rates to treatment. Shao et al. (11), in their study that included triple-negative and hormone-positive HER-2 IHC score "0" and low-positive HER-2 patients showed that HER-2 score "0" and "low" was an independent predictor for pCR in both the hormone-positive and triple-negative group. Our study showed that HER-2 IHC scores "0" and "low" positivity had no predictive effect on pCR in patients that including only hormone-positive tumors.

The Ki-67 labeling index appears to be a useful marker to identify high-risk patients in hormone-positive/HER-2-negative breast cancer. Measurement of Ki-67 as a marker of cell proliferation has been reported to be associated with the response to therapy in previous studies (12-14). Kim et al. (15), in their study on patients receiving anthracycline-based NACT, determined the 25% cut-off value for Ki-67 as a predictor of pCR. In another study, Jain et al. (16) showed that Ki-67 and high-grade tumors are markers that predict pCR. However, the relationship between pCR and prognosis in hormone-positive tumors is unclear, and markers that will replace the prognosis are being investigated. In line with the literature, in our study, the Ki-67 proliferation index was found to be an independent predictor of pCR.

Estrogen receptor expression, as Ki-67, is also seen as a predictor for pCR in studies. In a study, it was reported that estrogen level predicts a complete response in the nomogram model established for pCR (17). In another study, it was shown that estrogen positivity has an impact on pCR (18). In our study, estrogen receptor level was associated with pCR.

Study Limitations

Our study had some limitations. First, the study was designed retrospectively. Morover, the number of patients is relatively low according to the other studies investigating pCR, especially the number of patients with an HER-2 IHC score 2+. The strength of our study is that patients with aggressive tumors such as triple-negative and HER-2-positive with known strong associations with pCR were excluded, and patients with only hormone-positive were included.

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Table 2. Univariate analysis of factors predicting pathological response

		Univariate analysis	
Variable	**Category**	**OR (95% CI)**	**p-value***
Age	≤50/>50	1.02 (0.26-3.97)	0.982
Histological type	Ductal/lobuler/other	0.78 (0.26-2.38)	0.061
Estrogen receptor	Continuous	0.97 (0.96-0.99)	**0.012**
Progesteron receptor	Continuous	0.99 (0.97-1.01)	0.399
Ki-67	Continuous	1.12 (1.06-1.18)	**<0.001**
HER-2	0/1+/2+	2.16 (0.85-5.46)	0.104
Grade	1/2/3	5.84 (1.13-30.36)	**0.036**
Tumor diameter	T1/T2/T3/T4	0.93 (0.85-1.02)	0.135
LVI	Positive/negative	0.11 (0.01-0.93)	**0.043**

HER-2: human epidermal growth factor-2, LVI: lymphovascular invasion, OR: odds ratio, CI: confidence interval, *significant values are indicated bold

Table 3. Multivariate analysis of factors predicting pathological response

Variable	Category	OR (95% CI)	p-value[f]
Estrogen receptor	Continuous	-	-
Ki-67	Continuous	1.10 (1.04-1.17)	0.001
Grade	1/2/3	-	-
LVI	Positive/negative	-	-

[f]forward:LR method, LVI: lymphovascular invasion, OR: odds ratio, CI: confidence interval

CONCLUSION

As a result, in hormone-positive breast cancer, we determined that the low-positive HER-2 group has no effect on the treatment response in patients treated with NACT. On the other hand, we found that Ki-67, estrogen receptor, LVI, and tumor grade were predictive for pCR.

Ethics Committee Approval: The study was approved by the Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (protocol no: 2020.238.10.06, date: 27.10.2020).

Informed Consent: Retrospective study.

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Determination of Physical Activity Level, Functional Capacity and Depression in Children with Digital Game Addiction

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ABSTRACT

Objective: The aim of this study was to determine the physical activity level, functional capacity, and depression in children with digital game addiction (DGA).

Methods: Ninety-nine children (mean age: 10±1.53 years) with DGA were included in the study. Demographic, physical, and clinical characteristics were recorded. DGA was evaluated using the Digital Game Addiction Scale for Children, physical activity level with the Primary School Students' Physical Activity Questionnaire, functional capacity with the 2-Minute Walk test, and depression with the Depression Scale for Children.

