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Original Articles

Letter to the Editors

Neuroradiology

Evaluation of Arachnoid Granulations in Cranial Dural Sinuses with Contrast-Enhanced 3-Dimensional T1-Weighted Magnetic Resonance Imaging

Veysel Kaplanoğlu[1], Hatice Kaplanoğlu[2], Aynur Turan[2], Alper Dilli[2]

ABSTRACT

Objective: Several studies in the literature have used contrast-enhanced magnetic resonance imaging to investigate arachnoid granulations protruding into the cranial dural sinuses. The current study aimed to investigate the protrusion of arachnoid granulations into the superior sagittal sinus, transverse sinus, straight sinus, and confluence of sinuses and determine the frequency of brain herniation into giant arachnoid granulations using contrast-enhanced 3-dimensional T_1-weighted magnetic resonance imaging.

Materials and Methods: Images of 550 patients with intra-sinus arachnoid granulations who underwent contrast-enhanced 3-dimensional T1-weighted thin-slice magnetic resonance imaging were retrospectively re-evaluated. Only 300 patients with at least 1 intra-sinus arachnoid granulation were included in the study. The protrusion of arachnoid granulations into superior sagittal sinus, transverse sinus, straight sinus, and confluence of sinuses was investigated. In addition, large arachnoid granulations and brain herniations into arachnoid granulations were also noted.

Results: A total of 889 focal filling defects of arachnoid granulations, at least 1 in the dural sinus, were detected. Of the filling defects of arachnoid granulations, 183 were in the right transverse sinus, 222 in the left transverse sinus, 265 in superior sagittal sinus, 185 in straight sinus, and 34 in confluence of sinuses. Brain herniation into arachnoid granulations was detected in 8 (2.7%) of the patients included in the study. All the filling defects detected in the dural sinuses on post-contrast 3-dimensional T1-weighted images were isointense with cerebrospinal fluid and had round, oval, or lobulated contours. A positive weak correlation was found between patient age and the size and number of arachnoid granulations ($r=0.181$, $P < .01$ and $r=0.207$, $P < .001$, respectively). It was observed that the size and number of arachnoid granulations increased as the age of the patients increased.

Conclusions: The distribution, shape, number, and size of intra-sinus arachnoid granulations can vary considerably. Brain herniation into arachnoid granulation can also be seen. Three-dimensional cranial magnetic resonance imaging sequences can be safely used in the evaluation of arachnoid granulations.

Keywords: Arachnoid granulations, dural sinuses, magnetic resonance imaging, 3D T1-weighted

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Introduction

Intra-sinus arachnoid granulations (AGs) are pseudopodial anatomical structures that protrude into the lumen of the venous sinuses. These structures are filled with cerebrospinal fluid (CSF) and are surrounded by pia-arachnoid membranes. Arachnoid granulations are typically a few millimeters in diameter, but giant AGs larger than 1 cm have also been described.[1] Most AGs are asymptomatic; however, rarely, they may also be ectatic, requiring differentiation from sinus thrombosis, meningioma, cavernous hemangioma, and meningocele.[2,3] Giant AGs can obliterate the venous sinuses or be present with the scalloping of the inner table of the calvarium.[4,5]

Typically, AGs are structures that have the same properties as CSF in terms of density or signal intensity, and they are visualized as structures protruding into the venous sinus lumen in routine computed tomography (CT) and magnetic resonance imaging (MRI).[6] This retrospective study aimed to determine the frequency of AGs protruding into the superior sagittal sinus (SSS), transverse sinus (TS), straight sinus (StS), and confluence of sinuses (ConfS) and determine the

frequency and nature of brain herniations into AGs using contrast-enhanced 3-dimensional (3D) T_1-weighted MRI.

Materials and Methods

This study was performed according to the ethical standards of the institutional review board. The examinations of the cases who underwent standard contrast-enhanced brain MRI for any reason were retrospectively and randomly evaluated, using the hospital's picture archiving and communication systems. Five hundred fifty patients who underwent a cranial MRI examination in the radiology clinic between January 2020 and June 2021 and had post-enhanced 3D T1 sequence images were included in the study.

All the cranial MRI examinations of 550 patients in the study were re-evaluated by a neuroradiologist with 10 years of experience. In the 3D contrast-enhanced examination, AGs were visualized as well-circumscribed, round or oval-shaped intra-sinus masses, or nodules associated with or adjacent to the cerebral sulcus and cistern, which were homogenous and hypointense on T1-weighted images.[3] Protrusion of AGs into SSS, TS, StS, and ConfS was investigated. In addition, large AGs and brain herniations into AGs were also noted. When evaluating AGs and brain herniations into AGs, we determined parameters including size, dural venous sinus in which it was located, shape (oval/round), signal characteristics, and presence of contrast-enhancement, which could help exclude other pathologies in the differential diagnosis. Only 300 patients with at least 1 intra-sinus AG were included in the study. Two hundred fifty patients with dural venous sinus thromboses, neoplasms, cranial surgery history or artifacts preventing the visualization of the sinuses, pediatric patients younger than 15 years, and patients without AG in the sinuses were excluded from the study (Figure 1). The basic demographic data (age, gender) of the patients and complaints at the time of presentation to the hospital were screened through the hospital information system.

All the participants were examined in the supine position with a 20-channel head coil using the 1.5 T (Philips Medical Systems, Eindhoven, Netherlands) MRI system. Standard MRI protocols with and without contrast material injection included axial T1-weighted, axial and coronal T2-weighted, axial and sagittal T2-weighted turbo inversion recovery magnitude dark-fluid, and axial Echo-planar imaging (EPI) diffusion sequences. After intravenous gadolinium infusion (Gadoterate meglumine, Dotarem, Guerbet Roissy, France) (0.1 mmol/kg) was administered to the patients, axial, reformatted, coronal, and sagittal 3D T1-weighted MRI images covering the entire cranium were obtained. The imaging parameters of the 3D T1-weighted sequence were as follows: repetition time, 7.3 ms; echo time, 3.5 ms; slice thickness, 1 mm; interslice gap, 0 mm; matrix, 256 × 232; field of view, 256 mm; flip angle, 8°; and scan duration, 3 minutes 36 seconds.

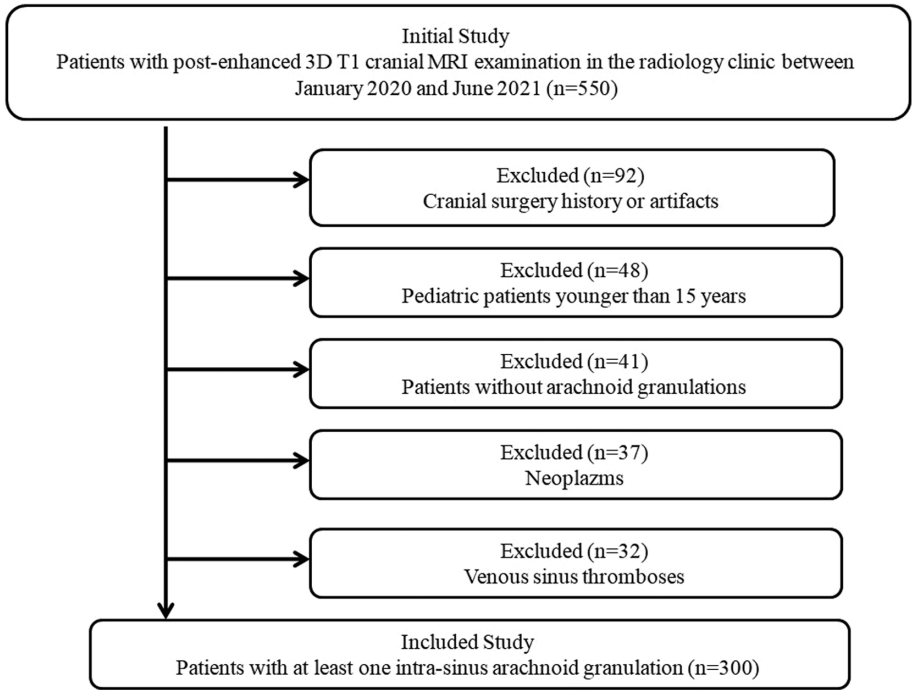

Figure 1. Flowchart shows the numbers of the patients enrolled in the study with inclusion criteria and reduced numbers with exclusion criteria.

Statistical Analysis

Mean, standard deviation, median, minimum, and maximum values were used as descriptive statistics for continuous data, and number and percentage values were given for discrete data. The Chi-square test was used for the comparison of AG distributions between the age groups (cross-tables). The relationship between age and size was analyzed using Kruskal–Wallis multiple analysis. International Business Machines' Statistical Package for the Social Sciences Statistics v. 20 was used in statistical analyses (IBM SPSS Corp., Armonk, NY, USA), and $P < .05$ was accepted as the statistical significance limit.

Results

The study population consisted of 300 patients, 113 men and 187 women, aged 44.99 ± 15.81 years (15-84 years). The complaints of the patients at the time of presentation to the hospital (headache, dizziness, blurred vision, blurred consciousness, diplopia, vision loss, syncope, vertigo, tinnitus, etc.) were determined, and the most common complaint was headache.

Using the post-contrast 3D T1-weighted MRI images, a total of 889 focal filling defects of AGs were detected in at least 1 dural sinus in each of the 300 patients. Concerning the distribution of the number of AGs, there was 1 AG in 23% of the patients, 2 AGs in 24.2%, and 8 AGs in 0.3%. The AGs identified in this study were highly variable in shape, size, and number of the filling defects of AGs, 183 were in the right TS, 222 in the left TS, 265 in SSS (Figure 2), 185 in StS, and 34 in ConfS. According to their localization, AGs were most common in the anterior superior portion of SSS, at the junction with the vein of Galen and in the lower 1/3 of StS, and in the midlateral portion of TS (Table 1). All the filling defects detected in the dural sinuses on the post-contrast 3D T1-weighted images were hypointense compared to the brain parenchyma, isointense with CSF, and had round, oval, or lobulated contours.

The mean AG size was 4.10 ± 2.54 mm (0.7-20 mm). According to their localization, the diameters of AGs were determined as 4.14 ± 2.57

Main Points

- Intra-sinus arachnoid granulations (AGs) can be found in all intra-cranial sinuses, especially in transverse sinus.
- Brain herniation into AGs can also be seen, and AGs may show inconsistent signals with cerebrospinal fluid.
- As the age of the patients increased, the size and number of AGs also increased.

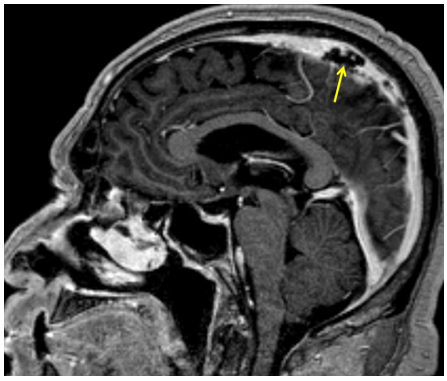

Figure 2. An intra-sinus giant arachnoid granulation in the anterior superior of the superior sagittal sinus (yellow arrow).

mm for the right TS, 3.85 ± 1.75 mm for the left TS; 4.46 ± 3.19 mm for SSS, 3.85 ± 2.21 mm for StS, and 4.64 ± 1.96 mm for ConfS. There was no difference in arachnoid granulation dimensions between localizations (P=.131). There was a difference between the age groups in terms of the AG size (P=.022). The AG size was found to be lower in patients aged 15-45 years compared to patients aged 45-60 years (Table 2, Figure 3). The number of AGs was found to be lower in patients aged 15-45 years compared to the 45-60 years group (Figure 4). A positive weak correlation was found between patient age and the size and number of AGs (r=0.181, P < .01 and r=0.207, P < .001, respectively). As the age of the patients increased, the size and number of AGs also increased.

Table 1. Distribution of AGs in the Venous Sinuses on Post-Contrast 3D T1-Weighted Images

AG localization	n	%
Right transverse sinus	**183**	**20.5**
Right transverse sigmoid junction	31	3.48
Right midlateral transverse	84	9.44
Right medial transverse near torcula	68	7.65
Left transverse sinus	**222**	**24.9**
Left transverse sigmoid junction	47	5.3
Left midlateral transverse	99	11.1
Left medial transverse near torcula	76	8.5
Superior sagittal sinus	**265**	**29.8**
Anterior and superior portion	170	19.1
Posterior portion	95	10.7
Straight sinus	**185**	**20.8**
Superior portion	37	4.2
Inferior third portion	68	7.6
Junction of the vein of Galen	80	9
Confluence of sinuses	**34**	**3.8**

AG, arachnoid granulation; 3D, 3 dimensional.

Table 2. Comparison of the Size of AGs According to Age Groups

	15-45 years	45-60 years	>60 years		
	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)	Test statistic	P
AG size	0.94 ± 0.64 0.77 (0.12-3.32)	1.23 ± 0.78 1.19 (0.21-2.93)	1.09 ± 0.98 0.97 (0.13-3.47)	χ^2 =7.646*	.022

AG, arachnoid granulation; SD, standard deviation.
*Kruskal–Wallis analysis of variance.

Brain herniations into AGs were detected in 8 (2.7%) of the patients included in the study (Figure 5a, b). Around 4 of the brain herniations were into ConfS, 2 were into the midlateral of the right TS, 1 was into the mid portion of the right TS, and 1 was into the left medial TS (Figures 5a, b). The mean size of the brain herniations into AGs was 4.93 ± 1.38 mm. The largest brain herniation was observed in ConfS, measuring 5.52 ± 1.73 mm. Signal characteristics not consistent with CSF were detected in 8 of the patients with brain herniations into AGs. Five cases were isointense with the brain parenchyma, 3 were mildly hypointense, and the remaining were hyperintense with reference to CSF. In 6 cases, brain parenchymal herniation and vascular structure were observed in AGs.

Discussion

In the evaluation of intra-sinus AGs, 3D high-resolution sequences provide more reliable results. Since 3D images are sequences with a 1-mm section thickness, high resolution, and multiplanar reconstruction capability, they allow for an accurate and reliable evaluation of AGs. Small AGs can be overlooked on standard MRI sequences due to the difficulty of distinguishing between small AGs and the patency of the cortical and bridging veins that connect to the sinuses.[3,4,7] In the current study, the post-contrast 3D T1-weighted sequences were used for this evaluation.

The AGs detected in the current study were highly variable in terms of shape, size, number, and location. There was 1 AG in 23% of the patients and the rest had more than 1. Two AGs were found most frequently in 24% of the patients. The most common location was TS (45.4%), followed by SSS, StS, and ConfS in the order of frequency. In a study by Tsutsumi et al.[3] AGs were most commonly detected in TS, followed by SSS, which is similar to our study.

We found AGs to be most commonly located in the anterior superior of SSS, at the junction of the vein of Galen and in the distal 1/3 of StS, and mid-lateral portion of TS, which is consistent with previous studies. Tsutsumi et al[3] reported that AGs were frequently located in the area close to the transverse-sigmoid sinus junction. In another study using CT and MRI, Leach et al[6] mostly detected AGs in TS and noted that their localization was associated with venous access,

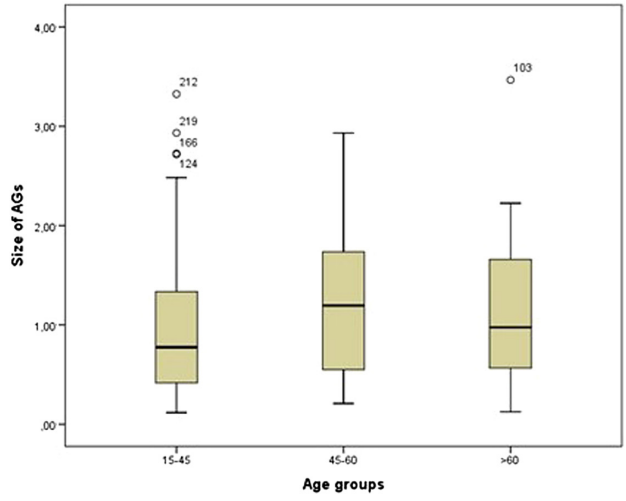

Figure 3. Comparison of the size of AGs according to age groups in the box plot graph. In plot charts, we draw a box from the first quarter to the third quarter. In the median is the line that goes through the box. Lengths go from each quarter to a minimum or maximum. AGs, arachnoid granulations.

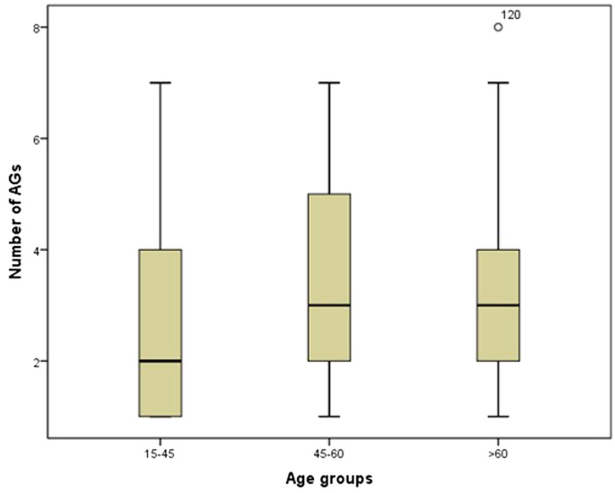

Figure 4. Comparison of the number of AGs according to the age groups in the box plot graph. AGs, arachnoid granulations

especially in the vein of Labbe. It has been suggested that the frequent occurrence of AGs at the venous junctions is related to the protrusion of the leptomeninges into the areas where the venous structures pass through the dura at the openings to the sinuses.[8]

Koshikawa et al[9] reported no significant correlation between patient age and the number and size of AGs. In addition, Tsutsumi et al[3] showed that the mean ages of the patients with and without intra-sinus AGs were similar. In contrast, Haybaeck et al[10] determined that the frequency of AGs increased with age and Leach et al[6] suggested that patients with AGs were older than those without AGs. In the current study, there was a positive correlation between patient age and the size and number of AGs. Accordingly, the size and number of AGs increased as the age of the patients increased.

In the literature, Haroun et al[7] reported that AGs had intermediate signal intensity in one-third of the patients and Leach et al[6] determined that AGs were hypointense in relation to the brain parenchyma in two-thirds of the patients in the Fluid attenuated inversion recovery (FLAIR) sequence and showed insufficient suppression with reference to CSF in the remaining cases. The authors attributed the occurrence of signal inconsistent with CSF in conventional MRI sequences to the partial volume effect, pulsation effect, and varying CSF flow motion characteristics.[6] In another study evaluating 45 patients with giant AGs, Oğul et al showed that AGs had an inconsistent signal with CSF in 38 patients. They detected a signal void phenomenon in the AGs of 28 of these patients and brain herniation into AGs in the remaining 10 and argued that the presence of an inconsistent signal with CSF in AGs in conventional MRI may be due to turbulent or jet CSF flow into these structures.[4] In the current study, the signal of AGs was inconsistent with CSF in patients with brain herniation into AGs. All the cases were isointense with the brain parenchyma and hyperintense with reference to CSF. In 6 cases, brain parenchymal herniation and vascular structure were observed in AGs.

Liebo et al[11] suggested that brain herniation into AGs may occur secondary to an increase in intracranial pressure or spontaneously. According to Battal et al.[12] the frequency of brain herniation into AGs in the calvarial or dural sinuses was 0.32%. Oğul et al[4] evaluated 45 giant AG cases extending to the dural sinus and detected brain herniation in 10 (22%). In our study, a higher rate of brain herniation (2.7%) was found compared to the study of Battal et al, but this rate was even higher in the study by Oğul et al. According to Oğul et al, this is considered to be due to the evaluation of giant AGs. Increasing AG size may increase the rate of intracranial herniation. In addition, Oğul et al used the 3D MRI system and obtained the 3D T1 MPRAGE and 3D SPACE sequences together, which may have facilitated the detection of herniation.

In the current study, the mean AG size was found to be 4.10 ± 2.54 mm (min 0.7-max 20 mm). There was no significant difference in the size of AGs located in different sinuses. In previous studies, the mean size of intra-sinus AGs has been reported to range from 2 to 8 mm. The form exceeding 1 cm and defined as a giant AG is rarely seen.[13] The strong side of our study is the large number of AG populations included in the study. There are some limitations to our study, the first of which concerns is its retrospective nature. The inhomogeneity of the patient groups in terms of age and the inclusion of only cases with intra-sinus AGs can be considered as other limitations of our study.

In conclusion, intra-sinus AGs can be found in all intra-cranial sinuses, especially in TS. The distribution, shape, number, and size of AGs can vary considerably. As the age of the patients increased, the size and number of AGs also increased. Brain herniation into AGs can also be seen, and AGs may show inconsistent signals with CSF, especially in cases with brain herniation. Knowing these imaging features of AGs can help distinguish especially benign giant AGs from other venous sinus pathologies.

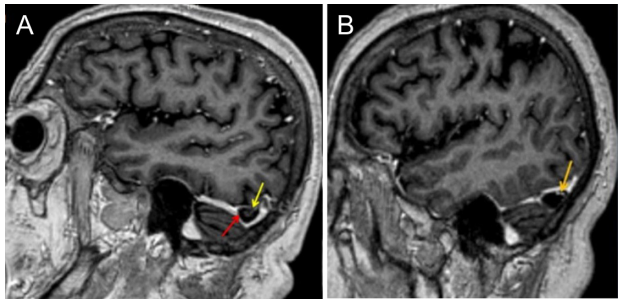

Figure 5. A, B. Sagittal post-contrast T1-weighted MR images show brain herniation (yellow arrow) into an intra-sinus giant arachnoid granulation (red arrow) in the midlateral of the right transverse sinus. MR, magnetic resonance.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Hospital (July 26, 2021/116/12).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.K., V.K.; Design - H.K., V.K., A.T.; Supervision - V.K., A.D.; Materials - V.K., A.D.; Data Collection and/or Processing - H.K., V.K., A.T.; Analysis and/or Interpretation - H.K., V.K., A.T.; Literature Review - H.K., V.K., A.D.; Writing - H.K., V.K.; Critical Review - A.T., A.D.

Declaration of Interests: The authors have no conflicts of interest to declare.

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Pathology

Investigation of Biopsied Non-Plaque-Induced Gingival Lesions in a Turkish Population: A 5-Year Retrospective Study

Alparslan Dilsiz, Sema Nur Sevinç Gül

ABSTRACT

Objective: The study aimed to analyze the distribution and frequency of individuals diagnosed with histopathologically non-plaque-induced gingival lesions and categorize them according to the non-plaque-induced gingival disease classification published at the 2017 World Workshop of Periodontology.

Materials and Methods: Clinical features of the gingival lesion with histopathological diagnosis data in the period 1998-2003 were retrospectively analyzed . The lesions were classified as reactive lesions, malignant neoplasms, premalignant neoplasms, autoimmune disorders, benign neoplasms, hypersensitive reactions, and genetic lesions. Their distribution according to age, gender, histopathological diagnosis, and oral sites was examined. Variables were analyzed using descriptive statistics.

Results: Among a total of 217 biopsied gingival samples, the most frequent pathologic nature of biopsied non-plaque gingival lesions were reactive lesions (n=80, 36.87%) and premalignant neoplasms (n=64, 29.49%). In addition, the 5 most frequent types of all cases included pyogenic granuloma (n=45, 20.74%), epithelial dysplasia (n=40, 18.43%), papilloma (n=33, 15.21%), epithelial hyperplasia (n=24, 11.06%), and calcifying fibroblastic granuloma (n=13, 5.99%).

Conclusions: In a Turkish population, the most frequently biopsied non-plaque-induced gingival lesions were reactive lesions and premalignant neoplasms. This study shows that the types of lesions that clinicians, in general, especially periodontologists, can expect to encounter in their practice are the most frequently applied gingival lesions.

Keywords: Non-plaque-induced gingival lesions, reactive gingival lesions, gingival premalignant neoplasms, gingival malignant neoplasms

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Introduction

The oral cavity is a complex structure in the head and neck region. It consists of various structures such as jaws, teeth, tongue, salivary glands, and soft and hard palate.[1] As the oral mucosa is always under the effect of various internal and external stimuli, it occurs in various developmental disorders, irritation, inflammation, and neoplastic lesions.[2]

Reactive lesions are hyperplastic structures caused by chewing the oral mucosa, poor oral hygiene, fractured teeth, and extended denture flanges.[3] Pyogenic granuloma, fibrous epulis, peripheral giant cell granuloma, and calcifying fibroblastic granuloma are the most common reactive lesions of the oral cavity.[4]

Neoplastic oral mucosal lesions are divided into premalignant lesions and malignant lesions. Premalignant lesions are examined under the heading of leukoplakia and erythroplakia, and malignant lesions are classified as squamous cell carcinoma, leukemia, and lymphoma.[5]

It is very important to know both the clinical features and the pathology of the lesions for the recognition, diagnosis, and treatment of common oral diseases. When any oral lesion is detected, the symptom, size, location, color, elapsed time, and the biopsy of the lesion should be taken and histopathologically evaluated. According to the European Federation of Periodontology (EFP)

and the American Academy of Periodontology (AAP) 2017 World Workshop, non-plaque-induced gingival diseases are classified as genetic lesions, specific infections, hypersensitive reactions, autoimmune diseases of the skin and mucous membranes, granulomatous inflammatory conditions, reactive processes, premalignant neoplasms, malignant neoplasms, endocrine, nutritional and metabolic diseases, traumatic lesions, and gingival pigmentation.