Results: Of the children, 17.2% were in the low-risk group, 41.4% were in the risky group, 26.3% were in the dependent group, and 15.2% were in the highly dependent group. DGA had a high negative correlation with physical activity level ($r=-0.659$; $p=0.001$), a weak positive correlation with depression ($r=0.342$; $p=0.001$), but no correlation with functional capacity ($p>0.05$). Simultaneously, it was found that physical activity and depression were found to be independent factors of the DGA with 43.4% of the variance. Additionally, a significant difference was found in terms of physical activity level and depression in children with DGA at different levels ($p<0.05$).

Conclusion: In this study, a negative relationship was found between DGA and physical activity level, and a positive relationship with depression. It is important to raise the awareness of children and families about DGA. Additionally, children can be directed to various exercise programs to increase physical activity levels and reduce depression associated with DGA.

Keywords: Dependency, exercise, child, depression, physical activity, physical capacity

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INTRODUCTION

Digital game addiction (DGA) is defined as children's desire to play games in digital environments (such as computers, game consoles, mobile phones, and tablets), not being able to limit the duration of the game, considering digital gaming as their primary job, and avoiding daily life responsibilities (1). It is seen that the prevalence of DGA varies between 0.6% and 15% (2,3).

It is stated that DGA may be associated with a lack of reward and that the mesocorticolimbic pathway and dopamine play an important role in addiction (4). If people are addicted, there is an increase in the production of dopamine, which is responsible for the pleasure and reward systems in the brain, and the insufficiency of dopamine receptors leads the person to the addicted substance/behavior (5). DGA can cause many negative consequences such as physical inactivity, obesity, headache, and aggressive and anti-social behavior (6-8). However, the effects of DGA on children's health are still largely unexplored (9).

Physical activity is defined as body movement performed by skeletal muscles using energy (10). Some studies have stated that there is no significant relationship between DGA and physical activity levels (9,11). However, there are also studies in the literature indicating that the level of physical activity decreases with the increase in DGA (12,13). Based on these contradictory results, we believe that more studies are needed to investigate the relationship between DGA and physical activity level. The functional capacity is expressed as the ability of individuals to conduct activities in daily life independently and is often used synonymously with exercise capacity and exercise tolerance (14). To the best of our knowledge, there exists no study investigating DGA and functional capacity in children.

DGA can also cause psychological problems such as loneliness, depression, anxiety, tendency to violence, attention deficit, and a decrease in positive social behavior (15-17). Examination of DGA and intervening in this situation will be beneficial for people's mental health. Depression is a common type of psychological disorder in society and indicates abnormal emotional states such as sadness and distress (18). When the literature is examined, studies investigating the relationship between the type of digital games and psychosocial and behavioral problems stand out (15,19,20). Studies investigating the depression in children with DGA are needed.

Therefore, the aim of this study was to investigate the relationship between DGA and physical activity level, functional capacity, and depression in children and to compare these parameters in children with different levels of DGA. The hypothesis of the study is that there is a relationship between DGA and physical activity level, functional capacity, and depression in children, and there are differences between these parameters in children with different levels of DGA.

METHODS

Study Design

This cross-sectional and descriptive study was approved by the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (decision no: 128, date: 05.10.2022). The study was conducted in October and November 2022 in accordance with the Declaration of Helsinki. After the study was explained to the participants and their families who met the inclusion and exclusion criteria and volunteered to participate in the study, the 'Informed Consent Form' was signed. Participants in the study were evaluated by the same specialist physiotherapist.

Participants

This study was performed out in children and their siblings presented to the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Child and Adolescent Psychiatry Clinic. Volunteering to participate and being 6-14 years old were the inclusion criteria. To have an orthopedic, neurological, or rheumatologic problem that may prevent physical activity, to have a chronic disease, to have vision and hearing loss, and to have cognitive or mental problems were the exclusion criteria. Written informed consent was obtained from the children participating in the study and their parents.

Evaluations

Demographic and physical characteristics of the children were collected face-to-face. In the evaluation form, age (year), gender, body mass index, diagnoses, education level, mother's education level, father's education level, digital gaming duration, and tool used for playing digital games were questioned.

DGA was evaluated using the Turkish version of the "Digital Game Addiction Scale for Children". The scale consisted of 24 items. It consists of 4 sub-factors: excessive focus and conflict toward digital gaming, development of tolerance for playtime and the value attributed to the game, postponing individual and social tasks/homework, psychological-physiological reflection of deprivation, and immersion in the game. A 5-point Likert-type scale was used to evaluate the expressions on the scale (1= Absolutely Disagree, 2= Disagree, 3= Undecided, 4= Agree, 5= Completely Agree). In this scale, a total score of 1-24 indicates normal-risk groups, a score of 25-48 indicates low-risk groups, a score of 49-72 indicates risky groups, a score of 73-96 indicates dependent groups, and a score of 97-120 indicates highly dependent groups (12).

Physical activity level was evaluated using the Turkish version of the "Primary School Students' Physical Activity Questionnaire" There are 10 items (the 10th item is excluded from the evaluation) in the form that questions the physical activity level of children in the previous week. The first item covers 21 activities, and each activity is scored between 1 and 5 according to the frequency of performing it. Items 2-8 question the frequency of physical activities at school, during break times, in the evening, and on weekends, and item 9 evaluates the frequency of physical activity.

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The total score was evaluated between 5 and 45. According to this scoring, children are classified as inactive/sedentary (5 points), low active (15 points), moderately active (20-25 points), active (35 points), and highly active (45 points) (18).

The 2-Minute Walk test (2MWT) was used to evaluate the functional capacity. According to this test, the children were asked to walk quickly (without running) and they were also instructed that they could stop in case of need, but the time would not be stopped. At the end of the time, the distance the children walked was recorded in meters. The 2MWT is a valid and reliable test for children (21).

Depression in children was evaluated with the Turkish version of the "Depression Scale for Children" (22). There are 27 items (3 statements for each item) in the scale. While marking the options, the children were asked to consider their experiences in the previous 2 weeks. The score that can be obtained from the scale varies between 0 and 54, and the cut-off point is 19 points. As the score obtained from the scale increased, the level of depression increases (22).

Statistical Analysis

In this study, the sample size was determined by the effect size calculated over the correlation values between children's DGA and physical activity levels. When the studies in the literature (12) were examined, it was seen that the effect size of the relationship was ρ=0.35. Accordingly, it was determined that 99 children should be included in the study to obtain 95% power with α=0.05 type I error and β=0.05 type II error. The sample size was calculated with the G*Power (Ver. 3.0.10, Franz Faul, Universität Kiel, Germany) package program.

A Pearson chi-square or Fisher's Exact test comparison test was used for the relationships between categorical variables. The Shapiro-Wilk test was used to evaluate whether the data were suitable for normal distribution. Relationships between quantitative variables were examined using the Pearson product-moment correlation test. Correlation coefficients >0.5 were considered a strong correlation; 0.3 to 0.5 was considered a moderate correlation; and 0.2 to 0.3 was considered a weak correlation. The stepwise multiple linear regression analysis was used to determine the variables that have the greatest influence on DGA. Significantly correlated variables with DGA were included in the regression model. Additionally, the regression equation formula of the study was also calculated. Cook's distance and centered leverage value were used to identify and treat outliers. A comparison of normally distributed DGA groups was performed with One-Way analysis of variance (ANOVA) and least significant difference multiple comparison tests. Within the scope of descriptive statistics, mean ± standard deviation was used for numerical variables, number and % values were used for categorical variables. Statistical analysis was performed using the SPSS Windows version 24.0 package program. Any p-value less than 0.05 was considered statistically significant.