This retrospective study aims to determine the frequency and distribution of oral lesions obtained from patients of all age and gender groups who applied to the Faculty of Dentistry, Atatürk University, diagnosed histopathologically, categorized according to the non-plaque-induced gingival disease classification published at the 2017 World Workshop and bring them to the literature.

Materials and Methods

A retrospective study was performed on biopsied gingival lesions collected over 5 years in the Atatürk University, Faculty of Dentistry. This study was independently reviewed and approved by The Institutional Internal Review and Ethics Board (April 19, 2009 No: 017) and conducted according to the 2008 Declaration of Helsinki and later amendments.

Medical records of all patients who underwent a biopsy during this period were evaluated. Patients with a lesion in the gingiva with defined histopathological diagnosis and patients with sufficient demographic information were included in the study. Patients with the following disorders were excluded from the study: (1) disorder of salivary gland, (2) bone lesions extending to the gingiva, and (3) plaque-induced-gingival diseases. An informed consent form was obtained from the patients included in the study. According to their histopathological diagnoses, pathologies belonging to 217 cases, 116 females and 101 males, the lesions are classified as reactive lesions, malignant neoplasms, premalignant neoplasms, autoimmune disorders, benign neoplasms, hypersensitive reactions, and genetic lesions. In the tables of the groups, the number of cases, average age, gender, sex ratio, frequency of lesions in their group, and incidence rates according to all lesions are given.

Chi-square test and descriptive statistics were applied to the data obtained, and their distribution according to age and gender was examined. All analyses were performed using Statistical Package for the Social Sciences® software version 20 (IBM Corp., Armonk, NY, USA). Among the results obtained, those with $P < .05$ were considered significant.

Main Points

- This study provides information about gingival pathologies. This article may give an idea for the histopathological diagnosis of gingival pathologies by the general dentist.
- The most frequently biopsied non-plaque gingival lesions were reactive lesions and premalignant neoplasms in a Turkish population.
- Dentists and medical practitioners should be careful about gingival lesions and precancerous and malignant pathologies.

Results

The most frequent histopathologic groups, along with age, sex, and location distributions, are summarized in Table 1.

According to Table 1, the 5 most frequent types of all cases included pyogenic granuloma (n = 45, 20.74%), epithelial dysplasia (n = 40, 18.43%), papilloma (n = 33, 15.21%), epithelial hyperplasia (n = 24, 11.06%), and calcifying fibroblastic granuloma (n = 13, 5.99%). The sixth most common diagnoses are peripheral giant cell granuloma (n = 12, 5.53%) and lichen planus (n = 12, 5.53%). Hereditary gingival fibromatosis was the seventh most frequent type (n = 11, 5.06%). In addition, one of the hyperplastic lesions, fibrous epulis, was the eighth diagnosis (n = 10, 4.61%). The ninth most frequent diagnosis and most common type of cancer was squamous cell carcinoma (n = 8, 3.69%).

Gingival lesions were diagnosed in patients with a wide range of ages, from 6 to 80 years, with a mean age of 37.49 years.

Table 1 also shows a comparison of gender and location; 53.5% (n = 116) of total cases were females, and 46.5% (n=101) were males.

In addition, a slight majority of cases were obtained from maxillary gingiva (n = 122, 56.2%), more than mandibular gingiva (n = 95, 43.8%).

To classify these different types of lesions into more specific categories, we divided the lesion types into several groups according to their pathological characteristics (Table 2).

As shown in Table 2, the most frequently observed biopsied lesions were "reactive lesions" (n = 80), reaching up to 36.87% of all lesions. In "reactive lesions," the largest proportion was pyogenic granuloma, followed by calcifying fibroblastic granuloma, peripheral giant cell granuloma, and fibrous epulis.

Table 1. Frequencies of Various Histopathologic Groups with Age, Gender, and Location Distributions

				Gender		Location	
Classification	N	Percentage (%)	Age (years) Mean ± SD	Female N (%)	Male N (%)	Mand N (%)	Max N (%)
Pyogenic granuloma	45	20.74	36.73 ± 20.39	29 (64.4)	16 (35.6)	20 (44.4)	25 (55.6)
Epithelial dysplasia	40	18.43	35.2 ± 17.31	22 (55.0)	18 (45.0)	14 (35.0)	26 (65.0)
Papilloma	33	15.21	40.30 ± 21.25	16 (48.5)	17 (51.5)	13 (39.4)	20 (60.6)
Epithelial hyperplasia	24	11.06	35.29 ± 17.03	9 (37.5)	15 (62.5)	9 (37.5)	15 (62.5)
Calcifying fibroblastic granuloma	13	5.99	21.92 ± 13.18	8 (61.5)	5 (38.5)	7 (53.8)	6 (46.2)
Peripheral giant cell granuloma	12	5.53	27.42 ± 15.76	8 (66.7)	4 (33.3)	10 (83.3)	2 (16.7)
Lichen planus	12	5.53	31.75 ± 13.22	9 (75.0)	3 (25.0)	4 (33.3)	8 (66.7)
Hereditary gingival fibromatosis	11	5.06	30.27 ± 19.87	4 (36.4)	7 (63.6)	3 (27.3)	8 (72.7)
Fibrous epulis	10	4.61	63.8 ± 10.67	6 (60.0)	4 (40.0)	8 (80.0)	2 (20.0)
Squamous cell carcinoma	8	3.69	60.13 ± 14.21	2 (25.0)	6 (75.0)	4 (50.0)	4 (50.0)
Hemangioma	4	1.84	60.0 ± 17.15	2 (50.0)	2 (50.0)	2 (50.0)	2 (50.0)
Plasma cell gingivitis	3	1.38	36.33 ± 22.14	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
Pemphigus vulgaris	2	0.92	50.5 ± 10.61	0	2 (100)	0	2 (100)
Total	**217**	**100.0**	**37.49**	**116 (53.5)**	**101 (46.5)**	**95 (43.8)**	**122 (56.2)**

SD, standard deviation.

Table 2. The Number and Frequency of Different Biopsied Lesions According to Pathological Nature

Pathologic Nature	Total, n (%)	Histopathological Diagnosis
Reactive lesions	80 (36.87)	Pyogenic granuloma Peripheral giant cell granuloma Calcifying fibroblastic granuloma Fibrous epulis
Premalignant neoplasms	64 (29.49)	Epithelial dysplasia Epithelial hyperplasia
Benign neoplasms	37 (17.05)	Papilloma Hemangioma
Autoimmune disorders	14 (6.45)	Pemphigus vulgaris Lichen planus
Genetic lesions	11 (5.07)	Hereditary gingival fibromatosis
Malignant neoplasms	8 (3.69)	Squamous cell carcinoma
Hypersensitive reactions	3 (1.38)	Plasma cell gingivitis
Total	**217 (100)**	

Discussion

In this study, we conducted a retrospective study to investigate the frequency and distribution of the biopsied non-plaque-induced gingival lesions analyzed in a Turkish population. We arranged and identified the current results of the new classification of gingival health and gingival diseases/conditions established in the 2017 World Workshop by EFP and AAP. The existing gingival lesions were divided into 7 groups. The most common and least seen are reactive lesions, premalignant neoplasms, benign neoplasms, autoimmune disorders, genetic lesions, malignant neoplasms, and hypersensitive reactions.

The diagnostic classifications of biopsies taken in previous studies were categorized into 3 types: non-neoplastic lesions, benign lesions, and malignant lesions,[6-8] and the majority of biopsied samples were non-neoplastic lesions. Consistent with the previous reports,[6-9] most of the lesions we examined were reactive lesions, with 36.87% of all lesions. Among these, pyogenic granuloma is the most common diagnosis, with a rate of 20.74%. The results of this study are consistent with previous studies.[7,10,11] About 55.6% of cases of pyogenic granuloma were found in maxillary gingiva, which was lower than those reported by Ababneh[11] (64%) and Alblowi[12] (57.73%) and higher than those reported by Zhang et al[13] (47.10%). Pyogenic granuloma represented nearly one-fifth of all gingival lesions, with a peak incidence of appearance at 36.7 years, which was somewhat older than previous reports. It is more common in females in our study population, which is inconsistent with earlier reports.[6,7,10-12,14] Pyogenic granuloma was followed by peripheral giant cell granuloma, calcifying fibroblastic granuloma, and fibrous epulis.

Malignant neoplasms of lesions were calculated as 3.69%. Squamous cell carcinoma (SCC) was the only one malignant lesion reported in gingival biopsy specimens in this study, which was consistent with the outcomes of other reports.[6,8,10] In our study, SSC most frequently appeared in the sixth decade, and only 1 case was detected below 40 years. We also detected that the mean age of SCC was 60.13, fewer than that of Makridis et al.[15]

In this study, premalignant neoplasms resulted in about 30% of all biopsies; oral premalignant neoplasms include oral leukoplakia, oral lichen planus, lichenoid lesions, and oral erythroplakia. Oral leukoplakia is categorized according to the presence or absence of epithelial dysplasia, classified as without epithelial dysplasia and with epithelial dysplasia; 18.43% of the investigated group were diagnosed with epithelial dysplasia of different degrees. Li et al[9] reported a prevalence of gingival epithelial dysplasia of 6.95%. Previous studies described the prevalence of leukoplakia without dysplasia ranging between 18% and 38%,[16-18] while our study has detected a prevalence of gingival without epithelial dysplasia of 11.06% within the studied population. Other studies have reported the frequency of leukoplakia without epithelial dysplasia as 6.36% and 4.94%, respectively.[9,19] The difference in these results may be related to the population studied. Our study determined that these lesions were generally seen in the mandible, and these data are compatible with the previous study.[9] However, these lesions were detected more frequently in the maxilla region in other studies.[6,19] This difference may be due to the differences in life expectancy between the regions where the studies were conducted, as leukoplakia is affected by more than 1 etiological factor. For example, tobacco and alcohol consumption are the most important etiological factors. However, other etiological factors include human papillomavirus (HPV), tooth restoration, mechanical irritation, candidiasis, low serum vitamin A, and carotene.

The autoimmune disorders were investigated under the title of lichen planus and pemphigus vulgaris. The prevalence of lichen planus was determined as 5.53%, which was slightly higher than reported by Alblowi et al[12] (5%) and Li et al[9] (4.23%). The frequency of the other study diagnosed with lichen planus on biopsy specimens was quite low, which was inconsistent with our study.[19] On the other hand, Carbone et al[6] reported that the prevalence of oral lichen planus is just about 10%.[6] Pemphigus vulgaris was detected in only 2 cases (0.92%), they were on average 50.5 years old, and both were male. While the incidence of pemphigus vulgaris was 2.41% in one study,[6] it was 1.25% in another study.[9] We think these differences may be related to the sample size of the study group and the patient population.

Benign neoplasms were usually detected in the gingiva; papilloma is the most prevalent (15.21%). It is known that squamous cell papilloma, thought to be caused by HPV, is transmitted from mother to child and spouses to each other. Our results are inconsistent with previous studies due to its infectious pathology.[6,9,19,20] Hemangioma, another benign neoplasm, was detected at a rate of 1.84%, and this rate is slightly higher than other studies.[6,19]

Plasma cell gingivitis, which is one of the hypersensitive reactions, is a rare condition characterized by a hypersensitivity response in the gingival tissue. Plasma cell gingivitis was detected in only 3 patients (1.38%). Although the cases were mostly seen in women, we observed it in 2 males and 1 female. The mean age is 36.33, which was more common in the maxilla.

Hereditary gingival fibromatosis is a genetic disease characterized by gingival enlargement and is a frequently encountered phenomenon. Hereditary gingival fibromatosis was encountered in approximately 5% of our study group, which is considerably higher than in previous studies.[9,19] Since this genetically inherited disease can be seen in all family members, the high rate can be explained for this reason. The prevalence of consanguineous marriages in this area was thought to be one of the factors that increased the frequency.

One of the limitations of this study is that the number of samples is limited due to collection

from only 1 center. The other limitation is some inconsistencies when categorizing pathologically diagnosed biopsy lesions by pathological nature classification and new gingival disease classification. The benign neoplasm option was not available in the new classification; hemangioma and papilloma were collected under the title of benign neoplasms in this study. Papilloma has been evaluated in the new classification of infectious diseases of viral origin. However, the benign neoplasm title was preferred because there was no other case of infectious origin in our study, and there was no title in the 2018 classification for hemangioma.

As in all pathological formations, the relationship between the primary lesion and subsequent histological findings in non-plaque gingival pathologies is important for formulating a diagnostic hypothesis with specific clinical features. In the study of the American Board of Specialists in Oral Medicine examining the current approaches for the diagnosis and treatment of oral premalignant lesions, it was reported that most of the clinicians refer to the initial clinical diagnosis before taking a biopsy to make a diagnosis.[21] While this may be useful for starting treatment without delay, for this approach to be successful, the initial clinical diagnosis must be correct and no features have been overlooked. For this reason, it has become crucial to investigate the level of accuracy of clinical diagnoses made by clinicians against the definitive diagnosis reached by histopathological examination.[22]

In conclusion, the most frequently biopsied non-plaque gingival lesions were reactive lesions and premalignant neoplasms in a Turkish population. The types of lesions that clinicians in general and periodontists, in particular, can expect to encounter in their practice, as this study shows that they are the most frequently consulted gingival lesions. Considering the relationship between clinical diagnosis and histological findings, the accuracy of the initial clinical diagnosis can be increased by developing diagnostic hypothesis formulations.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Atatürk University (approval No: 017).

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

Peer-review: Externally peer-reviewed.

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Histology-Embryology

Protective Effects of Alpha Lipoic Acid Against Ionizing Radiation-Induced Hepatotoxicity in Rats

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ABSTRACT

Objective: Radiation is used to treat cancer but causes serious complications, such as liver toxicity. In this study, the protective effects of alpha lipoic acid against the unwanted effects of radiation used in many cancer treatments which can cause damage after treatment were investigated.

Material and Methods: The sample consisted of 32 Sprague–Dawley male rats randomized equally into 4 groups. The control group received no intervention. The alpha lipoic acid group was administered 50 mg/kg (dissolved in 0.9% NaCl) for 3 days. The ionizing radiation group was exposed to a total of 30 Gy radiation in 10 Gy fractions per day. The ionizing radiation + alpha lipoic acid group was administered 50 mg/kg alpha lipoic acid® prior to exposure to a total of 30 Gy radiation in 10 Gy fractions per day. Rats were sacrificed by cervical dislocation, and the liver was removed for histopathological studies and superoxide dismutase and malondialdehyde assays. Liver tissues were histopathologically assessed using hematoxylin-eosin staining after 4 weeks of the experiment.

Results: The ionizing radiation + alpha lipoic acid group had significantly less severe necrosis than the ionizing radiation group. Compared to the ionizing radiation group and the ionizing radiation + alpha lipoic acid group, superoxide dismutase enzyme activity was decreased with the addition of alpha lipoic acid. In addition, when the amount of malondialdehyde, which is a marker of oxidative stress, was examined, it was determined that the amount of malondialdehyde in the ionizing radiation + alpha lipoic acid group was lower than in the ionizing radiation Group.

Conclusion: Alpha lipoic acid® mitigates radiotherapy-induced damage in liver tissue.

Keywords: Alpha lipoic acid, liver, radiation, rat

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Introduction

Radiotherapy (RT) is a type of cancer treatment involving high doses of x-rays or other types of energy to kill cancer cells. Radiation is also referred to as ionizing radiation (IR) because it passes through tissues and ionizes atoms and molecules by removing electrons from them. Ionizing radiation can change genes or kill cells, which stops cell growth. The extent of radiation-induced damage depends on the dose of the radiation. It is possible to increase success rate in tumor control with increasing doses. However, the higher radiation dose means higher risk of complications in healthy tissues. Ionizing radiation affects healthy tissues directly or indirectly.[1] It not only affects the target molecule, DNA (direct effect), but also ionizes cellular atoms and causes molecular degradation (indirect effect).[2] Ionizing radiation affects tissues and cells in different ways.[3] It causes an increase in the number of free oxygen radicals, which adversely affect cellular membrane lipids, proteins, DNA, and the antioxidant defense mechanisms.[4] Therefore, radiation toxicity is a common side effect associated with reactive oxygen radicals causing oxidative damage.[5] Antioxidants suppressing free oxygen radicals can reduce radiation-induced tissue damage. There is a growing body of research on radiation radioprotectors to minimize radiation-induced oxidative damage.[6] The higher the radiation dose, the greater the cell cycle disruption leading to abnormal mitosis or cell death.[7]

The liver is the largest and an important organ in the human body. It is responsible for producing bile, storing glycogen, protein synthesis, production of hormones and enzymes necessary for digestion, ensuring the absorption of food metabolites, eliminating waste products, and breaking down red blood cells. Due to its physiological and biochemical functions, it is exposed to numerous toxicities and medications.[8] The liver has a low tolerance to radiation. However, a part of the liver may be exposed to a certain dose of radiation in the distal esophagus, upper abdomen, right lung, and whole abdomen or whole body.[9,10] Irradiation causes liver diseases, such as hepatitis and hepatocyte death.[11]

Laboratory experiments on animals allow us to work with populations with minimal individual variability and test appropriate doses of radiation and active substances and evaluate their biological effects. Moreover, laboratory experiments on animals provide insight into the effects and underlying mechanisms of IR because in vivo systems may react differently to radiation than in vitro systems.[12]

Many people undergo radiotherapy for cancer every year. Therefore, the effect of radiation on organs has been a matter of curiosity. Researchers have sought ways to prevent both acute and late toxicity due to radiation-induced toxicity that can sometimes be much worse than the first lesion for which treatment was received. Therefore, this study histopathologically and biochemically investigated the protective effects of alpha lipoic acid® (α-LA) against IR-induced damage to liver tissues in rats.

Materials and Methods

The study was approved by the Local Ethics Committee on Animal Experiments of our university (No: 8/215). The experiment adhered to the criteria outlined by the European Community Guidelines. The sample consisted of 32 Sprague–Dawley male rats (250 ± 20 g) bred at the Medical Experimental Application and Research Center of our university. The rats were kept in plastic cages under standard laboratory conditions at a constant temperature of 19-21°C for 12 hours of light/darkness throughout the experiment. They were fed with pellet feed *ad libitum* throughout the experiment.

Main Points

- Ionizing radiation therapy can cause damage to healthy liver tissue.
- Alpha lipoic acid can be used to reduce radiation-induced liver damage.
- We hope that if our study is supported by experimental studies in the future, alpha lipoic acid will find a new indication area.

Alpha lipoic acid® was supplied from Solgar Inc. Co. Ilko (Pharmaceutical Industry and Trade Inc., Turkey). It was dissolved in 0.9% NaCl and mixed until homogenized to produce α-LA suspension. Alpha lipoic acid® was administered by gavage to rats (50 mg/kg) in the α-LA group once daily for 3 days. Rats in the IR+ α-LA group were administered α-LA by gavage (50 mg/kg) for 3 days prior to exposure to radiotherapy.[13]

Rats were randomly classified into 4 experimental groups (groups 1-4): Control group received no therapy and only food and water; α-LA group was administered with 50 mg/kg α-LA ®, IR group was administered with ionized radiation (30 Gy), and IR+ α-LA group received both IR and α-LA, respectively (Table 1). The IR and IR+ α-LA groups were irradiated using a linear accelerator (Elekta Synergy®) at the Department of Radiation Oncology. Total body irradiation was performed using x-rays in a box made of wood with a size of 30 × 30 × 5 cm and a depth of 3 cm. The rats were mildly sedated with Sevoflurane (Sevorane®, Abbott Lab. Istanbul, Turkey) and irradiated in groups. A perforated tray was placed at the top of the box to allow the rats to get oxygen during irradiation. The total body irradiation was performed for 3 days with daily 10 Gy/fraction irradiation.

Histological Analyses

The rats were administered 20 mg/kg thiopental sodium and 5% sevoflurane inhalation anesthesia on the 30th day of the experiment. Necropsy was performed to collect liver tissues, which were fixed in 10% neutral formalin solution. Tissues were dehydrated in ascending grades of alcohol (50%, 70%, 90%, and 100%) for 3 hours and cleared in 2 changes of xylene (clearing agent) for 3 hours. The tissues were then infiltrated and embedded in paraffin wax (Sigma Aldrich), cut with a rotary microtome (Leica, RM2255), and stained using hematoxylin and eosin (H&E) staining technique.[14] Hepatocytes in 6 random regions were semi-quantitative as necrotic and degenerative; it was evaluated under light microscope as no (−), light (+), moderate (++), and (+++) by using the image analysis computer program named Image J 1.43, according to the intensity of staining: none (0), mild (1), moderate (2), and severe (3).[15]

Table 1. Experimental Groups

Groups	Alpha Lipoic Acid (mg/kg)	Radiation (Gy)
Control	No	No
α-LA	50	No
IR	No	30
IR+α-LA	50	30

α-LA, alpha lipoic acid (50 mg/kg); IR, ionized radiation (30 Gy); IR+α-LA, ionized radiation (30 Gy) + alpha lipoic acid (50 mg/kg).

Biochemical Analyses

The prescribed method for the determination of superoxide dismutase (SOD) activity proposed by Mc Cord and Fridovich[16] was followed Superoxide dismutase enzyme activity was expressed as U/mg protein. Malondialdehyde (MDA) analysis was determined using the method proposed by Draper and Hadley[17] and the results were given as nmol/g.

All data were analyzed using the Statistical Package for Social Sciences v. 20 (SPSS) (IBM. Corp., Armonk, NY, USA) at a significance level of $P < .05$. The Kruskal–Wallis test was used to determine between-group differences. The Mann–Whitney *U*-test was used for comparisons.

Results

Alpha lipoic acid® did not adversely affect the liver parenchyma. Control animals and α-LA group exhibit similar histological properties, which show normal histology with virtually intact central vein and healthy-looking hepatocytes ($P > .05$) (Figure 1 and 2). In the IR group, extensive necrosis was observed in hepatocytes (Figure 3). The IR+ α-LA group had significantly less severe necrosis than the IR group as shown in Figure 4. However, there were significant differences between the groups ($P < .05$) as presented in Table 2.

When we examined the SOD values of our study, it was seen that the SOD values in the IR group were significantly lower than the control group ($P < .001$). In the IR+ α-LA group, on the other hand, it was observed that the decreased

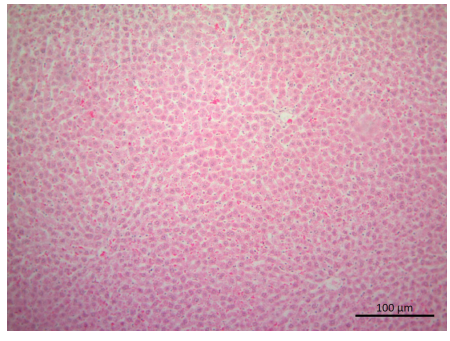

Figure 1. Control group, normal histopathology. ×100-H&E. H&E, hematoxylin and eosin.

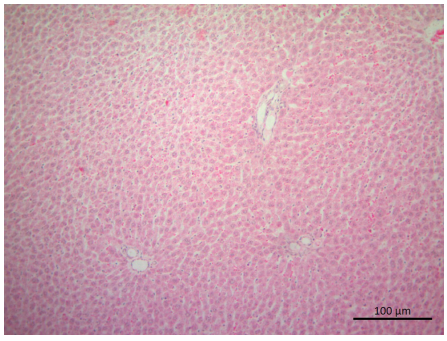

Figure 2. α-LA group, normal histopathology. ×100-H&E. α-LA, alpha lipoic acid; H&E, hematoxylin and eosin.

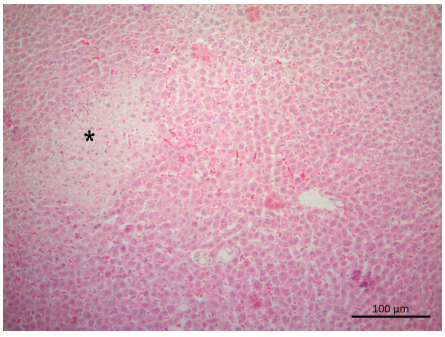

Figure 3. IR group, severe necrosis in hepatocytes (*).×100-H&E. IR, ionizing radiation; H&E, hematoxylin and eosin.