RESULTS

Within the scope of the study, 105 children were reached. Six children were excluded because they did not meet the inclusion criteria. The study was performed out with a total of 99 children (Figure 1). The demographic and physical characteristics of the children are shown in Table 1. Of the children, 57 (57.6%) were males and 42 (42.4%) were females. The mean age was 10±1.53 years. According to the DGA scores, 17 (17.2%) children were in the low-risk group, 41 (41.4%) were in the high-risk group, 26 (26.3%) were in the addicted group, and 15 (15.2%) were in the highly dependent group. The mean score of DGA in children was 68.42±20.65; the mean physical activity score was 24.35±7.37; the mean depression score was 23.77±6.09, and the mean walking distance for 2 minutes was 185.21±16.27 m (Table 2).

DGA correlated negative with physical activity level (r=-0.659; p=0.001), a weak positive correlation (r=0.342; p=0.001) with depression, and no correlation with functional capacity (Table 3). There was a correlation between the DGA score and physical activity ($p \leq 0.001$) and depression ($p \leq 0.001$). In this context, physical activity and depression scores were included as independent variables in the regression model to determine the possible factors for DGA. The stepwise multiple regression analysis demonstrated that the physical activity and depression scores were significant and independent factors of for DGA with 43.4% of the variance. The regression equation formula for the dependent variable (DGA) was calculated using explanatory variables (physical activity and depression scores) and coefficients. The regression equation formula for DGA is: DGA =95.083 + (-1.651 x physical activity score) + (0.576 x depression score) (Table 4).

Demographic, physical, and clinical characteristics of children with DGA at different levels were compared. There was no difference between the groups in terms of gender, age, body mass index, and 2MWT. However, it was found that the education level of the father (p=0.014), the education level of the mother (p=0.033),

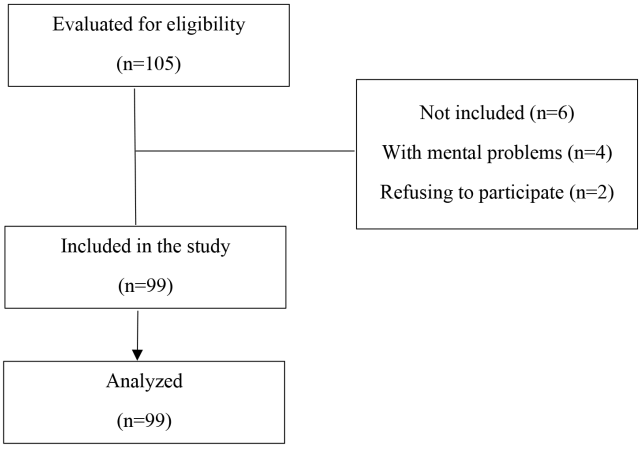

Figure 1. Flowchart of participants

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and the duration of playing digital games differed between the groups (p<0.001). Additionally, significant differences were found between the groups in terms of physical activity level (p<0.001) and depression (p=0.002) (Table 5).

Table 1. Demographic, physical, and clinical characteristics of children

Characteristics	
Age (years, $\bar{x}$ ± SD)	10±1.53
Gender (n, %)	
Male	57 (57.6)
Female	42 (42.4)
BMI (kg/m^2 $\bar{x}$ ± SD)	17.77±4.34
Diagnoses (n, %)	
Attention deficit and hyperactivity disorder	20 (20.20)
Oppositional defiant disorder	10 (10.10)
Nocturnal enuresis	4 (4.04)
Tic disorders	4 (4.04)
Siblings of children coming to treatment	61 (61.61)
Education level (n, %)	
Primary school	47 (47.5)
Middle school	52 (52.5)
Mother's education level (n, %)	
Primary-middle school	47 (47.5)
High school	37 (37.4)
University	13 (13.1)
Father's education level (n, %)	
Primary-middle school	43 (43.4)
High school	40 (40.4)
University	15 (15.2)
Digital gaming duration (n, %)	
Half an hour	13 (3.1)
1 hour	20 (20.2)
2 hours	26 (26.3)
3 hours and more	40 (40.4)
Digital gaming group (n, %)	
Low risk group	17 (17.2)
Risky group	41 (41.4)
Dependent group	26 (26.3)
Highly dependent group	15 (15.2)
Tool used for playing digital games (n, %)	
Computer	10 (10.1)
Game console	15 (15.15)
Telephone	52 (52.52)
Tablet	22 (22.22)
Physical activity level (n, %)	
Inactive	9 (9.1)
Low level	47 (47.5)
Moderately active	33 (33.3)
Active	10 (10.1)
Depression (n, %)	
Yes	84 (84.8)
No	15 (15.2)

n: number, $\bar{x}$: mean, SD: standard deviation, %: percentage, kg: kilogram, m: meter, BMI: body mass index