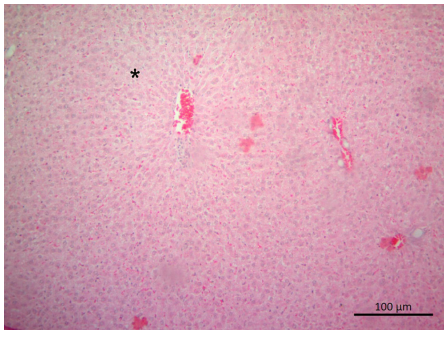

Figure 4. IR+ α-LA group, mild necrosis in hepatocytes (*).×100-H&E. H&E, hematoxylin and eosin; α-LA, alpha lipoic acid; IR, ionizing radiation.

Table 2. Histopathological Evaluation of Liver Tissue

Groups	Necrosis in Hepatocytes
Control	0.33 ± 0.51[a]
α-LA	0.33 ± 0.51[a]
IR	2.83 ± 0.40[b]
IR+α-LA	1.83 ± 0.40[c]

α-LA, alpha lipoic acid; IR, ionized radiation; IR+α-LA, ionized radiation + alpha lipoic acid. [a,b,c]Between-group differences ($P < .05$).

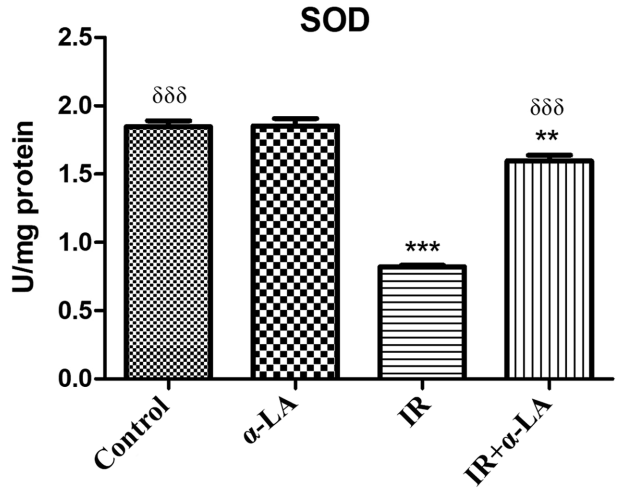

Figure 5. SOD values of groups. α-LA, alpha lipoic acid; IR, ionized radiation; IR+ α-LA, ionized radiation + alpha lipoic acid; SOD, superoxide dismutase. *Analysis of SOD values compared to the control group. [δ]Analysis of SOD values compared to the IR group. Significant difference, $P < .05$.

SOD values due to IR increased significantly with the administration of α-LA ($P < .001$) (Figure 5). Superoxide dismutase enzyme values of rats are presented in Table 3.

When we examined the MDA values of our study, it was seen that the MDA values in the IR group increased significantly compared to the control group ($P < .001$). In the IR+ α-LA group, it was observed that the increased MDA values due to IR decreased significantly with α-LA administration ($P < .001$) (Figure 6). Malondialdehyde values of rats are presented in Table 3.

Discussion

Radiation causes protein oxidation, lipid peroxidation, DNA chain breaks, as well as macromolecular changes. It also attacks certain cellular components and promotes various conditions, such as genomic instability and DNA damage, resulting in tissue damage.[18] Despite all the advances in radiotherapy, the early and late side effects of RT should never be ignored due to the effects of RT on normal healthy tissues. In some cases, the dose of RT cannot be given as

Table 3. SOD Enzyme Values and MDA Values in Rats of Given Groups (U/L)

Groups	SOD	MDA
Control	1.9	1.8
α-LA	1.99	1.2
IR	0.82	10.39
IR+α-LA	1.61	6.07

α-LA, alpha lipoic acid; IR, ionized radiation; IR+α-LA, ionized radiation + alpha lipoic acid; SOD, superoxide dismutase; MDA, malondialdehyde.
[a,b,c]Between-group differences ($P < .05$).

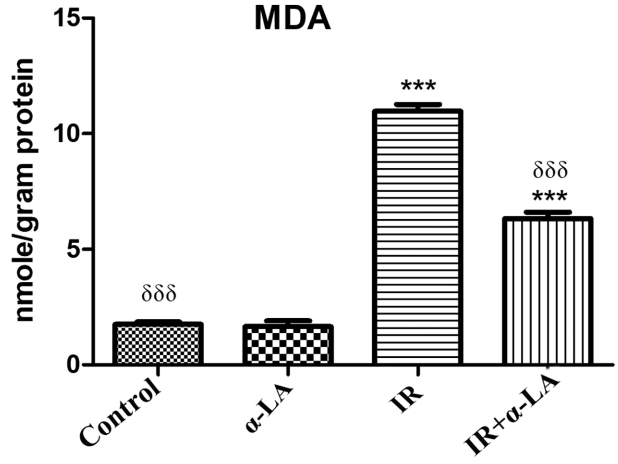

Figure 6. MDA values of groups. α-LA, alpha lipoic acid; IR, ionized radiation; IR+ α-LA, ionized radiation + alpha lipoic acid; MDA, malondialdehyde. *Analysis of MDA values compared to the control group. [δ]Analysis of MDA values compared to the IR group. Significant difference, $P < .05$).

high as desired because normal healthy tissue is very radiosensitive.[19]

Histological examination of the liver tissue of rat was carried out in this study which supports the biochemical findings after administering a 30 Gy dose of total body radiation. There was observed cellular damage and necrosis in hepatocytes in liver tissues. Karahan et al[20] reported an increase in the number of binucleated hepatocytes and a reduction in the number of proliferating hepatocytes in the liver of irradiated rats (10 Gy). Kim and Yung[21] determined that radiation caused fibrotic changes and cell damage in rodent livers. Cheema et al[22] observed metabolic changes in the liver tissues and slight changes in the other tissues of primates exposed to total body radiation (7.2 Gy). The findings of the present study indicated that the IR and α-LA group rat shows mild necrosis in hepatocytes which is an indication of pathologic improvement in most accumulative doses.

Hepatocytes are parenchymal cells that play an important role in many of their metabolic functions and account for approximately 80% of the formations in the liver. Radiation-induced toxicity causes dysfunctions and different lesions in hepatic cells.[23] The liver is a vital organ that is responsible for disposing of toxic metabolites and medications. The liver is mostly included in the RT field in the irradiation of upper abdomen malignancies. For this reason, some or all of the liver is exposed to the RT dose at certain rates.[24]

In our study, it was observed that SOD activity was higher in the IR group than in the IR+ α-LA group which shows that histological damage induced in the liver of irradiated rats was associated with the decrease in the activity of the antioxidant enzymes SOD. It was also observed that the amount of MDA was higher in the IR group than in the IR+ α-LA group. High levels of MDA, which is a determinant of lipid peroxidation, indicate that it causes cell damage. The results of our study are in accordance with the findings in a study by Saada et al[25], which suggested that histological damage induced in the liver of irradiated rats was associated with an increase in the content of lipid peroxides and a decrease in the activity of the antioxidant enzymes SOD and catalase. In addition, exposure to radiation causes injury to blood vessels provoking anoxia of tissues with degeneration and necrosis of hepatic parenchyma.[26] Also, cytoplasmic changes such as swelling, vacuolization, and alteration in the various components of the plasma membrane were seen.[27] Based on this, radiation is said to induce liver cell damage and is significantly inhibited by α-LA. The result of the present study shows that α-LA has protective properties against the undesirable effects of radiation due to the presence of natural antioxidant in α-LA.

Many cancer patients undergoing radiotherapy suffer from liver tissue damage because it enters the radiation field. The effects of IR on the organism depend on many factors that should be addressed from a broad spectrum. Limitations of this research include low access to funds and other high throughput equipment and molecular techniques to study the possible mutations induced by radiation. In conclusion, we can state that α-LA can be used to reduce radiation-induced liver damage. However, further preclinical and clinical research is warranted to better understand its molecular basis and effects and find answers to its toxicity, tolerability, and dose.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Atatürk University (Date: 21 September, 2021, Approval No: 215-8).

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

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Author Contributions: Concept – A.G., E.L., M.K.B.; Design – A.G., E.L., M.K.B.; Supervision – A.G.; Resources – A.G., E.L., M.K.B.; Materials – A.G., E.L., M.K.B.; Data Collection and/or Processing – A.G., E.L., M.K.B.; Analysis and/or Interpretation – A.G., E.L., M.K.B.; Literature Search – A.G., E.L., M.K.B.; Writing Manuscript – A.G., E.L., M.K.B.; Critical Review – A.G.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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Lutetium-177 Prostate-Specific Membrane Antigen-617 Treatment in Metastatic Castration-Resistant Prostate Adenocarcinoma: Results of Single-Center Experience

Adem Maman

ABSTRACT

Objective: Lutetium-177 prostate-specific membrane antigen-617 is a novel alternative therapeutic option in metastatic castration-resistant prostate cancer, especially useful for patients who do not respond to standard therapy methods. The aim of this study was to define the efficacy and safety profile of lutetium-177 prostate-specific membrane antigen-617 treatment in a group of patients with metastatic castration-resistant prostate cancer.

Materials and Methods: Study group included 34 men with metastatic castration-resistant prostate cancer (median, 69.6 ± 7.7 years) who were treated with lutetium-177 prostate-specific membrane antigen-617 therapy (22/34; 4 courses, 12/34; 2 courses). Patients were evaluated by physical examination, Eastern cooperative oncology group performance status, gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography, brief pain inventory-short form questionnaire, biochemical tests, and complete blood counts. Treatment response and adverse effects were examined by brief pain inventory scores, SUV_{max} values, biochemical tests, and complete blood counts. Independent variables were analyzed statistically (significance; $P < .05$).

Results: The Eastern cooperative oncology group performance was grade 0 in 5/34 (14.7%), grade 1 in 25/34 (73.5%), and grade 2 in 4/34 (11.8%) patients. Distribution of patient numbers according to brief pain inventory scores (score: <1, scores: 1-4, and scores: 5-10) was 2, 10 and 22 at the beginning, 6, 16 and 12 after the second course, and 10, 10 and 2 after the fourth course of treatment, respectively. Serum prostate-specific antigen decreased in 15 of 22 patients (68%) ($P < .05$). Before and after the treatment, we found a substantial decrease in SUV_{max} values (22.3 vs. 11.8, $P < .001$) and brief pain inventory scores (score ≥ 5; 22/34 pts vs. 0/22 pts). The counts of white blood cells ($P < .05$), hemoglobin ($P < .05$), and thrombocytes ($P = .001$) were all significantly lower at the conclusion of the therapy. The most important adverse events were severe leukopenia (1/34 pts; 2.29 × 10^3/μL) and thrombocytopenia (3/34 pts; 32 000, 36 000, 32 000 × 10^6/L).

Conclusion: We found that lutetium-177 prostate-specific membrane antigen-617 therapy is a promising treatment method for metastatic castration-resistant prostate cancer patients who are unresponsive to conventional therapy, according to our biochemical, positron emission tomography/computed tomography, and pain score outcomes.

Keywords: Prostate cancer, 177Lu-PSMA-617, 68Ga-PSMA-11 PET/CT, PSA, pain score, SUVmax

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Introduction

Prostate adenocarcinoma is the second commonest cancer worldwide and one of the leading causes of cancer death. It still has significant morbidity and mortality despite diagnostic and therapeutic advances.[1,2] Androgen deprivation therapy (ADT) is the gold standard method for patients with prostate cancer. In spite of the high initial response rates, cancer treatment with ADT is of limited duration; many men eventually develop progressive disease, so-called metastatic castration-resistant prostate cancer (mCRPC) following ADT.[3] Since the approval of docetaxel as the first-line chemotherapy in 2004, several new life-prolonging systemic therapies such as abiraterone, enzalutamide, cabazitaxel, and ^{223}radium have become available for mCRPC patients. Despite these treatments, many patients have progressed to advanced cancer stages despite new treatment modalities. Today, effective therapeutic alternatives are needed to control disease-related symptoms and to improve quality of life.

Lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA-617) has become a potent treatment agent thanks to the increased expression of PSMA in most men with mCRPC.[4,5] It has been reported that ^{177}Lu-PSMA-617 treatment is valuable in providing biochemical and symptomatic pain control and improving quality of life in mCRPC patients.[5]

Prostate-specific membrane antigen, also called folate hydrolase I or glutamate carboxypeptidase II, is expressed at high levels in prostatic adenocarcinoma cells. It has been reported that there is a significant increase in PSMA levels of patients who have either high-grade or castration-resistant cancers. Prostate-specific membrane antigen represents an excellent biomarker for both imaging and treatment of prostate cancer and so this topic has become the focus of extensive research. Some tissues have varying degrees of PSMA expression, including prostate epithelium, small intestine, renal tubules, and salivary glands.[6]

Prostate-specific membrane antigen is a type II transmembrane protein with 2 monomers and corresponding intracellular transmembrane and extracellular domains that are enzymatically active proteins in homodimeric form.[7] In ligand binding, PSMA undergoes clathrin-mediated endocytosis.[8] Identification of the substrate and binding site has spurred the development of urea-based high-affinity PSMA inhibitors with favorable biodistribution and high tumor-to-background uptake rates.[6] Lutetium-177 prostate-specific membrane antigen-617 synthesis was originally developed by the German Cancer Research Center (DKFZ, DeutschesK rebsforschungszentrum) in collaboration with University Hospital Heidelberg. It is a small molecule inhibitor that binds to PSMA with high affinity. The short-range 1 mm path length of the beta particle emitted by ^{177}Lu ensures effective delivery of radiation to tumoral tissue while minimizing damage to surrounding normal tissues.[9]

Main Points

- Lutetium-177 prostate-specific membrane antigen-617 (^{177}Lu-PSMA-617) therapy is an important treatment option for metastatic castration-resistant prostate cancer (mCRPC) patients who do not respond to conventional treatment protocols.
- ^{177}Lu-PSMA-617 treatment significantly reduces the pain that negatively affects the quality of life in patients with metastatic prostate cancer.
- ^{177}Lu-PSMA-617 treatment appears to be safe in patients with mCRPC with a low side effect profile.

The aim of this retrospective study was to report our results and confirm the efficacy and side effect profile of ^{177}Lu-PSMA-617 treatment in mCRPC patients.

Materials and Methods

Study Group

A total of 42 consecutive patients, between February 2017 and November 2021, were referred to the Department of Nuclear Medicine of Atatürk University Medical Faculty Hospital. All patients were discussed by an interdisciplinary tumor board for ^{177}Lu-PSMA-617 therapy recommendation due to mCRPC. The study protocol conforms to the Declaration of Helsinki and was approved by the local ethics committee (decision date: November 25, 2021; decision number: 08-26). Since this study was a retrospective study, informed consent form could not be obtained from the patients. After evaluation according to exclusion criteria, the final study group consisted of 34 mCRPC patients (age range; 69.6 ± 7.7 years) who underwent ^{177}Lu-PSMA-617 therapy.

Pre-Evaluation and Exclusion Criteria of Patients

At the time of hospitalization, all patients with mCRPC who were candidates for ^{177}Lu-PSMA-617 therapy were subjected to a physical examination by an experienced medical doctor, and necessary tests were performed for preliminary evaluation. Patients were graded by the Eastern cooperative oncology group (ECOG) performance status and Brief Pain Inventory (BPI) score according to previously published criteria.[10] Routinely measured laboratory parameters in each patient included complete blood counts and biochemistry tests [liver function enzymes, serum creatinine, and prostate-specific antigen (PSA) levels]. Each patient underwent a gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA-11 PET/CT) prior to treatment to demonstrate the presence of PSMA over-expression in their lesions.

We used some exclusion criteria and 8 patients were excluded from this study. The criteria for blood picture are as follows: liver enzymes more than 5 times the upper limit, total white blood cell (WBC) count less than 3×10^9/L, platelet count less than 75×10^9/L, and hemoglobin less than 8 g/dL. We excluded 4 patients (n = 4) due to low platelet counts. The other 4 excluded patients (n = 4) had metastases on CT but no PSMA expression on ^{68}Ga-PSMA-11 PET/CT.

Lutetium-177 prostate-specific membrane antigen-617 therapy

We followed a previously published ^{177}Lu-PSMA-617 treatment protocol for all patients.[6] We applied 4 courses of treatment to 22 of 34 (64.7%) patients. We had to apply 2 courses of treatment in 12 of 34 patients due to the following reasons; six patients refused to continue the next courses of the treatmente clinicians decided to terminate the treatment in four patients, two patients died due to another concomitant disease before the third course of the treatment. The interval between each course of treatment was 6-8 weeks. During each administration, patients received an infusion of 1 L of normal saline at 300 mL/h, 30 min before ^{177}Lu-PSMA-617 administration with an average dose of 7315 ± 573 MBq. We did not use a special protection method for the salivary glands.

Evaluation of Treatment Response

A rate of change in BPI score, serum PSA, and lesion SUV_{max} values obtained before and after administration of ^{177}Lu-PSMA-617 was examined to evaluate the treatment response. Follow-up BPI score assessments were repeated 2 times; 45 days after the fourth course of the treatment in 34 patients and 1 month after the fourth course of the treatment in 22 patients. Serum PSA measurements and ^{68}Ga-PSMA-11 PET/CT were routinely performed in each patient 1 month after the last course of ^{177}Lu-PSMA-617 administration.

Evaluation of Side Effects

All patients were evaluated in order to define treatment-related side effects. They were questioned for the presence of newly developed symptoms after each course administration. They were examined by complete blood counts and biochemistry tests 1 month after the last course of treatment and test results were analyzed for change before and after ^{177}Lu-PSMA-617 therapy. Toxicity-attributed side effects and hematologic changes were documented according to version 4.0 of the Common Toxicity Criteria for Adverse Events.

Statistical Analysis

Statistical analyses were performed using the International Business Machines' Statistical Package for the Social Sciences Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilks test) to determine whether or not they are normally distributed. Data with normal distribution

are given as mean ± standard deviation (SD), and the data whose distribution was not normal are given as median (interquartile range). After checking the normality distribution of scale variables, independent samples were compared with appropriate significance tests (e.g., the Mann–Whitney *U* test, Kruskal–Wallis H test). The results with $P < .05$ were considered statistically significant.

Results

The characteristics of the patients included in the study are given in Table 1. The mean age of 34 patients was 69.6 ± 7.7 years. Eastern cooperative oncology group performance status of the patients was grade 0 in 5/34 patients (14.7%), grade 1 in 25/34 patients (73.5%), and grade 2 in 4/34 patients (11.8%). All patients had bone metastases, whereas 14/34 patients (41.2%) had lymph node metastases. In addition to ^{177}Lu-PSMA-617 administration, 10/34 patients (29.4%) received a standard chemotherapy regimen and 12/34 patients (35.3%) received a standard chemotherapy regimen + second-generation hormone therapy. Around 12 of 34 patients (35.3%) did not receive standard chemotherapy or second-generation hormone therapy prior to ^{177}Lu-PSMA-617 treatment.

The BPI score values of 34 mCRPC patients before and after treatment are given in Table 2.

The distribution of patient numbers according to BPI scores (score:<1, score:1-4 and score:5-10) were 2, 10 and 22 at the beginning, 6, 16 and 12 after the second course, and 10, 10 and 2 after fourth course of treatment, respectively. No acute event development was observed during the treatment applications. Following 177Lu-PSMA-617 administration, patients' bone pain and quality of life improved progressively. Initially, 32 of 34 patients (94.1%) had pain complaints. After the second course of treatments, the number of patients with pain decreased from 32 to 25 (82.3%). While the number of patients who experienced moderate/severe pain at the beginning was 22, 10 patients had moderate/severe pain after 2 courses of 177Lu-PSMA-617 treatment (decrease from 64.7% to 35.3%). In addition to these, it is reported that 22/34 patients who completed 4 courses of treatment. Among these, 10/22 patient (45.5%) no longer complained of pain. Only 2/22 patient (9%) had moderate pain while 10/22 patients (45.5%) had mild pain.

Table 3 summarizes the results of biochemical markers, complete blood counts, and ^{68}Ga-PSMA-11 PET/CT-derived semiquantitative SUV_{max} values of the patients and the comparisons of pre- and post-treatment values to assess treatment response and side effects. When we compared pre- and post-treatment PSA levels of the patients, we found a statistically significant difference between these 2 data sets ($P < .05$, 115 vs. 24 ng/mL, Figure 1). After the fourth course of ^{177}Lu-PSMA-617 therapy, a PSA decline was detected in 15 of 22 patients (68.1%). Thirteen of these 22 patients (59%) had a decrease of more than 50%, and there was more than 80% reduction in 9 of them (40.9%). In agreement with the decreasing PSA values, we found a statistically significant difference between pre- and post-treatment bone SUV_{max} values ($P < .001$) and a distinct decrease in median SUV_{max} values (22.2 vs. 11.8). Gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography images of a patient before and after 4 sessions of ^{177}Lu-PSMA-617 treatment are given in Figure 1.

After ^{177}Lu-PSMA-617 treatment, no significant change was detected in serum creatinine and calcium levels of the patients ($P > .05$). A statistically significant decrease was found in the WBC, hemoglobin, and platelet counts of the patients after ^{177}Lu-PSMA-617 treatment (*P* values; <.05, <.05, =.001, respectively) (Table 3 and Figure 2). In addition, severe leukopenia (2.29 10^3/μL) was observed in 1 patient and severe thrombocytopenia (32 000, 36 000, 32 000 10^6/L) developed in 3 patients.

Discussion

Prostate cancer is one of the most common types of human urogenital system malignancies. It still has serious morbidity and mortality

Table 1. Demographical and Clinical Features Before ^{177}Lu PSMA of 34 Patients with mCRPC Treatment

Parameters	Values
Number of patients (n)	34
Age (mean ± SD)	69.6 ± 7.7
ECOG Index (n/%)	
Grade 0	5/14.7
Grade 1	25/73.5
Grade 2	4/11.8
PSMA-RLT before (n / %)	
Chemotherapy	10/29.4
Chemo-hormonal therapy	12/35.3
Metastatic lesion (n / %)	
Bone	34/100
Lymph node	14/41.2

ECOG Index, Eastern Cooperative Oncology Group Index; PSMA-RLT, prostate-specific membrane antigen directed radioligand therapy.

Table 2. Distribution of mCRPC Patients' BPI Scores at the B eginning (n = 34) and After the Second Course (n = 34) and Fourth Course (n = 22) of 177Lu-PSMA-617 Therapy

	Initial	After the Second Course of Treatment	After the Fourth Course of Treatment
	n (%)	n (%)	n (%)
No pain (score: <1)	2 (5.8)	6 (17.6)	10 (45.5)
Mild pain (scores: 1-4)	10 (29.5)	16 (47.1)	10 (45.5)
Moderate to severe pain (scores: 5-10)	22 (64.7)	12 (35.3)	2 (9)

BPI, brief pain inventory; mCRPC, metastatic castration-resistant prostate cancer.

Table 3. Comparison of Pre- and Post-treatment Values for Biochemical Markers, Complete Blood Counts, and PET-Derived Semiquantitative SUV_{max} Index of mCRPC Patients

Parameters	Pre-treatment Value	Post-treatment Value	*P*
Creatinine (mg/dL)	0.85 (0.73-1.1)	0.78 (0.54-1.01)	NS
WBC (10^3/μL)	7.2 ± 2.2	5.9 ± 2.1	<.05
Hemoglobin (g/dL)	11.8 ± 1.9	10.8 ± 1.9	<.05
Platelet (10^3/mm^3)	248 ± 75	176 ± 79	.001
Calcium (mg/dL)	9.1 (8.7-9.6)	8.9 (8.4-9.3)	NS
Bone SUV_{max}	22.3 (13.7-35.6)	11.8 (5.8-14.5)	<.001
PSA (ng/mL)	115 (24-188)	24 (4.5-115)	<.05

mCRPC, metastatic castration-resistant prostate cancer; NS, not significant ($P > .05$); PSA, prostate-specific antigen; WBC, white blood cells.

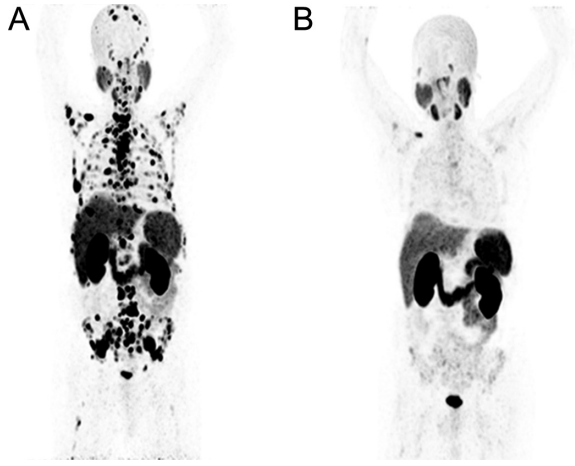

Figure 1. Baseline (A) and follow-up (B) after 4 cycles ^{68}Ga-PSMA-11 PET/CT of a patient with mCRPC, who was treated with 7315 ± 573 MBq ^{177}Lu-PSMA-617. Prostate-specific antigen (PSA) response was as follows: 107.8 ng/mL (baseline) and 2.92 ng/mL (after 4 cycles). ^{68}Ga-PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography; ^{177}Lu-PSMA-617, lutetium-177 prostate-specific membrane antigen-617; mCRPC, metastatic castration-resistant prostate cancer.

despite the use of new treatment protocols and advanced diagnostic imaging methods. Androgen deprivation therapy is positioned as the first-line application in the treatment algorithm of prostate cancer. A combination of chemotherapy, radiotherapy, and a second-generation anti-androgen drug is often preferred in patients with advanced prostate cancer. In recent years, ^{177}Lu-PSMA-617 has been used more frequently as an alternative or complementary treatment option in advanced disease, especially for mCRPC patients.[1,2]

Prostate-specific antigen is a useful biomarker approved by US Food and Drug Administration for diagnosing and monitoring prostate cancer.

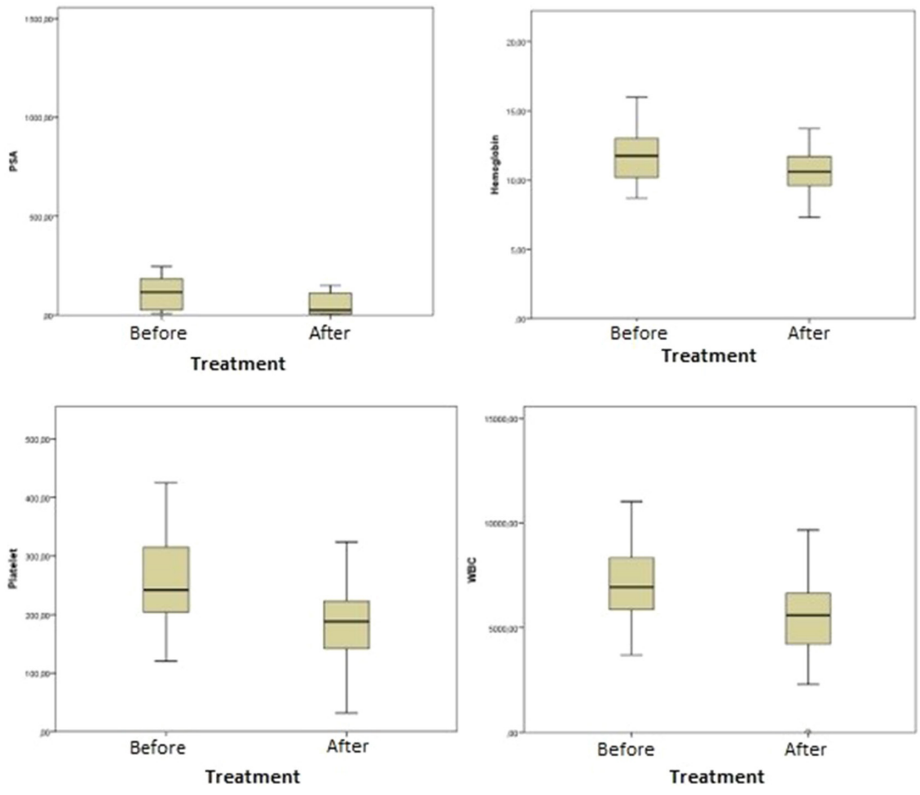

Figure 2. Box plots of prostate-specific antigen (top left), platelet (bottom left), hemoglobin (top right), and white blood cells (bottom right) of metastatic castration-resistant prostate cancer patients before and after lutetium-177 prostate-specific membrane antigen therapy-617 (^{177}Lu-PSMA-617).

It is especially useful in the follow-up of patients with advanced disease and it correlates well with their clinical status. According to the results of a pooled meta-analysis studied on 10 different studies which are investigating the efficacy of ^{177}Lu-PSMA-617 therapy, there was a decrease in PSA level in 165 of 238 patients (69.3%).[11] This meta-analysis also confirmed our results (68%). Extreme low and high efficacy values were also observed. However, some studies have reported lower and higher rates. In the study by Ahmadzadehfar et al.[12] a decrease in PSA level after ^{177}Lu-PSMA-617 therapy was found to be 79.1%, while Kratochwil[9] found it to be 72%. Rahbar et al[13], on the other hand, measured the decrease in PSA as 59.7%.

According to meta-analysis by Emmett et al.[14] hematological side effects are common and significant, especially for bone metastasis. In their analysis, hemoglobin levels ranged from 10% to 32%, platelet counts ranged from 0% to 25%, and WBC counts ranged from 3% to 15%. Our study is compatible with the meta-analysis of Emmett in terms of hematological side effects. In our study, hemoglobin level, platelet, and WBC count decreased by 8.94%, 29%, and 18%, respectively. This side effect is mostly observed either in grade 1 or grade 2. However, severe side effects could be reported in patients who take chemotherapy before the ^{177}Lu PSMA.

The significant decrease in PSA value, which is accepted as the most important biomarker of prostate cancer, can predict that patients respond positively to ^{177}Lu-PSMA-617 treatment. In our study, ^{177}Lu-PSMA-617 treatment was administered to patients who progressed despite chemotherapy and second-generation anti-androgen therapy and to patients who were unsuitable or did not accept this treatment. In our series, when we evaluate PSA and bone SUV_{max} values of patients, a significant decrease was found in the PSA levels ($P < .05$), and a significant decrease was observed in the SUV_{max} values of the patients ($P < .001$) according to the ^{68}Ga-PSMA-11 PET/CT scores obtained before and after the treatment. This significant decrease in SUV_{max} values is another good indicator of response to the treatment. When these 2 parameters were integrated, it was seen that the patients have a positive response to this alternative treatment. According to our survey on pain scores, it was reported that patients felt severe bone pain before and after the therapy. A remarkable decrease was observed in many patients even after the administration of the first dose. Significant pain reduction was observed in 27 (79.41%) of 34 patients; although there was

no decrease in PSA level in 3 patients, a decline in pain score was also observed.

In all patients, WBC, calcium, hemoglobin, platelet, and creatinine levels were followed; even if some of those values decreased during therapy, the values were within normal limits. It was reported that only 1 patient developed severe leukopenia and 3 patients developed severe thrombocytopenia. Taking into account all mentioned findings and the severity of present side effects, we emphasized that the ^{177}Lu-PSMA-617 treatment does not have a serious side effect profile, as well as it has promising results and remarkable improvements in the patient's quality of life.

This study has some limitations as it was carried out with a limited number of patients in a small group. For more precise results, the patient group should be enlarged. Another limitation of the study is that we could not complete the standard 4 courses treatment regimen in all patients. This expectation is difficult to meet due to patient compliance, other treatment options, co-morbidities, and social reasons. Nevertheless, we think that our findings still remain reliable since most of the patients in the study group (22/34; 64.7%) met this requirement.

In conclusion, ^{177}Lu-PSMA-617 therapy is an important treatment option for mCRPC patients who do not respond to conventional treatment protocols. It has a low side effect profile and can improve patients' quality of life thanks to its therapeutic effect on metastatic lesions.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Atatürk University (Date: November 25, 2021, Approval No: 26).

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

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Hematology

Should Core Needle Lymph Node Biopsy be a Relevant Alternative to Surgical Excisional Biopsy in Diagnostic Work Up of Lymphomas?

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ABSTRACT

Objective: Surgical excisional biopsy is accepted as the standard of care approach in the diagnosis of lymphomas. Financial issues related to the increased cost and the invasive nature of the procedure forced physicians to use some alternative diagnostic methods. Percutaneous core needle biopsy, which gained a reputation for the diagnosis of lymphomas with the advent of improved pathological, immunohistochemical, and molecular analysis, made it possible to have an accurate diagnosis with limited tissue samples. In this retrospective study, we aimed to compare the diagnostic yield of surgical excisional biopsy and core needle biopsy.

Materials and Methods: This study included 131 patients who were diagnosed with lymphoma with a nodal biopsy which was acquired via surgical excisional biopsy or core needle biopsy between 2014 and 2020 in our center. Around 68 patients underwent surgical excisional biopsy and the remaining 63 underwent core needle biopsy. Samples that allowed to the identification of the exact tumor type and/or subtype were accepted as fully diagnostic. Sufficient amount of tissue that the pathologist could have any suspicious findings considering malignant lymphoma was classified as partial diagnostic group. Inadequate samples were the ones who were not enough to report any final diagnosis.

Results: The patients who underwent a core needle biopsy were significantly older than the patients who underwent to surgical excisional biopsy (56.8 vs. 47.6, $P=.003$). Despite the full diagnostic ability of surgical excisional biopsy outperformed core needle biopsy (95.2 % vs. 83.8 %, $P=.035$), in 92.6% of the patients whose tissue samples were obtained via core needle biopsy were accepted to have a sufficient diagnosis to initiate the treatment and not required a second biopsy, which was comparable with the ones achieved by surgical excisional biopsy (92.6% vs. 95.2%, $P=.720$).

Conclusion: According to the results obtained in our study, we may conclude that core needle biopsy is a viable and comparable alternative to surgical excisional biopsy, offering a less invasive and less-expansive approach.

Keywords: Core needle biopsy, diagnostic, excisional biopsy, interventional, lymphoma

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Introduction

Lymphoid malignancies are the tumors of immune system originating from B and T lymphocytes and rarely natural killer (NK) cells. Lymphomas generate an extremely heterogeneous group of disorders based on their biological, molecular, and genetic features, histological forms, sites of clinical presentation, and response to treatment. This heterogenetic complexity led to the development of some controversial and complicated classification systems. The World Health Organization (WHO) classification for lymphoid neoplasms is classification that is accepted all around the world and was recently updated in 2016.[1]

Diagnosis of lymphoproliferative disorders is based on obtaining a tissue sample and histological examination of this sample by hemato-pathologists. Aside from other malignancies, lymphoma diagnosis needs much more sample to observe whole architecture, especially in lymph nodes. Diagnostic methods can differ according to the preference of the center, logistic, and financial factors. Surgical excision biopsy (SEB), percutaneous fine-needle aspiration (FNA), and core needle biopsy (CNB) are the main sampling modalities in this regard.

Fine-needle aspiration is a faster and cheaper technique when compared to the CNB and SEB. However, due to its high false-negative rate and low specificity, it is not accepted as a proper choice for the evaluation of lymphadenopathies for hematological malignancies.[2] The WHO system for lymphoma classification relies on histological findings from excisional biopsies.[3] Also, current lymphoma guidelines like the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network emphasize SEB as a standard of care for the diagnosis and classification of lymphoid neoplasms.[1,4,5]

The excisional biopsy of a whole lymph node is regarded as the gold standard for the diagnostic workup of lymphomas; however, CNB should also be a viable alternative to this approach. European Society for Medical Oncology guidelines indicate CNB as an alternative diagnostic approach in lymph nodes which are not easily accessible.[6] Before the advent of recent modern immune-histological methods, pathologists generally needed to investigate whole background architecture of an excisional biopsied tissue to make certain diagnosis and sub-typing of a lymphoma. But nowadays, they can make a final diagnosis and sub-typing with small tissue samples. Even SEB is accepted as the gold standard approach in the diagnosis of lymphomas, CNB is increasing in frequency and gaining more reputation.[7]

Another issue is that surgical excision of a lymph node or a tissue requires sedation or a general anesthesia, which makes it a more invasive and costly approach throughout the process of diagnostic workup. However, CNB can be applied by local anesthesia and can be finalized in less than half an hour. Also, it is much cheaper when compared to SEB. One other major advantage of CNB is the remaining tissue which allows a more accurate follow-up after the initial treatment.[8] Core needle biopsy offers a less-invasive and cost-effective approach and possibly serves as a perfect alternative to excisional biopsy.

Main Points

- Core needle biopsy (CNB) alone has a highly satisfying diagnostic ability according to the results of the study.
- Comparison of total diagnostic yield which allowed the patients to proceed with appropriate treatment was statistically not different between CNB and surgical excisional biopsy group.
- Core needle lymph node biopsy is an alternative diagnostic approach in workup of lymphomas, not only in patients who have deep and un-accessible lymph nodes but also the ones who have superficial lymph nodes.

With these regards, we wanted to compare the diagnostic yield of CNB samples comparing with the samples obtained via excisional biopsy from our center.

Materials and Methods

Biopsies performed with CNB or SEB technique to rule out malignant or non-malignant pathologies were retrospectively retrieved from the archives of the department of pathology at our institution from the year 2014 until 2020. All of the CNB and SEB biopsies in the archives of pathology department were evaluated regardless of the samples' origin of department. All specimens were evaluated at a tertiary University Hospital by dedicated hemato-pathologists who were experienced in the diagnosis of lymphoproliferative disorders.

Patients who were under the age of 18 at the time of biopsy and biopsies which revealed a benign pathology and the biopsies which revealed a malignant pathology except lymphomas were excluded. Totally, 753 biopsy samples were evaluated. The total number of samples obtained with SEB was 443 and CNB was 350. After excluding the patients who were under the age of 18 at the time of biopsy, benign pathologies, non-lymphoma malign pathologies, and non-nodal samples, we had 68 biopsies to analyze for CNB group and 63 biopsies for SEB group (Figure 1). A written informed consent was obtained from every patient who was included in the study.

Samples were separated into 2 groups consisting of SEB and CNB. All demographic data including age, gender, patient, and disease-specific characteristics and the location of the specimen obtained were recorded alongside the final diagnosis. All the biopsies were re-classified into 3 groups according to the sufficiency of the diagnostic yield "fully diagnostic," "partial diagnostic," and "inadequate." Samples that allowed to the identification of the exact tumor type and/or subtype or which were accepted to be sufficient for the initiation of the lymphoma treatment were grouped as fully diagnostic. Sufficient tissue that pathologist could have any suspicious findings considering malignant lymphoma classified as partial diagnostic group. The last group was inadequate tissue group as its name describes not enough sample to conclude any diagnosis, generally, these samples were necrotic or quite small samples. Also, all CNB samples were evaluated as if there were any need for an additional SEB to make the final diagnosis or a diagnosis to initiate the proper treatment.

Samples were classified according to the dimensions of tissues, smaller than 3 cm, between 3 and 6 cm, and larger than 6 cm. F-fluorodeoxyglucose (FDG) avidity of the lymph node was recorded, if the patient had a Positron Emission Tomography (PET) scan before the biopsy. Imaging method before the biopsies, sample number of CNB tissues, and size of the core needle were also recorded.

All CNB were performed by 1 interventional radiologist using coaxial biopsy technique. After local anesthesia, 17-gauge coaxial needle (Argon Medical Devices, Inc. Athens, Tex, USA) was inserted into the lymph node under ultrasound (US) guidance in superficial locations and under computed tomography (CT) guidance in deep locations. An 18-gauge core biopsy needle (Tru-Core II Biopsy Instrument, Argon Medical

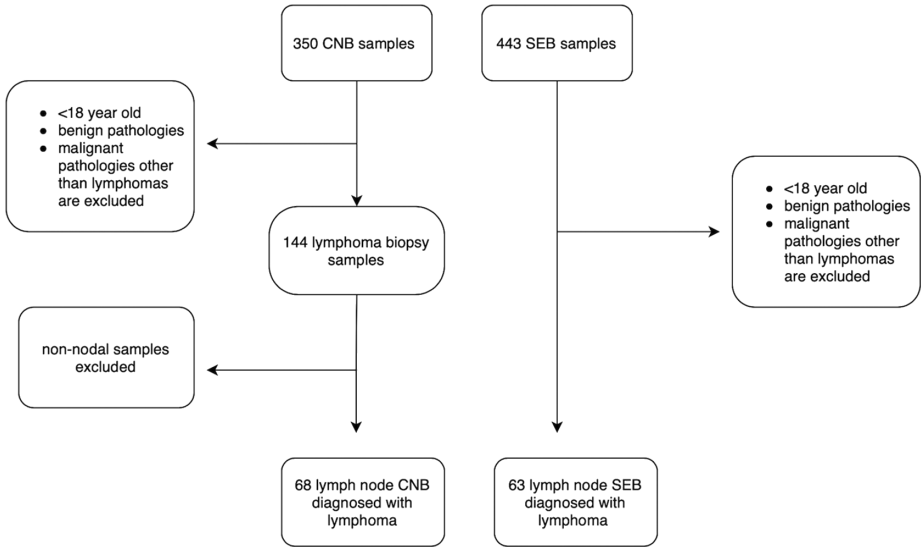

Figure 1. Flow chart defining the inclusion, exclusion criteria, and the production of final dataset.

Devices, Inc) which has 2 cm tissue core length was then introduced through the coaxial needle to reach the lymph node and fired at least 8 times to obtain adequate biopsy samples from different regions of the lymph node. Core needle biopsy samples were just visually inspected by a dedicated interventional radiologist and there was not any rational sample competency assessment at the time of procedure.

This study was approved by institutional local ethical committee with the approval id of E-10840098-772.02-793.

Statistical Analysis

Variable distributions were assessed by the Shapiro–Wilk normality test. According to the variable distribution, Student's *t*-test or Mann–Whitney *U* test was applied for the comparison of groups regarding quantitative data. Categorical variables were compared by the χ^2 test and fisher's exact test accordingly. Statistical analysis was performed using Statistical Package of Social Science (SPSS Inc., Chicago, Ill, USA), version 22.0 for Windows. Data were expressed as median (range) and a *P* value less than .05 was accepted as statistically significant.

Results

Totally, 131 lymph node biopsies were evaluated retrospectively according to the pre-defined inclusion and exclusion criteria. Patients' cohort consisted of 78 males and 53 females, and the median age was 55. A total of 68 (51.9%) of 131 histopathologic samples were CNB and 63 (48.1%) were SEB. There was a statistically significant difference between age in 2 groups. Median age was 56.81 in CNB group and 47.57 in SEB group ($P=.003$). When we checked out the biopsy locations, most of the samples were obtained from head and neck in both groups (44.1% and 65.1%). Patients' demographics and biopsy locations are summarized in Table 1. When the locations of biopsies obtained were compared between SEB and CNB groups, there was a statistically significant difference, and this difference was attributed to an increased number of biopsies from head and neck region in favor of SEB (65.1%) and vice versa from abdomen in favor of CNB (44.1%). Samples that were obtained from deep lymph node stations such as paraaortic, mesenteric, splenic, iliac, or mediastinal were favored in CNB group with the rate of 30.9%, comparing to 4.8% in SEB group ($P < .001$). The median number of samples that were obtained with coaxial technique in CNB group was 11.5 (2-45). There was not any significant difference between number of samples and diagnostic ability in CNB group.

Table 1. Patient Demographics, Biopsy Locations, and Diagnosis Among CNB and SEB Groups

	Core Needle Biopsy (n=68)	Surgical Excisional Biopsy (n=63)	*P*
Gender, n (%)			
Male	38 (55.9)	40 (63.5)	.375
Female	30 (44.1)	23 (36.5)	
Age, median (range)	56.8 (19-86)	47.6 (19-87)	.003*
Number of samples obtained	11.5 (2-45)	-	
Location, n (%)			
Head and neck	30 (44.1)	41 (65.1)	.001*
Chest	1 (1.5)	0 (0)	
Axilla	6 (8.8)	8 (12)	
Abdomen	19 (27.9)	2 (3.2)	
Inguinal	12 (17.6)	12 (19)	
Location due to accessibility			
Superficial	47 (69.1%)	60 (95.2%)	<.001*
Deep	21 (30.9%)	3 (4.8%)	
Diagnosis			
Hodgkin lymphoma	19 (27.9)	26 (41.3)	.315**
Non-Hodgkin lymphoma			
Diffuse large B cell lymphoma	11 (16.2)	7 (11.1)	
Peripheral T cell lymphoma	2 (2.9)	10 (15.9)	
High-grade B cell lymphoma	8 (11.8)	6 (9.5)	
Follicular lymphoma	10 (14.7)	9 (14.3)	
Marginal zone lymphoma	3 (4.4)	2 (3.2)	
Mantle cell lymphoma	6 (8.8)	0 (0)	
Atypical lymphoid proliferation	3 (4.4)	1 (1.6)	
Others	6 (8.8)	2 (3.2)	

*$P < .05$; **Hodgkin lymphoma and non-hodgkin lymphoma groups were compared.
CNB, core needle biopsy; SEB, surgical excisional biopsy.

The lymphoma frequencies and sub-types in both groups are also presented in Table 1. The most common lymphoma subtype in both groups was Hodgkin lymphoma in terms of diagnosis (CNB 27.9% and SEB 41.3%). The distribution of non-Hodgkin lymphomas was different in the 2 groups. While Diffuse Large B Cell Lymphoma (DLBCL) (16.2%) was the most common lymphoma subtype in CNB group, T-cell lymphoma was the most common in the SEB group with a rate of 15.9%. Follicular lymphoma was the most common indolent lymphoma type in both groups (CNB 14.7% vs. SEB 14.3%). There was a limited number of patients in both groups which were categorized as atypical lymphoid proliferation, 4.4% in CNB group and 1.6% in SEB group, respectively.

PET-computed tomography was the most commonly used imaging technique in patients with lymphadenopathy. Around 36.6% of the patients had a PET-CT before the biopsy. Other imaging techniques which were used less commonly were ultrasonography (19.1%), CT (9.9%), and magnetic resonance imaging (2.3%). 32.8% of the lymph nodes in diagnostic sampling were smaller than 3 cm in size, 28.2% were between 3 and 6 cm, and 2.3% were larger than 6 cm in size.

When the diagnostic ability of the 2 techniques was evaluated, inadequate samples were 2.9% in CNB group and 3.2% in SEB group ($P=.939$). 89.3% was accepted fully diagnostic with regard to all samples. Fully diagnostic ability was 83.8% in CNB and 92.6% in SEB group ($P=.035$). Totally 66 (97%) of patients in the CNB group and 60 (95.2%) of patients in the SEB group either had a fully or partial diagnostic ability ($P=.938$) (Table 2). Only 5 (7.4%) patients who were in CNB group needed an excisional biopsy and 3 (4.8%) of the patients in the SEB group

Table 2. Diagnostic Sub-Categories of CNB Versus SEB

	Core Needle Biopsy (n=68)	Surgical Excisional Biopsy (n=63)	P
Diagnosis (n,%)			
Fully diagnostic	57 (83.8)	60 (95.2)	.028*, .938**
Partially diagnostic	9 (13.2)	1 (1.6)	
Inadequate	2 (2.9)	2 (3.2)	

*Three diagnostic groups were compared;**Fully and partial diagnostic yields were compared with inadequate yield.
CNB, core needle biopsy; SEB, surgical excisional biopsy.

needed a second biopsy. Two of the patients who needed a second biopsy after CNB were diagnosed with Hodgkin lymphoma and the others were diagnosed with non-Hodgkin lymphoma. Total diagnostic yield which allowed the patients to proceed with appropriate treatment was 92.6% and 95.2% for CNB and SEB groups, respectively (*P*=.720) (Table 3). Two samples from different regions are detailed in the Figures 2 and 3.

Hodgkin lymphoma was the most common lymphoma subtype in both CNB and SEB groups. Diagnostic yield of the CNB for Hodgkin lymphoma was 90.5% and 100% in SEB group (*P*=.194). Regarding all non-Hodgkin lymphoma sub-types, the diagnostic yield of CNB and SEB was 82.6% and 94.4%, respectively (*P*=.173). The diagnostic yield of CNB and SEB among patients who were diagnosed with DLBCL was 100% for both, and regarding the major indolent lymphoma sub-group, patients who were diagnosed with follicular lymphoma, the diagnostic yield of CNB was 80% and SEB was 100% (*P*=.474).

Discussion

The major advances in the field of hematopathology, especially the novel immune-histochemical studies, made it possible to obtain a diagnosis of lymphoma even with small-sized tissue samples. The growing confidence and ability of interventional radiologists who apply CNB in a regular fashion have also appealed to the interest of clinicians to refer their patients to a less-invasive alternative. This gradually increasing confidence in CNB has also led to studies in which the diagnostic ability of CNB was evaluated.[9,10] A meta-analysis of Frederiksen et al[3] has indicated a 74% diagnostic yield of FNA/CNB in 5707 nodal and extra-nodal samples obtained between 1989 and 2012. Another review by Seviar et al[11] has documented a 79%-97% diagnostic yield of CNB as the first diagnostic tool, when combining results of 13 different trials which were held between 2015 and 2020. This review has reported a median diagnostic yield of 91.7%. In the comparison group which included samples obtained by SEB, the diagnostic yield was reported between 93.5% and 100% with a median of 97.5%. We have observed an 83.8% fully diagnostic ability of CNB and 95.2% of SEB (*P*=.003) according to the results obtained in our study. Regarding fully diagnostic ability, there was a statistically significant difference between 2 groups. But when the diagnostic yield was the concern, only 5 out of 68 patients who underwent CNB required a re-biopsy with SEB in order to be treated according to a proper diagnosis. Core needle biopsy, itself, allowed 92.6% of patients to proceed with the appropriate treatment accordingly without a need for a re-biopsy, and this ratio was 95.2% in SEB group (*P*=.720).