DISCUSSION

In this study, different levels of DGA were detected in children. It was determined that DGA had a negative relationship with physical activity level and a positive relationship with depression. It was found that physical activity level and depression have the greatest influence on DGA, whereas these variables explain 43.4% of the variance in the ultrasonography. No relationship was observed between DGA and functional capacity. Additionally, physical activity level was found to be markers of depression DGA. Differences were found in physical activity levels and depression in children with DGA at different levels. Additionally, there is a difference between the education level of the mother, the education level of the father, and the duration of playing digital games in children with DGA at different levels.

The person is diagnosed as "game addict" if they show 5 or more criteria (out of 9) according to the DSM V criteria of the American Psychiatric Association (23). These criteria are constant thoughts of the game in the mind; emotional status such as irritability, anxiety, and sadness when the game is not played; gradually increasing the amount of the game played; not being able to quit the game even if desired; loss of interest in the previously enjoyable activity; continuing to play the game despite the problems related to the psychological state; mislead people about the duration and frequency of the game played; misinformation about people; turning to the game to avoid negative emotions; work, education, and career are in jeopardy because of the game (23). DGA starts when the mind stays with the game even when the person is not playing (24). The number of studies is increasing day by day to understand DGA, which is an increasingly important problem, and to explain its causes and consequences (25,26). Digital gaming duration is an indicator of DGA, and there should be a relationship between DGA (26). In this study, a difference was found between the digital gaming duration in children with DGA at different levels. In studies on DGA, it is seen that variables such as gender, having/not having a computer, having/not having an internet connection, grade level, education level of parents, academic achievement, and age of the participants are examined (26). Şimşek and Yılmaz (26) found a positive relationship between parental education level and DGA in most of the studies they included in their systematic review (27,28), whereas few studies they reviewed either found no relationship or found a negative relationship (29,30). In this study, it was determined that DGA increased as the education level of the parents decreased. This may be due to the low educational

Table 2. Descriptive statistics of parameters measured in children

Parameters	$\bar{x}$ ± SD	min-max
Digital game addiction	68.42±20.65	25-108
Physical activity level	24.35±7.37	10.57-41.29
2MWT (m)	185.21±16.27	155-222
Depression	23.77±6.09	8-44

$\bar{x}$: mean, SD: standard deviation, 2MWT: 2-Minute Walk test, m: meter, min: minimum; max: maximum

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Table 3. The relationship between DGA and physical activity level, functional capacity, and depression

		Physical activity level	Functional capacity	Depression
Digital game addiction	r	-0.659**	0.029	0.342**
	p	0.001	0.775	0.001
	n	99	99	99
Physical activity level	r	-	-0.210	-0.347**
	p	-	0.835	0.001
	n	-	99	99
Functional capacity	r	-	-	-0.060
	p	-	-	0.556
	n	-	-	99

DGA: digital game addiction, **the correlation coefficient is significant at the 0.01 level, *the correlation coefficient is significant at the 0.05 level

Table 4. Stepwise multiple linear regression model of DGA

Coefficients[a]						
Model		**Unstandardized coefficients**		**Standardized coefficients**	**t**	**p-value**
		B	**Std. error**	**Beta**		
1	(Constant)	112.909	5.536	-	20.396	<0.001
	Physical activity	-1.818	0.217	-0.648	-8.388	<0.001
2	(Constant)	95.083	10.088	-	9.425	<0.001
	Physical activity	-1.651	0.228	-0.589	-7.256	<0.001
	Depression	0.576	0.275	0.170	2.099	0.038

DGA: digital game addiction
DGA= 95.083 + (-1.651 x physical activity score) + (0.576 x depression score), [a]Dependent variable: digital game addiction, R=0.668; R^2=0.446; adjusted R^2=0.434; p=0.038

level of the parents and their low technology literacy (30). Therefore, parents may not be aware of the content of the time their children spend in the digital environment and they may not be aware of their purpose (30). In this context, the results related to the education level of the parents cannot be generalized, and this issue should be investigated further with future studies. It is important to determine the factors that cause this outcome and to take preventive measures.