In routine clinical practice, CNB is much more preferred to evaluate lymph nodes that are not easily accessible or in patients who are prone to complications of anesthesia regarding co-morbidities or age. In our study, when we compare the lymph nodes whether they are easily accessible or not (according to their location as deep or superficial), lymph nodes in CNB group were in deeper locations and hard to access. Despite the excessive number of tough lymph node locations in CNB group, 83.8% fully diagnostic ability of the CNB in our study was quite satisfying. The decision to proceed with either a CNB

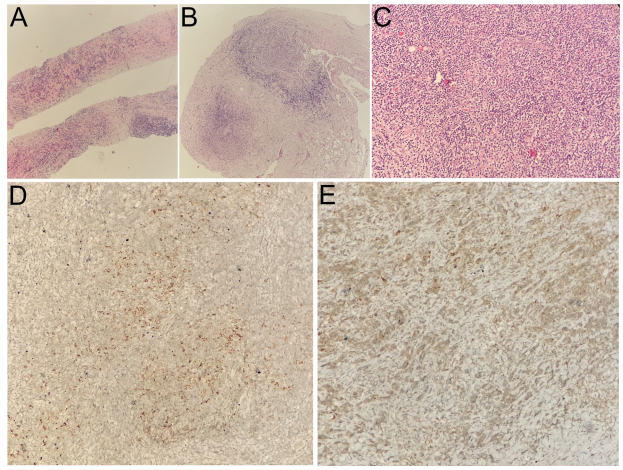

Figure 2. (A) Core needle biopsy of anterior mediastinal mass reveals sclerotic areas and small lymphocytes (HE, ×40). Diagnostic result could not be obtained in the immunohistochemical study applied to very few atypical suspicious cells. Incisional biopsy showed both areas similar to core biopsy (B) (HE, ×40) and areas rich in atypical cells (C) (HE, ×100). (D) CD30 expression in foci rich in atypical cells (CD30, ×100) and (E)CD30 expression in sclerotic foci (CD30, ×100) in incisional biopsy. This case was diagnosed as atypical lymphoid proliferation in core biopsy and classical Hodgkin lymphoma in incisional biopsy.

Table 3. Need for a Second Biopsy

	Core Needle Biopsy (n=68)	Surgical Excisional Biopsy (n=63)	P
Need for a second biopsy (n,%)			
Yes	5 (7.4)	3 (4.8)	.720
No (total diagnostic yield)	63 (92.6)	60 (95.2)	

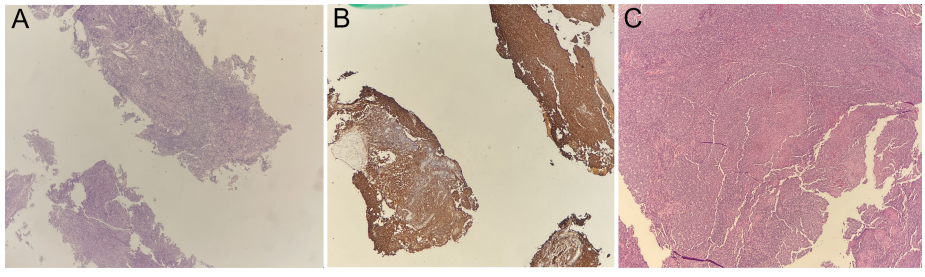

Figure 3. (A) In the core biopsies taken from the submandibular region, a lymphoid tissue sample consisting of partially monotonous cells and partial involvement is observed (HE, ×40). (B) Cores with diffuse and patchy staining are seen with CD20 (CD20, ×40). Biopsy with other immunohistochemical markers (bcl6, CD10) was reported as B-cell lymphoma of follicle center origin, but excisional biopsy was requested for subtyping and grading. (C) Grade 2 follicular lymphoma with partial lymph node involvement was diagnosed in excisional biopsy (HE, ×40).

or SEB was totally up to the physicians' discretion who was involved in the diagnostic process. Despite this being a retrospective study and there were not any specific pre-defined selection criteria to decide on the technique, like the age of the patient, location of the lymph node, and accessibility of the biopsy site, our results showed a statistically significant difference in terms of location of lymph nodes and age between the 2 group. As the results indicated in our cohort, patients in the CNB group have significantly deeper and un-accessible lymph node locations nevertheless they have 83.8% fully diagnostic ability. We can say that CNB is a viable option for deeper locations. The guidelines also support this kind of preference over SNB.[5] Johl et al[12] have reported that CNB comprised 15.7% of all biopsy samples in Kiel lymph node registry and was more preferred in elderly patients and to sample lymph nodes which are not easy to access. Despite these infrequent reports, Assaf et al[13] have documented an increased frequency of CNB, comprising more than half of all samples, regardless of age, gender, or a clinical judgment suggesting a possible malignancy. Our results also indicated a statistically significant difference between the median ages of patients who underwent CNB or SEB (56.8 vs. 47.75 respectively, $P = .003$). Core needle biopsy was the most preferred technique among elderly patients as the first diagnostic tool because of frailty. According to our study population, preference rate of CNB was 44.1% in all cases.

A 17-gauge coaxial needle with the 18-gauge core biopsy needle was used to obtain samples in our study. One equal size needle was used in all lymph nodes apart from the anatomical location. There are studies that favor to use different sizes of needles in deep or superficial samples,[14] but we may conclude that using coaxial technique made it possible to obtain enough number of samples with a median of 11.5 (2-45) samples with just 1 puncture in our study. Even, there was no significant difference between number of samples obtained with the procedure and diagnostic ability in CNB group.

The variation in diagnostic yield between lymphoma sub-types has previously been reported.[15] There was significant difference between Hodgkin and non-Hodgkin lymphoma groups in 2 previous studies.[7] Diagnostic yield of CNB in Hodgkin lymphoma was 50% in Burke et al[7] study which evaluated 171 different patients presented with lymphoma from head and neck regions. Core needle biopsy was diagnostic in 30/38 (78.9%) of Hodgkin lymphoma patients in a retrospective cohort study including 114 lymphoma patients.[16] This probably reflects the heterogeneity in histological background of lymph nodes in Hodgkin lymphoma and the chance of tissue sampling to detect critical features such as Reed–Sternberg cells might not be present in the core. In our study, CNB was 90.5% diagnostic in Hodgkin lymphoma patients.

It is recognized that, despite the recent diagnostic advances, the relative lack of architectural assessment in core biopsies may result in difficulty in some cases, particularly in low-grade non-Hodgkin lymphomas and those with aberrant profiles.[17] In terms of the diagnostic ability of CNB in follicular lymphoma, this entity is well described in literature; in our study, we found that CNB was 80% diagnostic in follicular lymphoma. Unfortunately, the total number of patients who were diagnosed with follicular lymphoma was only 10, and this might not exactly reflect the potency of CNB in the diagnosis of follicular lymphoma. DLBCL, another subgroup of non-Hodgkin lymphoma CNB, had a very high diagnostic ability with no need for further excisional biopsy.

Another important issue about CNB is false negativities or positivities. There are a few studies that evaluated predictive value of CNB in the literature. Data from the German cohort showed that 121 patients who underwent US-guided lymphadenopathy, 54 of them needed to be re-evaluated with second excisional biopsy because of the ambiguous cases.[18] There were 2 false-negative and 2 false-positive patients in NHL group and 5 false-negative Hodgkin Lymphoma (HL cases in 76 lymphoma diagnosis. Also, CNB was sufficient in 65 of 76 lymphoma patients. Another study from Turkey has evaluated 291 patients who needed a second biopsy after following up to 6 months.[19] Core needle biopsy was reported to be benign in 11 of 60 patients and 7 of 11 patients were misdiagnosed as having a lymphoma in this cohort. However, publications from single institutions like our study show a conclusive result for the diagnosis of lymphoma by CNB specimens in over 80%-90% of the cases. Negative CNB results should be considered with excessive precaution, and close follow-up and secondary biopsies are recommended according to the clinical aspects of the patient and radiological features of the affected lymph nodes. The lack of a comparison group consisting of the benign pathologies and their follow-up results is regarded as a limitation of our study. Besides, dedicated interventional radiologist to obtain the CNBs and a dedicated hemato-pathologist to report all the samples resemble the strength of our study.

This study has some limitations. One of our major limitation is retrospective nature of the data. Due to the retrospective nature of the data as we discussed above, there were not any specific predefined selection criteria to decide on between 2 techniques. It was all physician discretion. At this point, results obtained from the study described statistically significant differences in patient characteristics between CNB and SEB. However, these differences favor CNB group in terms of deeper location lymph nodes and advanced age, and theoretically could interpret as selection bias.

According to the results obtained in our study, we may conclude that CNB is a viable and comparable alternative to SEB, offering a less-invasive and less-expansive approach to diagnose lymphoma.

Ethics Committee Approval: Ethical approval was obtained from the local ethical commitee of Medipol University (approval ID: E-10840098-772.02-793).

Informed Consent: Informed consents were obtained from patients.

Peer-review: Externally peer-reviewed.

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Pediatric Psychiatry

The Hypothetical Psychological Impact of the COVID-19 Pandemic on Pediatrics and Pediatric Emergency Admissions: Evidence from Autoregressive Distributed Lag Model Method

Hatice Genç Kavas[1], Ahmet Şengönül[2]

ABSTRACT

Objective: The COVID-19 pandemic and related deaths affected the number of admissions of patients to hospitals. However, no study has been found that examines the short and long-term psychological effects of children or their possible psychiatric admissions to hospitals during the pandemic period. In this context, the study aims to analyze the behaviors of individuals under the age of 18 in their health service utilization during the COVID-19 pandemic period.

Materials and Method: For the study, whether the pandemic and psychiatry department (PSY) admissions affect the pediatrics department (PD) and pediatric emergency department (PED) admissions of children was investigated. The sample was taken from hospitals in Sivas between 2019 and 2021. Autoregressive distributed lag (ARDL) model is applied. The ARDL is an econometric method that can estimate the existence of the long-term correlations (cointegration) of variables and the short and long-term effects of explanatory variables on the dependent variable.

Results: In the PED application model, the number of deaths, representing the impact of the pandemic, decreased the number of PED applications, while the number of vaccinations increased. On the other hand, applications to the PSY decreased in the short term, but increased in the long term. In the model of pediatric department admissions, in the long term, the number of new COVID-19 cases has decreased the number of PD admissions, while the number of vaccines has increased. While applications made to PSY in the short term have decreased the applications of PD, they have increased in the long term. As a result, the pandemic decreased both children's department admissions. In addition, admissions to PSY, which had greatly decreased in the short term, increased rapidly in the long term.

Conclusion: Providing psychological support to both children and adolescents and their guardians during and after the pandemic should be included in planning.

Keywords: Pediatry, psychiatry, covid-19, healthcare demand, time series analysis, patient behavior

Introduction

On March 11, 2020, a worldwide pandemic was declared due to the new coronavirus disease (COVID-19/severe acute respiratory syndrome coronavirus 2), and as of the time of the study, more than 6 million people died from this disease. The rapid spread of the disease and the increase in cases show us that the threat continues globally. The instinct of survival is the main source of motivation for all living things. Especially in cases where the risk of death is visible, individuals may exhibit different behaviors in their daily routines to feed their motivation. The COVID-19 pandemic also has an impact on behavior as it causes an increasing number of deaths. During the pandemic, a full lockdown was experienced in the world in certain periods, but also in the periods when the closure was not mandatory, the behavior of people was outside of normal life behaviors. In this study, it was analyzed how the children and adolescents in Sivas behaved before and after the introduction of COVID-19 into our lives and during the vaccination process against the disease, when they applied to the hospital, and whether there were psychological effects based on their behavior. In the reviewed literature[1-3] it was observed that while there was a significant increase in emergency department admissions for psychological reasons during COVID, there was a general decrease in admissions due to other diseases. And also, a study conducted in Turkey has shown that individuals are seriously affected psychologically by COVID-19.[4]

The study was presented in Turkish at the fifth International Health Science and Life Congress as a narrow-scoped paper. https://drive.google.com/file/d/1GZjyFF9gSQr1IGQQgU1fO2Tgw_YpLVry/view

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In this context, our study will hypothetically test whether there is a relationship between admissions to psychiatry departments and pediatrics departments, and pediatric emergency departments admissions.

There are many studies on the impact of the COVID-19 pandemic on healthcare utilization. It is questioned the whereabouts of children who are supposed to be admitted to the PED in Manchester UK under normal circumstances and why they do not use healthcare services.[5] The COVID-19 pandemic has had a major impact on non-COVID-19-related healthcare use, largely due to social restraint measures and changes in people's healthcare-seeking behavior; however, they say that the utilization of healthcare services for mental health disorders is increasing.[1] The admissions to PED for psychiatric reasons of individuals under the age of 18 increased compared to the pre-pandemic period during the pandemic outbreak of the pandemic,[2,3] and it can be seen by the studies that the demands for healthcare services, that is, admissions to PED, and the number of hospitalizations decreased very significantly in various regions of the World.[6-9] Again, based on this period, it was mentioned that there was a significant decrease in the demand for serious treatment, including cancer,[10] not only in PED but also in a wide variety of health services[11-13] in the healthcare system. According to a study published in 2021, the use of many different types of hospitals such as hospital visits, emergency admissions, diagnosis, and treatment decreased very seriously.[14] However, there are studies showing that admissions are shifted to the online system rather than face-to-face interviews[15] in these situations. It has been observed that there are delays in the care and treatment admissions of even cancer patients in Turkey, and therefore, there are significant changes in the utilization of healthcare services[16]. It is also stated that the pandemic causes increased anxiety and depression, and this is more common, especially among women in Turkey.[4] In this context, it can be seen that the COVID-19 pandemic is a major factor in healthcare utilization. However, when the studies were examined, it was not found that causality analysis was performed with explanatory variables affecting the use of healthcare services.

Main Points

- The COVID-19 pandemic has caused dramatic decrease in hospital admissions of children and adolescents.
- While the number of daily new COVID-19 cases and new deaths in Turkey caused a decrease in hospital admissions, the vaccination rates caused an increase in hospital admissions, albeit very slightly.
- During COVID-19, the increase in patient admissions to psychiatry department (PSY) has decreased the number of admissions to PD and PED in the short term. In other words, in the short term, patients under the age of 18 may have preferred to apply to hospitals for psychological reasons over physiological reasons. In the long term, they may have applied to the PD and PED mostly for physiological reasons, with the end of the treatment process due to the increase in admissions to PSY.
- Especially the significant decrease in pediatric emergency visits may be evidence that these patients can be treated at home without going to the emergency departments, even in the absence of a pandemic.

Materials and Methods

In our study, the weekly admission numbers of patients under the age of 18 between September 2019 and July 2021 in 4 hospitals within the scope of secondary and tertiary healthcare institutions in Sivas were used. The archive data were obtained from the statistics unit of all secondary and tertiary healthcare facilities in Sivas. In this study, the number of child patients who applied to the PSY, PD, and PED was included in models to measure the psychological impact on children. The cross-tabulation method using Statistical Package for Social Science Statistics 25 (IBM Corp., Armonk, NY, USA) was used to combine and classify the data. ARDL models used for econometric analyses were created with E-views 10 (IHS Global Inc., 4521 Campus Drive, #336 Irvine, CA 92612-2621, USA). Ethics Committee Report numbered 60263016-050.06.04-E.482051 and the research permits were obtained. The study was carried out retrospectively using the number of patient applications received from the statistics department of the hospitals. None of the personal data of patients are used. Informed consent was not obtained from the patients as there was no clinical study that used any personal data. Since there was no animal study, the NIH guidelines were not needed. As data, the number of weekly new cases, vaccinations, and deaths from COVID-19 in Turkey are used. The hypothesis to be tested in the study is that COVID-19 cases, deaths caused by COVID-19, vaccination against COVID-19, and PSY admissions that may affect PED and PD admissions. To test this hypothesis, a time series econometric model was established and analyzed, and a model known as the ARDL developed by Pesaran et al[17] was estimated for this analysis. While the ordinary least squares (OLS) method cannot distinguish between short term and long term, the ARDL model assumes that a time series of dependent variables is a linear function of the previous lag values itself and the current and previous lag values of the explanatory variables.[18] The ARDL model decomposes the effect of an explanatory variable on the dependent variable as short-term and long-term effects. For example, indeed, a model's influencing variable may sometimes increase the affected variable in the short run while decreasing it in the long run. For example, while a drug cures a disease within the required dose period (in the short term), if it is taken as an overdose (long term), it may make the patient worse.

In this context, 2 different models were considered. The models and their equations are as follows;

- Model 1: Pediatric Emergency (ER) (weekly deaths, weekly vaccines, weekly new cases, psychiatry)

General Model

$$Pediatric\ ER_t = \beta_0 + \beta_1\ weekly\ deaths + \beta_2\ weekly\ vaccines + \beta_3\ weekly\ new\ cases + \beta_4\ psychiatry + u_t$$

Autoregressive Distributed Lag (ARDL) 0;Model

$$\Delta pediatricER_t = \alpha_0 + \sum_{i=1}^{p} \beta_i \Delta pediatricER_{t-i} + \sum_{i=0}^{p} \sigma_i \Delta weekly\ deaths_{t-i} + \sum_{i=0}^{p} \delta_i \Delta weekly\ vaccines_{t-i} + \sum_{i=0}^{p} \rho_i \Delta weekly\ new\ cases_{t-i} + \sum_{i=0}^{p} \chi_i psychiatry_{t-i} + \lambda_1 pediatric\ ER_{t-1} + \lambda_2 weekly\ deaths_{t-1} + \lambda_3 weekly\ vaccines_{t-1} + \lambda_4 weekly\ new\ cases_{t-1} + \lambda_5 psychiatry_{t-1} + u_t \quad (1)$$

- Model 2: Pediatrics department (weekly deaths, weekly vaccines, weekly new cases, psychiatry)

General Model

$$Pediatrics_t = \beta_0 + \beta_1\ weekly\ deaths + \beta_2\ weekly\ vaccines + \beta_3\ weekly\ new\ cases + \beta_4\ psychiatry + u_t$$

Autoregressive Distributed Lag (ARDL) Model

$$\Delta pediatrics_t = \alpha_0 + \sum_{i=1}^{p} \beta_i \Delta pediatrics_{t-i} + \sum_{i=0}^{p} \sigma_i \Delta weekly\ deaths_{t-i} + \sum_{i=0}^{p} \delta_i \Delta weekly\ vaccines_{t-i} + \sum_{i=0}^{p} \rho_i \Delta weekly\ new\ cases_{t-i} + \sum_{i=0}^{p} \chi_i psychiatry_{t-i} + \lambda_1 pediatrics_{t-1} + \lambda_2 weekly\ deaths_{t-1} + \lambda_3 weekly\ vaccines_{t-1} + \lambda_4 weekly\ new\ cases_{t-1} + \lambda_5 psychiatry_{t-1} + u_t \quad (2)$$

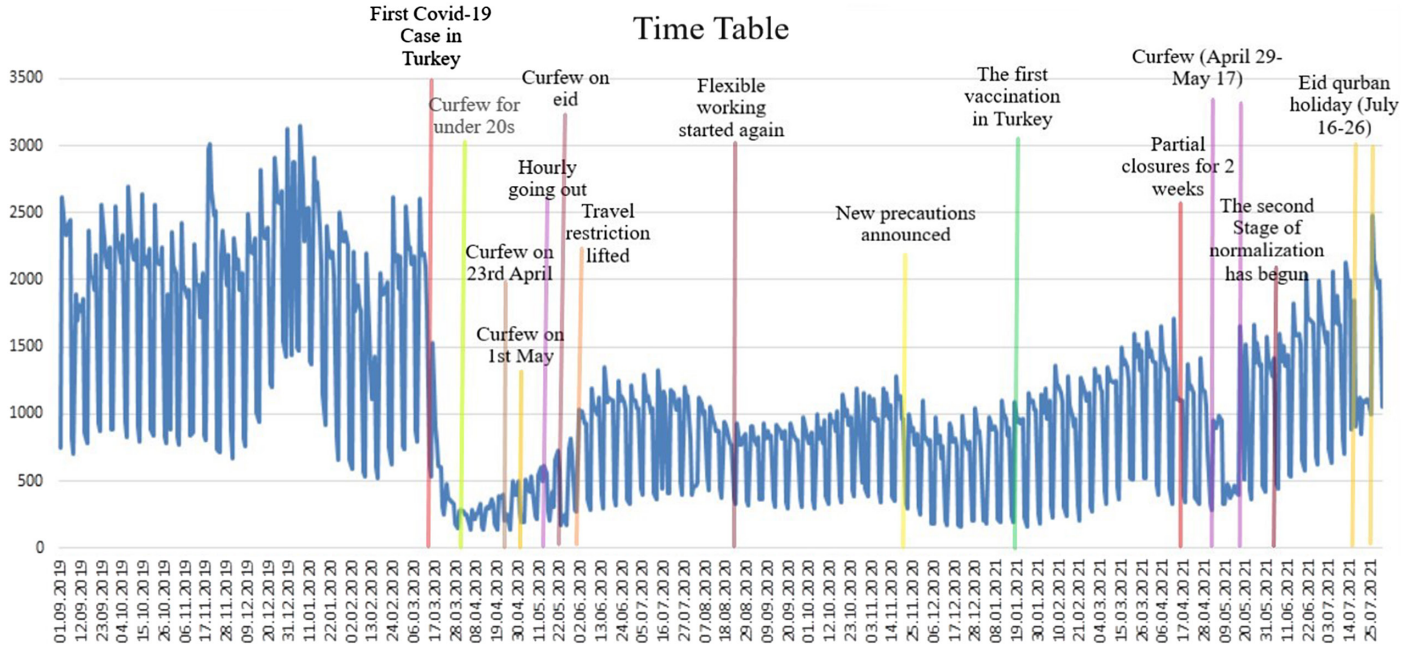

Figure 1. All admissions of individuals under 18s to secondary and tertiary healthcare facilities in Sivas between Semtember 1, 2019 and July 31, 2021. *Time indicators have been added to the chart based on the announcements of the relevant ministries.[19,20] **Departments that require treatment such as cancer, oncology, departments associated with these departments, family medicine, dentistry departments, and Covid-19 admissions were not included.

Definitions

The data set used in the models consists of the number of applications made to 3 different departments in the hospitals, the number of weekly new COVID-19 cases, the weekly number of deaths from COVID-19, and the weekly vaccination numbers against COVID-19. The data were retrospectively collected.

The departments in the models are pediatric emergency departments (PED), pediatrics departments (PD), and psychiatry departments (PSY).

Pediatric emergency departments: The number of applications made to PED represents PED in all the secondary and tertiary healthcare facilities in the city. All individuals under the age of 18 can apply to these departments in case of emergency or acute diseases.

Pediatrics departments: PD is a branch of science that deals with the diagnosis, follow-up, and treatment of individuals aged 0-17. In the study, the number of applications made to PD in all secondary and tertiary healthcare facilities in the city was used.

Psychiatry department: It is the service that individuals go to get psychiatric support. In the study, all applications made to psychiatry and psychology departments where individuals under the age of 18 applied for examination were evaluated as PSY admissions.

New cases: It is the number of new COVID-19 cases per week in Turkey.

Deaths: It is the number of deaths due to COVID-19 in Turkey per week.

Vaccine: It is the number of vaccinations against COVID-19 disease per week in Turkey.

Holidays: Refers to the national and religious holidays in Turkey during the time period within the scope of the study. Holidays, curfews, and restrictions are shown on the timeline in Figure 1.

Results

Table 1 shows the admissions made to all secondary and tertiary healthcare facilities in Sivas between September 1, 2019, and July 31, 2021.

The total number of admissions of children and adolescents to the PED, PD, and PSY of the secondary and tertiary healthcare facilities in Sivas during the current date range was 456.795. As the departments, PED (49.59% of the total admissions), PD (46.49% of the total admissions), and PSY (total of psychiatry and psychologist departments–3.91% of the total admissions) were taken as variables.

Figure 1 shows the graph of the number of children and adolescents who applied to the hospitals within the scope of the study between September 1, 2019, and July 31, 2021, and the timeline of cases, vaccinations, closures, and holidays in Turkey. The first COVID-19 case was seen in Turkey on March 11, 2020. The curfew for individuals under the 20s was declared on April 3, 2020. Mass vaccination started on January 14. The first COVID-19 case in Turkey and the declaration of the disease as a pandemic occurred simultaneously, and after this date, hospital admissions of children and adolescents in Sivas decreased dramatically. During the religious and national holidays before and after the onset of the pandemic and curfews, utilization of healthcare was minimal as the doctors of outpatient clinics were not working at that time in the outpatient clinics.

Admissions of individuals to PD decreased significantly with the first COVID-19 case in Turkey (Figure 2). During the pandemic and even after vaccinations, admissions remained well below pre-pandemic levels.

Table 1. Statistics of Patients Under the Age of 18 Applying to the Secondary and Tertiary Healthcare Hospitals in Sivas between September 1, 2019, and July 31, 2021

		N	%
Department	Pediatric ER	226.527	49.59
	Pediatric Department	212.390	46.49
	Psychiatry	17.878	3.91
	Total	456.795	100.00

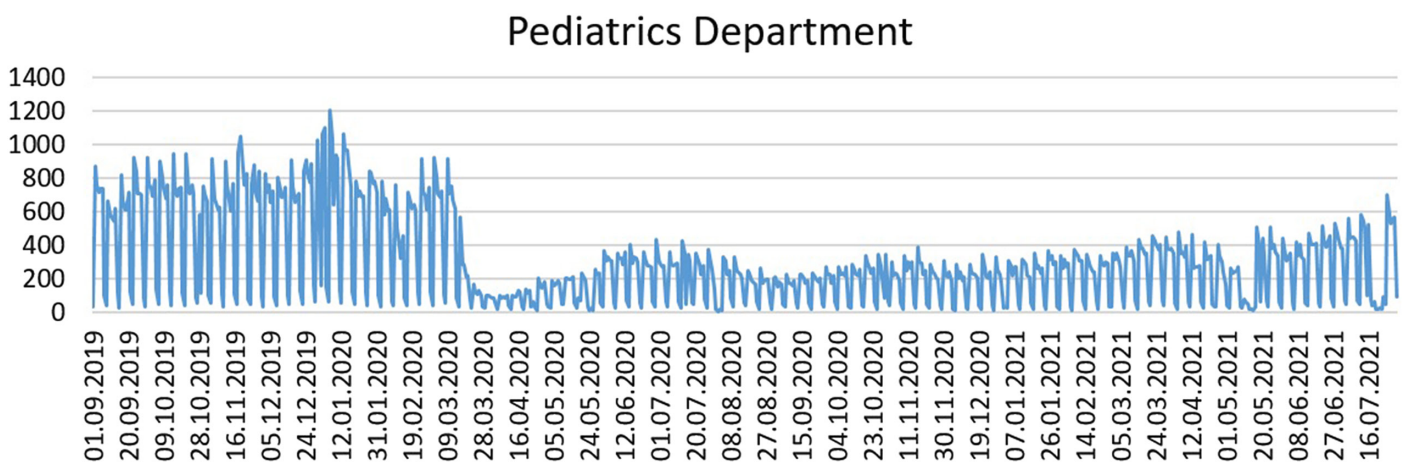

Figure 2. Application of individuals under 18 to secondary and tertiary healthcare facilities' pediatrics departments in Sivas between January 09, 2019 and December 07, 2021.

As seen in Figure 3, with the first occurrence of the COVID-19 case in Turkey, the number of PED admissions in Sivas decreased significantly. In July 2021, admissions to PED tended to return to pre-pandemic values.

Admissions to PSY of children and adolescents decreased with COVID-19 (Figure 4).

According to the models discussed, the dependent variables are the number of patients in the relevant department (PED — Model 1 and PD — Model 2) who applied to all secondary and tertiary healthcare hospitals in Sivas to use health services pre-COVID-19 and post-COVID-19 (September 1, 2019 to July 31, 2021). The explanatory variables of the models are the number of deaths per week from COVID-19, the number of vaccination per week, the number of new cases per week, as well as the number of weekly psychiatry admissions for model 1 and model 2.

Model 1: Pediatric ER (Weekly Deaths, Weekly Vaccines, Weekly New Cases, Psychiatry)

As can be seen in Table 2, since the adjusted R^2 is 0.95 in the ARDL equation, explanatory variables explain the model as a whole at a rate of 95%. According to ARDL results, a long-term causal relationship was found between PED admissions and psychiatry admissions, the number of deaths, and the number of vaccinations. While admissions to PSY and the number of daily vaccinations increase the number of applications to PED, the number of deaths decreases. Considering the short-term relationships, the number of vaccinations in the last 12 weeks, excluding the number of vaccinations 5 weeks ago ($P=.2133$), decreased the number of admissions to PED (e.g., 10.000 vaccinations 6 weeks ago decreases the number of PED visits this week by 3 — coefficient = −0.000347/$P=.0038$—). While death cases show their effect in the long term, there is no significant effect at the $P=.05$ level in the short term. While admissions to PSY increased the number of PED admissions in the long term, it decreased admissions with a very high effect in the short term (e.g., 1 PSY admission 7 weeks ago decreases the number of admissions to the PED this week by three — coefficient= −3.260418/$P=.0060$ —).

The number of admissions to the PED in the previous first, fifth, and eighth weeks increase PED admissions this week. (e.g., 10 admissions to PED 5 weeks ago increase the number of admissions to PED by 4 this week).

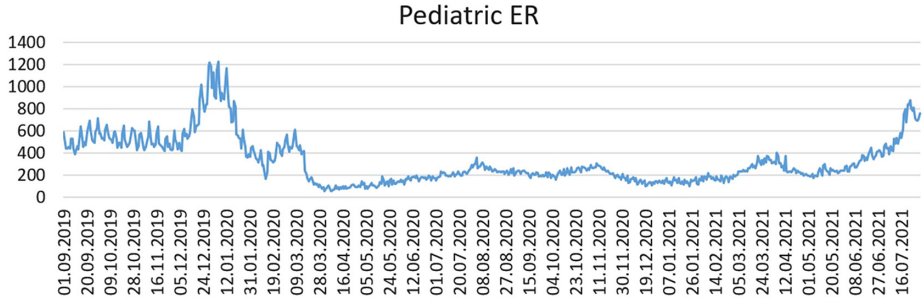

Figure 3. Application of individuals under 18s to secondary and tertiary healthcare facilities' pediatric emergency departments in Sivas between September 1, 2019 and July 31, 2021.

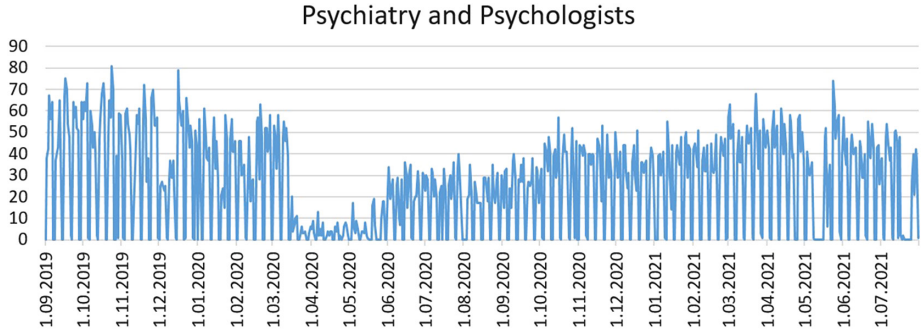

Figure 4. Application of Individuals Under 18s to Secondary and Tertiary Healthcare Facilities' Psychiatry and Psychologist Departments in Sivas between September 1, 2019 and July 31, 2021.

Model 2: Pediatrics Department (Weekly Deaths, Weekly Vaccines, Weekly New Cases, Psychiatry)

As can be seen in Table 3, since the adjusted R^2 is 0.948 in the ARDL equation, the explanatory variables explain the model as a whole at a rate of approximately 95%. Again, according to the ARDL long-term equation, the number of admissions to PD is affected at the $P=.05$ level depending on all other explanatory variables, except for death cases. However, while PSY admissions (coefficient = 11.28882, $P=.0000$) and vaccination (coefficient = 0.001015,

Table 2. Co-integration and ARDL Results for Pediatric Emergency Department

Dependent Variable: Pediatric ER		Observation Period: 2019-2021		
Test Name: ARDL		Selected Model: ARDL (9, 1, 12, 1, 12)		
Variable	Coefficient	Standard Error	*t*-Statistic	*P*
Long-term equation				
Death	−1.971082	0.463309	−4.254361	.0001
Vaccine	0.000538	0.000241	2.232478	.0303
New cases	0.006747	0.004519	1.492900	.1420
Psychiatry	15.78170	1.783727	8.847599	.0000
C	222.7474	328.8044	0.677447	.5014
Short-term equation				
D(Pediatric ER(−1))	0.868724	0.121068	7.175499	.0000
D(Pediatric ER (−2))	0.195560	0.149629	1.306973	.1974
D(Pediatric ER (−3))	0.115621	0.138299	0.836021	.4073
D(Pediatric ER (−4))	−0.016637	0.131373	−0.126640	.8998
D(Pediatric ER (−5))	0.401495	0.125440	3.200704	.0024
D(Pediatric ER (−6))	−0.207057	0.134804	−1.535984	.1311
D(Pediatric ER (−7))	0.213938	0.134362	1.592251	.1179
D(Pediatric ER (−8))	0.407690	0.136303	2.991054	.0044
D(Death)	−0.021157	0.336300	−0.062910	.9501
D(Vaccine)	−0.000159	6.92E-05	−2.302391	.0257
D(Vaccine (−1))	−0.000374	0.000102	−3.666.121	.0006
D(Vaccine (−2))	−0.000356	0.000102	−3.503601	.0010
D(Vaccine (−3))	−0.000524	0.000108	−4.835854	.0000
D(Vaccine (−4))	−0.000238	0.000101	−2.360898	.0223
D(Vaccine (−5))	−0.000135	0.000107	−1.261252	.2133
D(Vaccine (−6))	−0.000347	0.000114	−3.041973	.0038
D(Vaccine (−7))	−0.000472	0.000158	−2.984513	.0045
D(Vaccine (−8))	−0.000847	0.000184	−4.596964	.0000
D(Vaccine (−9))	−0.000792	0.000215	−3.692346	.0006
D(Vaccine (−10))	−0.000775	0.000211	−3.673309	.0006
D(Vaccine (−11))	−0.000526	0.000175	−3.004671	.0042
D(New Cases)	−9.98E-05	0.001693	−0.058927	.9533
D(Psychiatry)	0.816681	0.899329	0.908101	.3684
D(Psychiatry (−1))	−5.295801	1.376645	−3.846890	.0004
D(Psychiatry (−2))	−4.744132	1.315391	−3.606633	.0007
D(Psychiatry (−3))	−5.027811	1.286689	−3.907558	.0003
D(Psychiatry (−4))	−4.479287	1.109096	−4.038681	.0002
D(Psychiatry (−5))	−3.109667	1.118099	−2.781210	.0077
D(Psychiatry (−6))	−4.116569	1.164386	−3.535400	.0009
D(Psychiatry (−7))	−3.260418	1.132846	−2.878078	.0060
D(Psychiatry (−8))	−4.681898	1.144411	−4.091099	.0002
D(Psychiatry (−9))	−3.604724	1.100926	−3.274266	.0020
D(Psychiatry (−10))	−2.006856	0.961393	−2.087446	.0422
D(Psychiatry (−11))	−1.704754	0.845258	−2.016845	.0493
CointEq(−1)*	−0.395261	0.069452	−5.691139	.0000
	F-Statistic	Significance	I(0)	I(1)
Bounds test	4.888916	1%	3.29	4.37
R^2		0.975349		
Adjusted R^2		0.955321		

ARDL, autoregressive distributed lag model.

P = .0044) increase the admissions to PD, the number of daily cases (coefficient = −0.015408, *P* = . 0320) decreases. Considering the short-term co-integration, PD admissions are affected by all variables weekly, including the number of weekly deaths. While PSY admissions, death, and vaccination decrease the number of admissions to PD in the short term, the number of daily cases and admissions to PD has an increasing effect (e.g., each death 3 weeks ago decreases the number of pediatrics admissions this week by 2). Around 10 000 vaccines administered 1 week ago in Turkey decreases the number of applications made to PD by 6 this week. One PSY admission 7 weeks ago decreases PD admissions by 10 this week and 100 weekly cases of COVID-19 that emerged 4 weeks ago increased PD admissions by 1 this week, and 1 admission to PD 8 weeks ago increases by 1 admission to PD this week).

Discussion

In this study, the changes in the admissions of individuals under the age of 18 to PD and PED of the secondary and tertiary healthcare facilities in Sivas city center and how their motivations for these changes were affected in the short and long term were examined. According to econometric models; dependent variables in each model are explained very highly by explanatory variables ($R^2_{Model1} = 0.95$ and $R^2_{Model2} = 0.95$,). With the introduction of the COVID-19 disease into our lives, it can be understood from the time series analyzed that there has been a significant decrease in the admissions of individuals under the age of 18s to hospitals in Sivas. To explain the reason for the decrease in the number of PD and PED admissions, weekly deaths, weekly vaccinations, and weekly cases were added to the models, but a significant causal relationship could not be found. For this reason, in addition to these explanatory variables, other departments' admissions were added to the models. Among the explanatory variables made to PD and PED admissions models, the highest causality relationship was obtained by adding the admissions to PSY to the models. As a result, econometric models were analyzed based on the admissions to PSY. In both Models, co-integration (long-short term) relationships were found at the 1% significance level (Model 1's explanatory variables in long term; deaths (coefficient = −1.97; *P* = .0001), vaccines (coefficient = 0.0005; *P* = .0303), psychiatry (coefficient = 15.78; *P* = .0000); Model 2's explanatory variables in long term; vaccines (coefficient = 0.0010; *P* = .0044), new cases (coefficient = −0.015; *P* = .0320), psychiatry (coefficient = 11.288; *P* = .0000). Co-integration–causality relationships in short-term

Table 3. Co-Integration and ARDL Results for Pediatrics Department

Dependent Variable: Pediatrics		Observation Period: 2019-2021		
Test Name: ARDL		Selected Model: ARDL (12, 6, 12, 10, 11)		
Variable	Coefficient	Standard Error	*t*-Statistic	*Prob.*
Long-term equation				
Death	−0.219124	0.643104	−0.340728	.7355
Vaccine	0.001015	0.000331	3.063576	.0044
New cases	−0.015408	0.006873	−2.241916	.0320
Psychiatry	11.28882	1.117283	1.010381	.0000
C	680.8998	2.126355	3.202193	.0031
Short Term Equation				
D(Pediatrics(−1))	0.136120	0.135507	1.004526	.3227
D(Pediatrics(−2))	0.011128	0.129335	0.086042	.9320
D(Pediatrics(−3))	0.039347	0.118067	0.333255	.7411
D(Pediatrics(−4))	0.052735	0.108438	0.486316	.6301
D(Pediatrics(−5))	0.321142	0.111408	2.882580	.0070
D(Pediatrics(−6))	0.597210	0.131479	4.542253	.0001
D(Pediatrics(−7))	0.703773	0.156473	4.497734	.0001
D(Pediatrics(−8))	1.134601	0.169973	6.675188	.0000
D(Pediatrics(−9))	0.924576	0.190114	4.863269	.0000
D(Pediatrics(−10))	0.521924	0.162577	3.210312	.0030
D(Pediatrics(−11))	0.200468	0.115057	1.742342	.0911
D(Death)	−0.968932	0.516655	−1.875394	.0699
D(Death(−1))	−1.624827	0.540556	−3.005844	.0051
D(Death(−2))	−0.760088	0.497880	−1.526650	.1367
D(Death(−3))	−2.124096	0.533681	−3.980089	.0004
D(Death(−4))	0.762737	0.544337	1.401221	.1708
D(Death(−5))	−1.356942	0.547963	−2.476336	.0187
D(Vaccine)	5.28E-05	8.12E-05	0.649723	.5205
D(Vaccine(−1))	−0.000697	0.000141	−4.927075	.0000
D(Vaccine(−2))	−0.000721	0.000142	−5.064209	.0000
D(Vaccine(−3))	−0.000720	0.000162	−4.431073	.0001
D(Vaccine(−4))	−0.000854	0.000176	−4.866121	.0000
D(Vaccine(−5))	−0.000889	0.000174	−5.116743	.0000
D(Vaccine(−6))	−0.000757	0.000197	−3.832990	.0006
D(Vaccine(−7))	−0.001076	0.000206	−5.232050	.0000
D(Vaccine(−8))	−0.000646	0.000196	−3.294723	.0024
D(Vaccine(−9))	−0.000735	0.000196	−3.744446	.0007
D(New cases)	0.002189	0.002111	1.037245	.3074
D(New cases(−1))	0.013324	0.003054	4.363197	.0001
D(New cases(−2))	0.016010	0.003180	5.034282	.0000
D(New cases(−3))	0.011588	0.003374	3.434670	.0017
D New cases(−4))	0.013454	0.003117	4.316633	.0001
D(New cases(−5))	0.012502	0.003134	3.988975	.0004
D(New cases(−6))	0.010879	0.002621	4.150736	.0002
D(New cases(−7))	0.006034	0.002700	2.235168	.0325

(*Continued*)

Table 3. Co-Integration and ARDL Results for Pediatrics Department (*Continued*)

Dependent Variable: Pediatrics			Observation Period: 2019-2021	
Test Name: ARDL			Selected Model: ARDL (12, 6, 12, 10, 11)	
Variable	Coefficient	Standard Error	*t*-Statistic	*Prob.*
D New cases(−8))	0.008324	0.002453	3.393161	.0019
D(New cases(−9))	0.003598	0.002756	1.305484	.2010
D(New cases(−10))	0.005963	0.002153	2.769691	.0093
D(Psychiatry)	3.471791	0.850263	4.083195	.0003
D(Psychiatry(−1))	−7.355510	1.950862	−3.770390	.0007
D(Psychiatry(−2))	−5.275913	2.019113	−2.612985	.0136
D(Psychiatry(−3))	−6.961026	1.836116	−3.791169	.0006
D(Psychiatry(−4))	−5.615754	1.648729	−3.406110	.0018
D(Psychiatry(−5))	−6.975836	1.532279	−4.552588	.0001
D(Psychiatry(−6))	−8.419048	1.564537	−5.381176	.0000
D(Psychiatry(−7))	−1.030237	1.941541	−5.306285	.0000
D(Psychiatry(−8))	−1.515088	2.134547	−7.097935	.0000
D(Psychiatry(−9))	−1.217584	2.510341	−4.850274	.0000
D(Psychiatry(−10))	−8.420010	2.046209	−4.114931	.0003
D(Psychiatry(−11))	−4.152366	1.428880	−2.906028	.0066
CointEq(−1)*	−0.684943	0.119356	−5.738653	.0000
	F-Statistic	**Significance**	**I(0)**	**I(1)**
Bounds test	**4.746975**	**1%**	**3.29**	**4.37**
R2		**0.981050**		
Adjusted R2		**0.948480**		

ARDL, autoregressive distributed lag model.

equations be seen in Table 2 and 3. According to the results obtained, it has been revealed that the admissions of individuals under the age of 18 in Sivas to PED are mostly affected by death cases in the long and short term, while the admissions to PD are affected by death cases in the short term. In this context, it can be said that the psychological effect of death has become more specific with COVID-19. Considering the ARDL results in Table 2, long-term admissions of children and adolescents to PSY have an increasing effect on PED admissions (1 PSY admission increases PED admissions by 15). Considering the short term, PSY admissions decrease the number of admissions to PED. According to the ARDL results in Table 3, while admissions to PSY have an increasing effect on PD admissions in the long term, it has a decreasing effect in the short term. ARDL results show us that there is an important correlation between PSY, PD, and PED visits. For PSY admissions (Figure 4), an increasing trend is observed in a short time unlike in other departments. It even reached the pre-pandemic period values about 1 year later. Admissions to the hospital for mental health were different from those for physical illnesses. The proportion of individuals under the age of 18 who applied to PSY during the COVID-19 period we studied was not significantly affected as in other departments. The need for psychological support during the pandemic period has not disappeared in any way, on the contrary, it has increased as time progressed. Besides, according to our econometric analysis, it can be seen that psychology may affect physiology and mental health may be more prominent than physical disorders during the pandemic period. Because, while it is seen that psychological relief from PSY visits decreases PD and PED admissions in the short term, it can be interpreted that this relief may cause an increase again in the long term when this relief ends. In addition, the healthcare demand of children and adolescents should not be considered separately from their parents or guardians. In this context, it can be interpreted that individuals under the age of 18 who apply to PED and those who are responsible for them experience short-term relief, but in the long term, individuals need psychological support (Table 2). The number of new COVID-19 cases, the number of deaths, and the number of vaccinations added to the models may be an indicator of psychological behavior. Because when the PSY admissions were examined, a very high correlation was obtained. In the literature, there are studies on the increase in hospital and emergency department visits due to mental illnesses (such as suicide, depression, and anxiety) along with the pandemic.[1-3] It was seen that individuals were psychologically affected by the pandemic, especially women in Turkey.[4] Considering the effects of PSY admissions in PD and PED admissions in models, and the increase in mental illnesses during the pandemic period, it can be interpreted that mental ailments can trigger physical ailments. Providing psychological support to both children and adolescents and their guardians during pandemic periods will ensure the growth of healthier individuals. When all models are evaluated, thinking about the existence of psychological effects in healthcare utilisations will lead to correct solutions. Apart from these, considering all admissions to hospitals, the COVID-19 pandemic may have caused individuals to avoid treatment for diseases other than COVID-19 that may cause them to lose their health. Although patients from both other provinces and abroad came to the hospitals in Sivas

included in the study, the inability to make a generalization for the use of health services in other provinces may be the limitation of this study. At the same time, only secondary and tertiary healthcare facilities admissions were included in the study, and primary healthcare facilities were excluded. The lack of a case-based analysis is the shortcoming of the study. In the literature, there are studies on the demand for health services for children and adolescents during the COVID-19 period. However, as in our study, a detailed examination of the causality relationship between departments has not been analyzed as far as we know. In addition, such a study does not exist in Turkey as far as we know. We can say that our study offers unique information for the pandemic and post-pandemic periods. For this reason, it will be a basis for longer-term and many comprehensive kinds of research to be studied in the future. Our study, which we handle with an interdisciplinary approach, will make important contributions to many fields such as health economics, health services planning, patient behavior, marketing, supply and demand, insurance, sociology, and psychology.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Sivas Cumhuriyet University (Date: September 28, 2020, Approval No: 5).

Informed Consent: The study was carried out retrospectively using the number of patient applications received from the statistics department of the hospitals. Personal data of patients are not used. Informed consent was not obtained from the patients as there was no clinical study that used any personal data.

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Histology-Embryology

Nicotinamide Riboside Preserves Ovarian Injury in an Experimental Sepsis Model in Rats

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ABSTRACT

Objective: The aim of the study is to investigate the protective effects of nicotinamide riboside on oxidative stress in an experimental sepsis model created by cecal ligation and puncture.

Materials and Methods: Rats were divided into 3 groups randomly: sham-operated (control) group, sepsis group, and nicotinamide riboside-treated group. Sepsis model-induced cecal ligation and puncture was applied to sepsis group rats. Animals in the nicotinamide riboside-treated group were administered nicotinamide riboside intraperitoneally (500 mg/kg). Tissue specimens from rats were biochemically calculated for their activities of catalase, superoxide dismutase, glutathione peroxidase, myeloperoxidase, and malondialdehyde levels. Ovarian tissues of all rats were histopathologically evaluated.

Results: Catalase, superoxide dismutase, and glutathione peroxidase activities were lower in the sepsis group compared to the sham-operated (control) group. Superoxide dismutase activity was significantly higher in the nicotinamide riboside-treated group than in control and sepsis group ($P < .05$). Myeloperoxidase activities and mean malondialdehyde concentration of ovarian tissue were lower in nicotinamide riboside-treated group than in sepsis group ($P < .05$). The light microscopic assessment revealed that ovarian tissue was protected, and inflammation and interstitial edema decreased in nicotinamide riboside-treated group. The follicular damage findings were notably decreased in nicotinamide riboside-treated group in comparison to sepsis group ($P<0.05$).

Conclusion: Our findings indicated that nicotinamide riboside diminished ovarian injury in sepsis via inhibiting tissue infiltration and increasing endogenous antioxidant capacity. Nicotinamide riboside administration may represent a new treatment approach for the prevention of sepsis-induced ovarian injury.