In the literature, studies examining DGA have found conflicting results regarding gender (31-33). While some studies have reported that men have more DGA than women (31,32), some studies have stated that gender is not effective in DGA (33). In this study, the DGA ratio was found to be similar in girls and boys. This may be due to both boys and girls playing games to get away from routine life in the 21st century. Additionally, the lack of significant gender differences may be because both genders have the same access to technological devices (33).

Basha (33) reported that age did not affect DGA in adolescents. Likewise, Frölich et al. (34) stated that DGA did not change with age in adolescents. The results of this study are also compatible with the studies in the literature, and it was observed that the DGA was high in a certain age range. The reason for this may be the easy access of children to technological devices with the developing technology, the sedentary life brought by the pandemic and the negative conditions such as the increase in screen exposure, the influence of individuals from each other and the similar social development (33).

The physical and mental development of active children is positively affected (35); however, it is stated that the rate of children not participating in physical activity is approximately 80% worldwide (22,23). Physical inactivity causes many health problems (cardiovascular diseases, diabetes, obesity, etc.). If the habit of being inactive from childhood continues as the age progresses, individuals become physically inactive in their lives (24). DGA is a risk factor for decreased physical activity level. Marufoğlu and Kutlutürk (11) stated with secondary school students that there was no significant relationship between DGA and physical activity level (11). Hazar et al. (12), on the other hand, found a significant negative correlation between DGA and physical activity level in secondary school students. According to Demir and Hazar (36), when the time to play digital games is not restricted, participation in physical activity decreases and performing tasks and meeting needs are disrupted. Additionally, Çakir (35) also stated that the increase in the time allocated to digital games affects the time left for other activities. In this study, it was found that as DGA increased in children, the level of physical activity decreased. With this result, the level of physical activity was found to be different in children with DGA at different levels. Additionally, it was found that

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the level of physical activity in the highly dependent group was even lower than the others. In this context, taking into account the effects of physical activity, children's physical activity level should be increased, and children's specific exercise programs should be created.

In this study, the 2MWT was used to assess the functional capacity. The results obtained in this test are like those of the 6MWT, and it is an effective evaluation method in terms of reducing fatigue by requiring less walking performance (37). Bohannon et al. (38) administered the 2MWT in 2707 healthy children aged 3-17 years and measured the mean distance as 122.9 m in the 3-year-old children, 200 m in those aged 10-12 years, and 209 m in 16-year-old children. In this study, the 2MWT result was 185.21±16.27 m in children aged 8-12 years. This result agrees with the results reported by Bohannon et al. (38). While studies on DGA generally examine physical activity; functional capacity has not been questioned to the best of our knowledge. In this study, no relationship was found between DGA and functional capacity. There was no difference in the functional capacity when children with different levels of DGA were compared. This result may be related to DGA duration. DGA, which continues for long periods, may result in decreased functional capacity. We think that the functional capacity should be questioned and examined in future studies, since the decrease in functional capacity may also affect the activities of daily living.