Keywords: Nicotinamide riboside, ovarian injury, oxidative stress, sepsis

Introduction

Hyperinflammation in sepsis is closely associated with multiple organ dysfunction. According to previous studies, mechanisms that cause multi-organ damage seem to be associated with the pathogenesis of sepsis, which induces the development of apoptosis through inflammation-triggered cytokine activation and reactive oxygen production, mitochondrial pathway.[1] An imbalance between the antioxidant defense system and emerging reactive oxygen species (ROS) results in the development of oxidative stress during sepsis. The endothelial cell–leukocyte interaction causes endothelial damage at the injection site, which results in the loss of endothelial integrity and tissue perfusion alteration.[2] Also, the formation of microthrombi in the vessels activated by the inflammatory response causes microvascular dysfunction, which is a significant mark of organ damage in sepsis. The cytokines have more versatile roles as ovarian regulators in ovulation, folliculogenesis, and ovarian hormone synthesis. In addition, cytokines associated with bacterial endotoxins lead to disruptions in ovarian function and hormonal regulation and affect fertility indirectly mechanism.[3] The cytokines such as IL-1 and TNF-α may affect the production of androstenedione and estradiol from theca and granulosa cells and inhibit the progesterone secretion from corpus luteum.[4] Furthermore, experimental sepsis studies highlight increased malondialdehyde levels (MDA) and myeloperoxidase (MPO) activity and reduced glutathione (GSH-Px) levels in the ovarian tissue as the significant finding of oxidative stress.[5] In the literature,

it has been noted that sepsis-induced oxidative stress may result in the depletion of antioxidant reserves in ovaries.[5] Therefore, it is logical to try to inhibit the degenerative effects of oxidative stress in ovary, which is an essential source of organ injury in sepsis.

Nicotinamide riboside (NR) is a form of vitamin B3 and is present in a wide variety of our daily foods, such as milk, milk-derived products, and yeast.[6] Nicotinamide riboside has attracted attention as a precursor of the nicotinamide adenine dinucleotide (NAD+). The administration of NR productively improves intracellular NAD^+ levels, a primary regulator of cellular oxidative stress, and may trigger sirtuins (SIRT) and poly (ADP-ribose) polymerases (PARPs) reactions.[7] Recent studies have shown the effects of NR in different pathologies as well as in inflammatory conditions, mitochondrial disorders, metabolic syndrome, fatty liver disease, DNA repair syndromes, and Alzheimer's disease.[8] Also, NR was shown to be successful in microvascular function improvement and attenuated endothelium damage in the ischemia-reperfusion model.[9] As decreasing levels of NAD^+ in sepsis have been reported in numerous studies, NR administration may be helpful in sepsis.[10]

In briefly, in this study, we aimed to investigate whether NR administration protects against oxidative stress and ovarian damage in a cecal ligation and puncture (CLP)-induced sepsis model.

Materials and Methods

Animals and Experimental Design

The present study was conducted according to national and international guidelines for using experimental animals. The protocols of experiments were reviewed and approved by the local and governmental committees for animal care and use (Ataturk University Local Ethics Committee, Aproval No: 2022-228). In total, 24 sexually mature female rats (Ataturk University Experimental Laboratories, Sprague Dawley, bodyweight 210-230 g) were used for all experiments in this study.

Main Points

- Sepsis is closely associated with multiple organ dysfunctions via inflammation.
- Reactive oxygen species of oxidative stress during sepsis affect ovary tissue.
- Nicotinamide riboside, a precursor of the nicotinamide adenine dinucleotide (NAD+), is a form of vitamin B3 and is present in a wide variety of our daily foods, such as milk, milk-derived products, and yeast.
- Nicotinamide riboside ameliorates sepsis injury by repairing the antioxidant system and, therefore, seems to be beneficial for overcoming inflammation in sepsis

The rats were divided into 3 groups (n = 8): (a) sham-operated control group, (b) sepsis group (CLP + saline), and (c) nicotinamide riboside-treated group (CLP + NR) group. The animals in each group were kept in different cages. Cages were individually ventilated with a 12-hour light/dark cycle and maintained at 22 ± 2°C. Standard rat food and tap water were given ad libitum.

Sepsis was induced by the CLP technique. Briefly, rats were anesthetized (general anesthesia) with a mixture of ketamine (80 mg/kg) and xylazine (10 mg/kg) intraperitoneally (i.p.). The abdominal skin was shaved and disinfected, and the cecum was exposed by making a 2 cm midline incision. The cecum was joined with 4.0 silk sutures at 1/3 of the proximal cecum and punctured 3 times with an 18 G needle and gently tightened to remove stool from the perforation site. After the cecum was repositioned, the laparotomy was closed with 4.0 silk sterile sutures. All animals were resuscitated by subcutaneous injection of saline (30 mL/kg) after CLP. Thirty minutes before and 12 h after the CLP surgery, rats were treated with an intraperitoneal injection of high-dose NR (500 mg/kg) in the CLP + NR group or the same amount of saline in the CLP + saline group. The administered dose was used as it could ameliorate sepsis-induced multi-organ dysfunction.[11] Nicotinamide riboside was obtained from BLD Pharmatech Ltd. (Cas: 23111-00-4, Shanghai, China) and dissolved in saline before use. The sham-operated group did not perform CLP, and other surgical procedures were the same as those of the CLP + saline group.

All CLP procedures were performed by the same investigator to minimize experimental variability. Twenty-four hours after CLP surgery procedure and respective treatments, rats (6 in the sham-operated group and 8 in each of the CLP + saline group and the CLP + NR group) suffered an assisted painless death with thiopental overdose (0.5 g/kg, i.p.) followed by decapitation. This time point was selected according to the fact that cytokine storm occurs between 12 and 16 hours after sepsis is created by CLP as reported in the literature.[12] The ovaries were quickly removed; half of each ovary was washed with ice-cold saline and stored at −80°C for further biochemical analysis. The other half of ovary was fixed in a 10% formalin in order to analyze histopathological alterartions.

Tissue Sample Preparation and Homogenization

For blind biochemical studies, ovarian tissue samples were labeled as groups 1, 2, 3, 4, etc., placed in liquid nitrogen promptly, and carried to the laboratory to measure lipid peroxidation levels and antioxidant and inflammatory enzyme activities. For the preparation of the ovarian tissue homogenates, all tissue samples were ground with liquid nitrogen in a mortar and then homogenized using a tissue homogenizer (Qiagen TissueLyser LT, Berlin, Germany) at 35 Hz (15 minutes at 4°C). The obtained homogenates were centrifuged at 1000 g for 10 min, and the supernatants were saved for analysis.

Assays for Tissue Lipid Peroxidation and Antioxidant Enzymes

As explained previously, lipid peroxidation levels in ovarian tissue homogenates were measured spectrophotometrically according to Okhawa et al.[13] The ovarian tissue samples were weighed as 15 mg in a sterile tube and homogenized in the cold with 1.5 mL buffers consisting of 100 g/L potassium chloride. The homogenates were centrifuged at 4°C, 10 000 g for an hour. Then, 0.25 mL of tissue homogenate was added to a solution containing 0.2 mL of 80 g/L sodium lauryl sulfate, 1.5 mL of 200 g/L acetic acid, 1.5 mL of 8 g/L TBA aqueous solution, and 0.3 mL of distilled water. The stirred mixture was heated in a boiling water bath for 45 minutes. After being cooled, 4 mL of n-butanol was added and layered by centrifugation. The absorbance of the supernatant was measured at 532 nm using a spectrophotometer (Bio-Tek, Winooski, VT, USA). 1,1,3,3 tetrametoxypropane was used to obtain the standard curve. Results were expressed in the unit of nanomoles per gram of tissue (nmol/g tissue). The superoxide dismutase (SOD) activity measurement was assigned according to Sun et al[14] and catalase (CAT) activity according to Aebi et al.[15] Estimation of the SOD activity was based on superoxide radical generation which was converted by the xanthine–xanthine oxidase system, the mentioned system reacts with nitroblue tetrazolium (NBT) for formazan dye creation. The assay of SOD activity was measured by NBT reduction method and the output was expressed as millimole per minute per milligram of tissue.

Catalase activity assay is based on the consumption of H2O2. For measuring CAT activity, the sample of supernatant was mixed with an H2O2 solution in phosphate buffer and measured in a quartz cuvette at 240 nm. Catalase activity was described as the amount of enzyme required to decompose 1 nanomole of H2O2 per minute, and results were expressed as mmol/min/mg.

The GSH-Px activity was evaluated in accordance with Paglia et al.[16] The reaction in a tube was initiated with the addition of H202 and

spectrophotometer was used to monitor the absorbance changes. Obtained results were expressed as mmol/min/g of tissue.

Assay of Myeloperoxidase Enzyme for Polymorphonuclear Leukocyte Response

The modified method of Bradley et al[17] was performed to determine MPO activity. Around 100 µL of the supernatant was added to 1.9 mL of 10 mmol/L phosphate buffer, and the homogenized tissue mixture (15 mg tissue in 1.5 mL buffer) was centrifuged for 10 minutes at 4°C. Myeloperoxidase absorbance changes were recorded at 460 nm every 30 seconds for 3 minutes after adding a solution that contained 1 mL of 1.5 mmol/L o-dianisidine hydrochlorides consisting of 0.0005% (w/v) hydrogen peroxide. The unit of MPO activity was defined as the amount required to degrade 1 µmol H2O2/min at 25°C. Results were expressed as units per milligram of tissue.

Histopathological Examination

Ovaries were collected from the rats and immediately fixed in 10% buffered formalin for 24-48 hours. Before the tissue processing protocol, all tissues were washed in running water for 20 minutes and formalin was removed. For the tissue processing protocol, all tissues were dehydrated in a graded alcohol series and cleared by xylene series. At the end of the histological processing, the tissue samples were embedded in paraffin wax. After tissue processing, tissue blocks were sectioned at 5µm thickness with a microtome (Leica RM2125RT, Leica Instruments, Nussloch, Germany). For staining, following deparaffinization and rehydration procedures, sections were stained with hematoxylin and eosin (H&E). All group sections were observed under a light microscope (Nikon Eclipse 80i), and the slides' photomicrographs were taken using a digital camera.

Data Analyses

In the present study, Statistical Package for Social Science (SPSS) version 20.0 for windows (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis, and descriptive statistical data were expressed as means ± standard error of mean. The significance of differences among different groups was analyzed by Duncan's multiple comparison test and one-way analysis of variance test. $P < 0.05$ was considered statistically significant.

Results

Biochemical Results

Results on ovarian tissue lipid peroxidation and antioxidant and immune response parameters during polymicrobial sepsis in high-dose NR-treated groups are shown in Figure 1A-E. High-dose NR inhibited oxidative stress associated with sepsis in ovarian tissue. The antioxidant enzymes SOD, CAT, GSH, leukocyte-derived enzyme MPO, and lipid peroxidation product MDA were detected 24 hours after the surgery modeling.

The ovarian MDA value was determined at the physiological level in the sham group (Figure 1A). The ovarian activities of SOD (69% and 37%, respectively), CAT (60% and 34%, respectively) enzymes, and the level of GSH (79% and 47%, respectively) were significantly lower in sepsis according to NR-treated group (Figure 1B-D). While the levels of MDA (68%) were significantly increased (Figure 1A), administration of NR significantly suppressed the MDA elevation levels (27%) in ovarian sepsis injury. Also, the activities of CAT, SOD, and GSH enzymes were significantly increased (101%, 65%, and 149%, respectively) in the CLP + NR group ovarian tissue, compared to the CLP + saline group (Figure 1B-D).

The lung MPO activities, an enzyme secreted by macrophages and activated neutrophils, were determined at the physiological level in the ovaries of the sham group (Figure 1E). High-dose NR treatment considerably decreased MPO activity that had been raised in the ovary by sepsis. The activities of the MPO enzyme were significantly increased (68% and 12%, respectively) either in the CLP + saline and in the CLP + NR groups. After NR treatment, the elevation in MPO activities (27%) was significantly lower in the CLP + NR group, compared to the CLP + saline group (Figure 1E).

Results of Histopathologic Investigations

Sham-operated (control) group ovaries exhibited a typical healthy appearance with the cortex and medulla, and no damage was observed in the ovarian tissue (Figure 2). The germinal epithelium surrounding the ovary is observed as a simple squamous epithelium. Many primordial, preantral, and antral planned follicles were located in the cortex and the medulla. Corpus luteums were marked slightly acidophilic.

There were severe inflammation and interstitial edema in CLP + saline group ovarian tissue samples. The pathological changes, such as massive neutrophil infiltration, increased vascular permeability, and tissue edema, primarily vascular endothelial damage, were conspicuous in this group's ovarian medulla (Figure 2). Sepsis caused an increase in necrotic and apoptotic cell numbers due to decline in granulosa cell viability. Cytoplasmic vacuolization was available in the luteinized granulosa cells of the corpus luteums and the granulosa cells of the primary and secondary follicles (Figure 2). Apoptotic and degenerative cells with nuclear changes consisting of hyperchromatic nuclei, pyknosis, and strongly eosinophilic cytoplasm were also visible in those kinds of follicles (Figure 2). However, there were no striking differences in the early stages of follicles. In addition, many atretic cells in the Graafian follicles and hypertrophic cell changes in the early-stage follicles were observed in sepsis-induced ovarian samples compared to the sham-operated group (Figure 2).

Nicotinamide riboside treatment significantly reduced histopathological changes due to sepsis and preserved ovarian structures. Although some leukocytes were seen in interstitial tissue of the ovarian sections of the CLP + NR group, dense inflammatory cell migration was significantly decreased compared to the CLP + saline group (Figure 2). Vascular structures were preserved, and edema was minimal, as NR provided an improvement in tissue architecture (Figure 2). Degenerative changes and apoptotic cell death in granulosa cells were very few compared to the sepsis group (Figure 2). Follicular development and generally follicular cell structure were similar to the sham-operated group (Figure 2).

Inflammation Scoring

Inflammation scoring on histopathological investigations was made according to the grading system in Table 1. It was obvious that polymorphonuclear leukocytes, vascular congestion, and edema scores were lower in CLP + NR group compared to the CLP + saline group.

Discussion

Numerous studies have described oxidative stress as significant event of sepsis,[18] which may lead to cellular damage and organ dysfunction.[19] Multiple generations of nitric oxide (NO) and ROS are the main sources of oxidative stress during sepsis.[18] Reactive oxygen species may damage vascular endothelial cells; free oxygen radicals induce the expression of tissue factors and contribute to sepsis-induced microvascular dysfunction.[20] Microvascular perfusion alterations and subsequent organ failure may develop due to septic conditions. Despite recent advances in therapeutic agents, organ failure in sepsis is still debated. As oxidative stress plays a critical role in initiating and establishing sepsis, supplementation with antioxidants seems beneficial and improves current sepsis therapies. For this purpose, we aimed to investigate the antioxidant effects of NR on ovarian damage in a CLP-induced sepsis model.

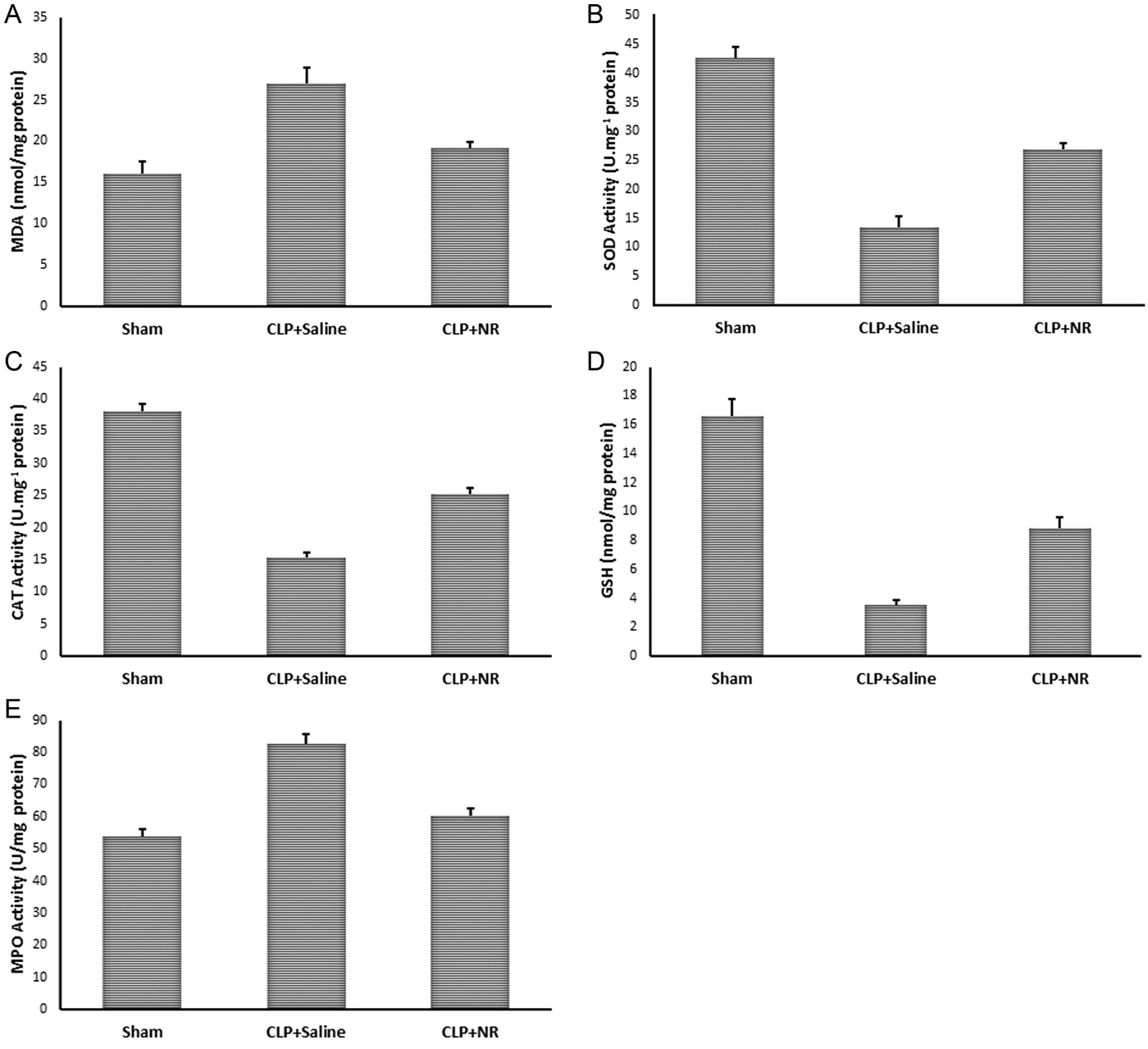

Figure 1. (A): The bar graph shows the mean level of MDA. (B): The bar graph shows the mean level of SOD activity. (C): The bar graph shows the mean level of CAT activity. (D): The bar graph shows the mean level of GSH. (E): The bar graph shows the mean level of MPO activity. CAT, catalase; SOD, superoxide dismutase; GSH, glutathione peroxidase; MPO, myeloperoxidase; MDA, malondialdehyde.

The activity of ROS scavengers like SOD and CAT considerably decreases in the tissues during sepsis.[20] In the present study, we revealed oxidative stress damage through measurements of MDA, MPO, SOD, CAT, and GSH-Px enzymes, as important endogenous antioxidants against oxidative stress damage in ovary. Increased MDA and MPO levels and decreased SOD and CAT activities demonstrate sepsis-induced ovarian tissue damage in the present study. The data also support the preservative effect of NR in a sepsis model of tissue injury. The crucial finding in present study was that NR administration resulted in a significant decrease in MPO activity as an indicator for active leukocyte accumulation in tissue. This finding suggests that NR can potentially influence tissue injury and inflammation.[11] Additionally, observed tissue recovery evidence supports this finding. Namely, the administration of NR in CLP-induced sepsis significantly decreased leucocyte infiltration and tissue edema and reduced apoptotic follicular cells by inhibiting oxidative stress.

Malondialdehyde is a typical product of oxidative damage and a good indicator of lipid peroxidation. Lipid peroxidation plays an essential role in membrane permeability changes, eventually leading to cell lysis.[21] This study found that MDA levels in the ovarian tissue increased in CLP-performed septic rats. Elevated tissue MDA levels were described in CLP-induced sepsis models in rats and humans.[22] Also, data from the present study exhibit that MDA content was high in ovarian tissue during sepsis; however, NR administration inhibited the MDA concentration increase in septic rats.

In a CLP-induced sepsis model, excessive ROS products such as superoxide (O_2^-) and H2O2 are metabolized by SOD, CAT, and GSH-Px, the major antioxidants that protect

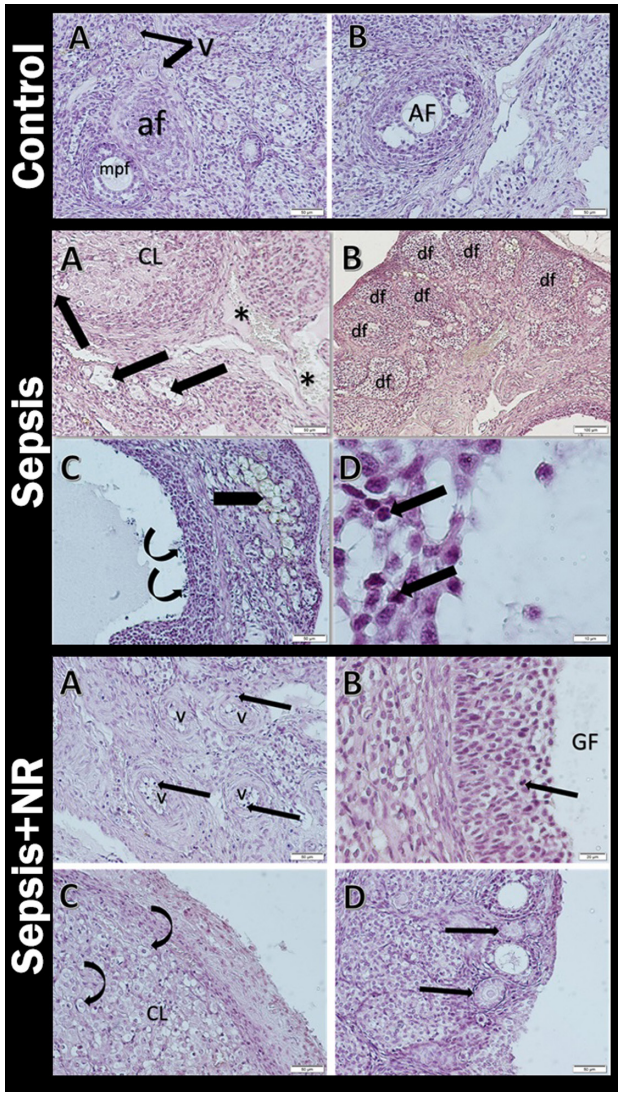

Figure 2. Control group: Representative photomicrographs of ovarian histology of sham-operated control group (A, B). af indicates atretic follicle; mpf, primary follicles with multiple layers; v, blood vessels; and AF, normal antral follicle. H&E staining; original magnification ×40. Sepsis group: Representative photomicrographs of ovarian histology of sepsis group (A, B, C, D). (A) shows corpus luteum (CL), cytoplasmic vacuolization (black arrow) of granulosa cells, vascular damage, and edema (*) in the stroma. (B) includes many degenerated (atresia) follicles (pdf). (C) shows apoptotic bodies (crooked arrow) in the Graafian follicle and widespread vascular damage (black arrow) in the stroma. (D) exhibits degenerative cells with nuclear changes (black arrows) consisting of pyknosis and karyorrhexis in the Graafian follicle. H&E staining, original magnification A (×40)—B (×20)—C (×40)—D (×100). Sepsis + NR group: Representative photomicrographs of ovarian histology of NR group. (A) shows blood vessels with normal morphology in the medulla of the ovary, and few leukocytes (black arrow) were observed. (B) exhibits theca and granulosa cells of the Graafian follicle (GF) with normal cellular structure and few leukocytes (black arrow). (C) demonstrates vacuolization in some cells of the corpus luteum (convoluted arrow). (D) shows healthy growing follicles (black arrow). H&E staining, A(×20)—B(×40)—C(×40)—D(×20)).

Table 1. Sepsis Injury on Histopathological Inflammation Scores of Ovarian Tissues of Rats

Groups	PMNL	VK	Edema
Sham operated (control)	0	0	0
CLP + saline	3	3	2
CLP + NR	1	2	1

The grading system was described as 0, no inflammatory cells (ICs); 1, a few ICs; 2, many ICs in the peripheral parts of the perivascular area; 3, numerous ICs in the perivascular area.
PMNL, polymorphonuclear leukocytes; VC, vascular congestion.

cytosolic organelles from toxic free radicals during oxidative stress.[11] Similar to our results, recent studies reported that SOD and CAT levels decreased during CLP-induced sepsis in the affected tissues.[23,24] Our data demonstrated that the administration of NR in the CLP septic group increased antioxidant enzyme activities. Glutathione peroxidase and SOD activity significantly improved in CLP+ NR group compared to CLP + saline group septic rats. These results suggest that NR attenuates ovarian tissue injury by preventing oxidative stress after CLP-induced sepsis. Nicotinamide riboside increased the antioxidant activity and attenuated inflammation and oxidative stress by activating macrophages.[25] Recent study indicates that pre-administration of NR supplies anti-inflammatory and protective effects against apoptosis through the NAD^+/SIRT1 signaling during the inflammation.[11] Interestingly, SIRT1 activation was significantly lower due to decreasing NAD^+ in sepsis.[26] As NR has been shown to be considerably effective in raising NAD^+ levels in humans[27] and experimental models,[11,28] it was suggested that NR may be useful in sepsis injury.