Although DGA is not defined as a psychiatric disorder by psychiatry authorities (4), prolonged digital game playing poses a threat to psychological health. Studies have shown that

Table 5. Comparison of demographic characteristics, physical activity level, functional capacity, and depression levels according to digital gaming risk groups

	Digital gaming risk groups				
	Low risk group (n=17)	**Risky group (n=41)**	**Dependent group (n=26)**	**Highly dependent group (n=15)**	**p-value**
Gender (n, %)					
Male	8 (47.1)	20 (48.8)	17 (65.4)	12 (80)	0.121
Female	9 (52.9)	21 (51.2)	9 (34.6)	3 (20)	
Age (years, $\bar{x}$ ± SD)	9.41±1.5	10.02±1.62	10.12±1.51	10.33±1.35	0.413
BMI (kg/m^2, $\bar{x}$ ± SD)	16.88±3.43	17.28±4.15	17.56±4.61	20.51±4.63	0.061
Mother's education level (n, %)					
Primary-middle school	9 (52.9)	18 (43.9)	15 (57.7)	7 (46.7)	0.033
High school	7 (41.2)	21 (51.2)	6 (23.1)	3 (20)	
University	1 (5.9)	2 (4.9)	5 (19.2)	5 (33.3)	
Father's education level (n, %)					
Primary-middle school	6 (35.3)	16 (39)	18 (69.2)	4 (26.7)	0.014
High school	6 (35.3)	20 (48.8)	4 (15.4)	10 (66.7)	
University	5 (29.4)	5 (12.2)	4 (15.4)	1 (6.7)	
Digital gaming duration (n, %)					
Half an hour	7 (41.2)	4 (9.8)	1 (3.8)	1 (6.7)	<0.001
1 hour	8 (47.1)	9 (22)	1 (3.8)	2 (13.3)	
2 hours	2 (11.8)	15 (36.6)	7 (26.9)	2 (13.3)	
3 hours and more	0 (0)	13 (31.7)	17 (65.4)	10 (66.7)	
Physical activity level (n, %)					
Inactive	0 (0)	0 (0)	6 (23.1)	3 (20)	<0.001
Low level	2 (11.8)	19 (46.3)	14 (53.8)	12 (80)	
Moderately active	8 (47.1)	19 (46.3)	6 (23.1)	0 (0)	
Active	7 (41.2)	3 (7.3)	0 (0)	0 (0)	
Functional capacity (m, $\bar{x}$ ± SD)					
2MWT	189.47±20.14	180.39±15.70	187.35±13.10	189.87±15.99	0.090
Depression (n, %)					
Yes	10 (58.8)	34 (82.9)	25 (96.2)	15 (100)	0.002

n: number, $\bar{x}$: mean, %: percentage, SD: standard deviation, BMI: body mass index, 2MWT: 2-Minute Walk test

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depression, anxiety, and stress accompany DGA (15,39). Mentzoni et al. (15) reported that the level of playing digital games increased with increasing depression and anxiety. Gentile et al. (39) investigated the relationship between DGA and depression in children and young adults and observed that the depression developed in gamers who became addicted. In this study, as DGA increases, the depression increases. Additionally, a difference was found between depression in children with different levels of DGA. In this context, children can be referred to appropriate health professionals for treatment via various methods involving mind-body unity (cognitive behavioral therapy, relaxation training, etc.) and various exercise programs (aerobic exercise, breathing exercise, etc.) for depression.

Study Limitations

This study had some limitations. First, the Primary School Students' Physical Activity Questionnaire was used to measure the physical activity level. For the results to be more objective, physical activity levels could be measured with an objective method such as accelerometry. However, the Primary School Students' Physical Activity Questionnaire was used because it was less costly and easier to apply. The second limitation is that the generalizability of the study results is affected due to the single-center nature of the study. This limitation can be avoided by conducting larger studies in the future.

CONCLUSION

In this study, it was seen that there was a negative relationship between DGA and physical activity level, and a positive relationship between depression. A difference was found between physical activity level and depression in children DGA at different levels. To increase the level of physical activity and reduce depression associated with DGA, children are referred to appropriate health professionals for treatment with various methods including mind-body association and various exercise programs. Families and children should be informed about the potential risks and associated problems of DGA. Additionally, with the results of this study, DGA awareness can be increased among health professionals, parents, and teachers.

Ethics Committee Approval: This cross-sectional and descriptive study was approved by the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (decision no: 128, date: 05.10.2022).

Informed Consent: After the study was explained to the participants and their families who met the inclusion and exclusion criteria and volunteered to participate in the study, the 'Informed Consent Form' was signed.

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Best Regards,

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