Apoptotic cell death of various tissues under sepsis conditions has been described in the literature.[29] Kafa et al[30] declare that the number of apoptotic cells in different brain regions significantly increased in CLP-induced sepsis model. In addition, cytoplasmic blebs, necrotic cells, apoptotic bodies, and cell membrane damage were shown in the murine sepsis model.[29] A recent study similar to our results[31] described an increased number of apoptotic cells, mainly in the Graafian follicles in the CLP-induced sepsis model. As excessive ROS production leads to oxidative tissue damage in the ovary, pharmaceutical agents should demonstrate an antioxidant effect to reduce ovarian tissue damage.[32] The proper antioxidant dosage of NR to initiate tissue protection has not been described in the literature. In experimental animal studies, the dosage of NR has varied between 100 and 500 mg/kg body weight.[11,33] We administered 500 mg/kg of NR for each rat to evaluate its antioxidant and anti-inflammatory effects on sepsis-induced injury. Nicotinamide riboside is a prescribed precursor of NAD^+, which is an essential regulator of oxidative stress and inflammatory responses. Nicotinamide riboside decreases oxidative damage and diminishes brain inflammation, karyopyknosis, and degeneration in brain tissue.[34] Also, present study results demonstrated that NR decreases leucocyte infiltration, tissue edema, degenerative changes, and apoptotic cell death in follicles. Our findings confirm Hong's study,[11] which reported that inflammatory cell infiltration, tissue edema, and apoptosis were reduced by NR at 500 mg/kg in septic mouse lungs. The selected dose of NR in the present study was based on this study.[11] We hope that mentioned properties of NR may be related to its effects on the apoptosis pathway and NF-kB as a main mediator of inflammation. Though, the limitation of our study is the lack of

measurement of NF-kB, caspase-3 activity, and cytokine levels.

In conclusion, this study is the first experimental model investigating NR on ovarian injury. The present study's data have shown that NR's protective effect may be due to its potent antioxidant property, which causes improvements in oxidative stress parameters in ovarian tissue. Nicotinamide riboside ameliorates sepsis injury by repairing the antioxidant system and therefore, seems to be beneficial to overcome inflammation in sepsis. It has long been used as a dietary supplement. Also, it could become a treatment modality for oxidative stress in sepsis-induced organ injury if further studies support our results. Based on our findings, dietary supplementation of NR may ameliorate ovarian injury and have therapeutic effects as a preservative approach in sepsis. However, clinical trials with larger sample sizes are required to investigate the antioxidant effect of NR in sepsis injury and to achieve precious decisions.

The limitations of our study were given as follows:

1. This study also aimed to evaluate NR effect on CLP. However, we had no diagnostic kits for the measurement of anti-inflammatory and inflammatory cytokine levels and we could not do it.
2. We could not evaluate immunohistochemically on ovary tissue due to lack of immunohistochemical kit and antibody.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ataturk University (Approval no: 2022-228).

Informed Consent: N/A

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Exercise Physiology

Effect of Swimming Exercise on Respiratory Muscle Strength and Respiratory Functions in Children with Autism

Emine Adin, Zarife Pancar

ABSTRACT

Objective: The aim of this study is to examine the effects of swimming exercise on respiratory muscle strength and respiratory functions in children with autism. Autism is a mental disorder that affects many areas such as sensory, cognitive, motor, and psycho-motor development in individuals.

Materials and Methods: For this purpose, 15 individuals with autism, 8 of which were in the experimental group and 7 in the control group, participated in the study. The experimental group was subjected to swimming exercise for 1 hour, 3 days a week, for 6 weeks. The control group was not included in this exercise. Respiratory muscle strength and pulmonary function tests were applied to both groups before and after the 6-week period. The obtained data were analyzed using Statistical Package for Social Sciences Program Version 22.0. Values were presented as minimum, maximum, mean, standard deviation, and standard error. The Shapiro-Wilk test was used to test for normality. Paired-sample *t*-test was used for pre-test and post-test, and independent-sample *t*-test was used for intergroup analysis.

Results: At the end of 6 weeks, according to the statistical analysis data, there was a significant difference in some of the respiratory function parameters of the experimental group ($P < .05$), and an improvement was observed in the respiratory muscle strength values, but no significant difference was found ($P > .05$). No significant difference was found in the respiratory functions of the control group as a result of respiratory muscle strength measurements ($P > .05$).

Conclusion: As a result, we can say that swimming exercise is effective in improving respiratory muscle strength and respiratory functions in children with autism.

Keywords: Exercise, strength, autism, respiratory, swimming

Introduction

Autism is a mental disorder that affects many areas such as sensory, cognitive, motor, and psycho-motor development in individuals.[1] They are unable or have difficulty in social interaction. It is very difficult for children with autism to communicate with other individuals other than their families. As a result of the researches, it is known that children with autism have looser muscle structure and their motor development progresses more slowly than healthy children.[2-]

It is known that physical activity has many psychological and health benefits for individuals. In its deficiency, different types of diseases such as cardiovascular diseases and various cancer types can be seen in individuals. These symptoms can also be seen in individuals with autism spectrum disorder (ASD), as well as creating great problems in areas such as socialization, communication, and meeting personal needs. In general, individuals with ASD lead a more sedentary and physically inactive life than individuals with normal development.[5-7]

Swimming is defined as a sport that aims to overcome or minimize the friction that prevents the movement in which the arms and feet work in coordination in the horizontal position on the water. Considering the pressure it creates on breathing, it can be said that the energy required for swimming is about 4 times the energy required for running, according to the energy data consumed by individuals who cover a distance by running and swimming.[8,9] The respiratory system is

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very important in terms of daily life, work performance, and sportive performance capacity of the individual.[10-12]

In addition to the explanations above, it is thought that swimming exercise will have positive effects on the general health status of children with autism and, as the main determinant, on respiratory functions. The swimming exercise program should be prepared and implemented for these predetermined purposes. The aim of our study is to examine the effect of swimming exercise on respiratory muscle strength and respiratory functions in children with autism.

Materials and Methods

The research was designed based on the control pretest–posttest design. Fifteen autistic children between the ages of 10 and 12 participated in the study. The subjects were divided into 2 groups as experimental (n=8; 2 girls, 6 boys) and control (n=7; 7 boys) groups. The respiratory functions and respiratory muscle strength measurements of the subjects were taken 1 day before and 1 day after the 6-week training program. Care was taken to form the subject groups, especially from individuals who did not do sports. The same pretest–posttest period was applied to the control group. This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (Gaziantep University Ethics Committee, decision no: 221-2020).

After the first measurements, a 6-week swimming exercise program was applied to the experimental group. The control group was not included in this training program. The exercise program was set as 1 hour and 3 days a week with 1-day intervals for each individual. At the beginning of the training, warm-up and stretching movements were applied for 10 minutes, and the training was applied according to the ready exercise program in the remaining 50 minutes. At the end of each 20 minutes of training, 5 minutes of free play was given. The full participation of all individuals in the experimental group was ensured in the 6-week exercise program and the same program was applied to everyone.

Main Points

- As a result of the applied swimming exercise, improvements were observed in the respiratory functions of individuals with autism.
- The respiratory system is physiologically coordinated to meet the increased oxygen demand.
- The 6-week swimming exercise period is sufficient for the development of respiratory functions value in children with autism.

Pulmonary Function Tests

Forced vital capacity measurement (Figure 1): Pocket Spiro USB-100 device was used. During the measurement, the subjects were allowed to wear light clothing. The subjects were told in advance that they had to do their best; otherwise, the results would be meaningless. A separate mouthpiece was carefully used for each subject. The subject's nose was blocked, and the mouthpiece was placed between the lips so that there was no gap in the corners of the mouth. During measurement, subjects first did 3 normal inspirations and exhalations, then inhaled at maximum force and rapidly, and then exhaled as quickly as possible to complete the measurement.[13-15]

Vital capacity measurement (Figure 2): During measurement, subjects first performed 3 normal inspirations and expirations, then completed the measurement by performing 1 slow maximum inspiration and 1 slow maximum expiration.[16]

Breath inspiratory flow and peak expiratory flow calculation: MEC Pocket Spiro MPM 100 electronic respiratory pressure gauge was used. The person is asked to make maximum expiration and maximum inspiration into the closed airway for 1-3 seconds. For peak expiratory flow (PEF), the person is given maximum inspiration and the person is asked to give maximum breath into the closed airway and continue this for 1-3 seconds. The measurement was repeated until the difference between the 2 best measurements was 10 cmH_2O and the result of the difference in the measurements of the individuals was recorded as cmH_2O.[17,18]

Statistical Package for Social Sciences Version 22.0 (IBM Corp., Armonk, NY, USA) program was used for statistical operations. The Shapiro–Wilk test was used to test for normality. The paired-sample *t*-test was used to compare pre- and post-test data, while the independent-sample *t*-test was used to compare the difference between pre-group and post-group tests.

Results

In this study, which investigated the effects of swimming on respiratory muscle strength and respiratory functions in children with autism, a total of 15 autistic individuals, 8 of which were in the experimental group and 7 in the control group, were included.

The descriptive data of the subjects participating in the study are shown in Table 1. Experimental group forced vital capacity (FVC) mean was 1.86 ± 0.71 lt, control group FVC mean was 1.44 ± 0.27 lt, experimental group 1 second forced expiratory volume (FEV1) mean was 1.20 ± 1.04 lt, control group FEV1 mean was 1.15 ± 0.55 lt, experimental group FEV1/FVC mean was

Figure 1. Forced vital capacity measurement.

Figure 2. Vital capacity measurement.

Table 1. Descriptive Parameters of the Subjects

		Min.	Max.	Mean	SD
Experimental group (n =8)	Age (years)	10.00	11.00	10.25	0.46
	Height (cm)	130.00	153.0	142.8	7.53
	Body weight (kg)	31.00	53.00	40.63	9.72
	BMI (kg/m^2)	15.40	23.60	19.68	3.11
	FVC (lt)	0.96	2.96	1.86	0.71
	FEV1 (lt)	0.00	2.78	1.20	1.04
	FEV1/FVC (%)	0.00	100.0	66.25	45.21
	PEF (lt/sn)	0.46	4.56	3.03	1.48
	PIF (lt/sn)	0.65	3.27	2.13	0.86
	MVV (lt/dk)	0.00	97.20	41.88	36.40
	VC (lt)	1.02	2.40	1.69	0.48
	TV (lt)	0.41	0.73	0.56	0.10
	IVC (lt)	0.76	1.53	1.09	0.31
Control group (n=7)	Age (years)	9.00	12.00	10.57	1.27
	Height (cm)	138.00	160.0	145.2	7.97
	Body weight (kg)	34.00	50.00	40.86	6.18
	BMI (kg/m^2)	14.80	25.00	19.46	3.32
	FVC (lt)	1.12	1.84	1.44	0.27
	FEV1 (lt)	0.00	1.71	1.15	0.55
	FEV1/FVC (%)	0.00	100.0	83.43	37.08
	PEF (lt/sn)	1.46	3.90	2.39	0.84
	PIF (lt/sn)	1.20	2.32	1.89	0.45
	MVV (lt/dk)	0.00	59.90	40.27	19.40
	VC (lt)	0.00	1.72	1.13	0.55
	TV (lt)	0.00	0.85	0.52	0.30
	IVC (lt)	0.00	1.72	1.04	0.56

FEV1, 1 second forced expiratory volume; FVC, forced vital capacity; IVC, inspiratory vital capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; PIF, breath inspiratory flow; SD, standard deviation; TV, tidal volume; VC, vital capacity.

66.25 ± 45.21%, control group FEV1/FVC mean was 83.43 ± 37.08%, mean PEF in the experimental group was 3.03 ± 1.48 lt/sec, mean PEF in the control group was 2.39 ± 0.84 lt/sec, mean PIF in the experimental group was 2.13 ± 0.86 lt/sec mean PIF in the control group was 1.89 ± 0.45 lt/sec, maximal voluntary ventilation (MVV) mean in the experimental group was 41.88 ± 36.40 lt/min, control group MVV mean was 40.27 ± 19.40 lt/min, experimental group vital capacity (VC) mean was 1.69 ± 0.48 lt, control group mean VC was 1.13 ± 0.55 lt, experimental group tidal volume (TV) mean was 0.56 ± 0.10 lt, control group TV mean was 0.52 ± 0.30 lt, the mean of the experimental group inspiratory vital capacity (IVC) was 1.09 ± 0.31 lt, and the mean of the control group IVC was 1.04 ± 0.56 lt.

Analysis of changes in respiratory function parameters as a result of swimming exercise is shown (Table 2).

While the pre-test FVC average of the experimental group was 1.86 ± 0.71 lt, the FVC average in the post-test was 2.50 ± 0.68 lt (Table 3). There was a significant difference between the pre- and post-test in the FVC value of the experimental group ($P < .05$). There was no significant difference between the pre-test and post-test in the FVC value of the control group ($P > .05$). There was a significant difference between the pretest and posttest in the FEV1 value of the experimental group ($P < .05$). There was no significant difference between the pre-test and post-tests in the FEV1 value of the control group ($P > .05$).

The analysis of the measurements taken from individuals with autism in the experimental-control groups in PEF and PIF values, which are respiratory muscle strength parameters, are given in Table 4.

Discussion

This study was conducted to examine the effects of swimming on respiratory muscle strength and respiratory function in children with autism. At the end of the 6-week exercise program, respiratory function and respiratory muscle strength were measured to determine whether the applied training program was effective or not.

In physical activities, the oxygen demand of the muscles increases and the respiratory system is physiologically coordinated to meet the increased oxygen demand. Increasing respiratory function according to the intensity and duration of breathing exercises; the development of respiratory muscles depends on the expansion ability of the lungs and chest cavity, the elasticity of the bronchi and bronchioles.[19] As a result of the applied swimming exercise, improvements were observed in the respiratory functions of individuals with autism. Considering the pre-test and post-test data obtained, a significant difference was found in the FVC, FEV1, MVV, and IVC values. An increase was observed in FEV1, FVC, VC, and TV values, but no significant difference could be obtained. No significant difference was detected in the respiratory parameters of the control group ($P > .05$).

Another study examined the effect of swimming on children's respiratory parameters. A 6-week swimming training was given to the

Table 2. Analysis of Respiratory Function Values

Characteristics		Mean	SD	*P*
FVC (lt)	Pre-test	1.66	0.57	.156
	Post-test	1.94	0.85	
FEV1 (lt)	Pre-test	1.17	0.82	.072
	Post-test	1.72	1.03	
FEV1/FVC (%)	Pre-test	74.27	41.11	.362
	Post-test	85.27	34.72	
MVV (lt/dk)	Pre-test	41.13	28.72	.073
	Post-test	60.15	35.96	
VC (lt)	Pre-test	1.43	0.57	.167
	Post-test	1.62	0.57	
TV (lt)	Pre-test	0.54	0.21	.135
	Post-test	0.66	0.18	
IVC (lt)	Pre-test	1.06	0.43	.096
	Post-test	1.30	0.42	

FEV1, 1 second forced expiratory volume; FVC, forced vital capacity; IVC, inspiratory vital capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; PIF, breath inspiratory flow; SD, standard deviation; TV, tidal volume; VC, vital capacity.
***P* < .05.**

Table 3. Comparison of Pulmonary Function Values Between Pre–Post Test and Groups

			Mean	SD	*P*
Experimental group (n=8)	FVC	Pre-test	1.86	0.71	.030
		Post-test	2.50	0.68	
	FEV1	Pre-test	1.20	1.04	**.017**
		Post-test	2.24	1.02	
	FEV1/FVC	Pre-test	66.25	45.21	.197
		Post-test	85.25	34.61	
	MVV	Pre-test	41.88	36.40	**.017**
		Post-test	78.26	35.53	
	VC	Pre-test	1.69	0.48	.209
		Post-test	1.93	0.63	
	TV	Pre-test	0.56	0.10	.127
		Post-test	0.72	0.23	
	IVC	Pre-test	1.09	0.31	**.025**
		Post-test	1.43	0.46	
Control group (n=7)	FVC	Pre-test	1.44	0.27	.537
		Post-test	1.31	0.50	
	FEV1	Pre-test	1.15	0.55	.957
		Post-test	1.13	0.70	
	FEV1/FVC	Pre-test	83.43	37.08	.931
		Post-test	85.29	37.62	
	MVV	Pre-test	40.27	19.40	.953
		Post-test	39.46	24.64	
	VC	Pre-test	1.13	0.55	.528
		Post-test	1.28	0.23	
	TV	Pre-test	0.52	0.30	.574
		Post-test	0.60	0.09	
	IVC	Pre-test	1.04	0.56	.668
		Post-test	1.16	0.33	

FEV1, 1 second forced expiratory volume; FVC, forced vital capacity; IVC, inspiratory vital capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow; PIF, breath inspiratory flow; SD, standard deviation; TV, tidal volume; VC, vital capacity.
***P* < .05.**

Table 4. Comparison of Respiratory Muscle Strength (PEF, PIF) Pre–Post Test Difference

			Mean	SD	*t*	*P*
Experimental group (n=8)	PEF	Pre-test	3.03	1.48	−1.549	.165
		Post-test	3.75	0.76		
	PIF	Pre-test	2.13	0.86	0.147	.887
		Post-test	2.09	0.38		
Control group (n=7)	PEF	Pre-test	2.39	0.84	−0.139	.894
		Post-test	2.42	0.7		
	PIF	Pre-test	1.89	0.45	0.088	.933
		Post-test	1.87	0.44		

PEF, peak expiratory flow; PIF, breath inspiratory flow.
***P* < .05.**

male swimmers (34 children aged 6-14 years) in the experimental group. It was concluded that FVC value was 6%, FEV1 value was 6.32%, MVV value was 6.52%, and FEF value was 20%-32% higher than that before the study.[20] In a study, as a result of 8-week swimming training, the VC value of the experimental group was 4.90 ± 1.20 lt in the pre-test and increased to 6.60 ± 1.20 lt in the post-test.[21] In different studies, a significant difference was found in the FVC, FEV1, FIV1, IC, and MVV values of the 8-12 age group as a result of 8 weeks of swimming exercise. Different from our age groups, 11 young women who study at the sports academy and do regular swimming training and 40 young women who do not train participated. In a study investigating the effect of 12-week swimming training on respiratory parameters, VC, FVC, and FEV1 values were found to be significantly different between women who did swimming training and women who did not.[22]

In a study conducted with adolescent swimmers, the pre-test and post-test values of VC, FVC, FEV1 parameters were found to be statistically significant among 310 elite swimmers aged 12-14 years for the spirometric evaluation of the respiratory system.[23] Respiratory muscles are an important criterion in revealing performance. It was also supported by sports experts. The endurance of the respiratory muscles is important in building resistance to fatigue.[24-26]

In order to determine whether autistic individuals participating in the study had a positive effect on respiratory muscle strength, the difference between the 2 measurements was checked by measuring PIF and PEF values during the study. As a result of this measurement, no significant difference could be reached between the data obtained from the experimental group and the control group. In a different study, it was shown that an 8-week regular core training program strengthened the respiratory muscles and reduced the fatigue of the respiratory muscles due to the resistance caused by the bicycle.[27-29]

A total of 16 individuals with Down syndrome underwent 4-week inspiratory muscle training, and respiratory muscle strengths were measured before and after the training. In the data obtained, the mean PEF value of the experimental group before the test was 1.22 ± 0.32 lt/s, while the mean PEF value after the test increased to 1.73 ± 0.59 lt/s and 43.96 ± 45.30%. In the experimental group, the pre-measured PIF mean value increased 1.02 ± 0.27 lt/s, and the post-measurement PIF mean

value increased to 1.32 ± 0.40 lt/s and 43.54 ± 79.85%. No significant difference was found in the PIF and PEF values of the control group.[11]

In a different study investigating the effect of swimming training on respiratory parameters, there was no significant difference in PEF values between women who did and did not train,[22] and in another study, it was investigated whether the breathing exercises performed by children of the same age during the 8-week study period had an effect on vital capacity. As a result of the study, it was observed that the FVC, FEV1, PIF, and FEV1/FVC values of the swimmers did not change.[25]

Swimming exercises are effective for the performance of autistic children. However, since the exercises should be one-to-one work, effective and sufficient time is needed. Longer duration or regular swimming exercise may be recommended for autistic children. In our study, we worked with a small number of autistic children and limited its duration. By increasing the number of researchers and the number of children, respiratory functions can be improved by swimming for a long time. At the same time, the effects of exercise on social behavior changes can be tested.

A limited number of autistic children were included in our study. Larger number can be included. Conducting a separate study with each autistic child made the study difficult in terms of time and measurements and caused it to be prolonged. Participation of autistic children in swimming activities brought positive results in terms of both performance and social aspects.

As a result, we can say that swimming exercise performed in line with the goal of our study provides improvements that support the development of respiratory functions of individuals with autism. The endurance of the respiratory muscles is important in building resistance to fatigue. Therefore, swimming exercises and respiratory muscle activities should be supported in children with autism.

Ethics Committee Approval: This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (*Gaziantep University Ethics Committee, decision no: 221-2020*).

Informed Consent: Informed consent was obtained from all parents whose children participated in this study.

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Public Health

Evaluation of Nurses' Vaccine Hesitancy, Psychological Resilience, and Anxiety Levels During COVID-19 Pandemic

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ABSTRACT

Objective: This study aimed to evaluate the vaccine hesitancy, psychological resilience, and anxiety levels of nurses during the COVID-19 pandemic.

Materials and Methods: This cross-sectional study was conducted with 676 nurses working at the survey time. Sociodemographic features, the status of hesitancy against the COVID-19 vaccine, the Coronavirus Anxiety Scale, and the Brief Resilience Scale were used in the questionnaire form to collect the data.

Results: Most participants (68.6%; n=464) stated they were hesitant about the COVID-19 vaccine. A significantly higher rate of hesitancy was detected in the age group of 20-39 years, those who did not have COVID-19 vaccine, and those who did not think the COVID-19 vaccine is protective ($P < .05$). It was determined that 6.8% (n=46) of the nurses had COVID-19 anxiety. A significantly higher rate of anxiety was detected in the age group of 40 years and older, those working in the emergency department, and those working in the COVID-19 unit during the pandemic period ($P < .05$). The median Brief Resilience Scale score of nurses is 19(6). A negative, weak, and significant relationship was found between the Brief Resilience Scale and Coronavirus Anxiety Scale scores ($P = .001$).

Conclusion: During the pandemic, higher rates of anxiety were detected in healthcare personnel and those working in COVID-19 units. It was also found that as the level of anxiety increased, the level of psychological resilience decreased. To reduce the anxiety level and strengthen the psychological resilience of nurses, the cornerstones of the health system, fast, effective, and curative interventions should be made.

Keywords: COVID-19 pandemic, nurses, vaccine hesitancy, psychological resilience, anxiety

Introduction

On December 31, 2019, some cases of pneumonia of unknown etiology were reported in the city of Wuhan, Hubei province of China. The World Health Organization (WHO) announced on January 9, 2020, that the Chinese authorities determined that this pandemic was caused by a new coronavirus. On February 11, 2020, they named it COVID-19. With the rapid spread of the disease globally, this situation was declared as a pandemic on March 11, 2020.[1,2] According to the data of WHO, as of April 2022, 500 186 525 confirmed cases and 6 190 349 deaths were detected worldwide.[3]

One of the most important public health issues that were highlighted and extensively discussed during COVID-19 are vaccine hesitancy and anti-vaccination. World Health Organization defines vaccine hesitancy as delay in acceptance or refusing vaccines despite the availability of vaccine services.[4] Furthermore, it defines anti-vaccination as total opposition to vaccination or advocating against or total refusal of self or one's child's vaccination. During the pandemic, healthcare workers were also affected by negative publicity about vaccines and developed hesitancy.[5,6] This hesitancy of the healthcare workers negatively impacted the public. Therefore, overcoming the hesitancy of healthcare workers will play a crucial role in gaining the trust of the public.

Psychological resilience is defined as the ability to cope with crises, adapt positively, and successfully overcome difficulties.[7] In a study done in the United States during the pandemic, the

participants displayed very low psychological resilience. The study also found a significant link between low psychological resilience and negative psychological conditions such as depression, anxiety, or suicidal tendencies.[8]

Studies have shown that healthcare professionals who work in high-risk and stressful situations during the pandemic are more prone to experience psychological problems such as fear, depression, anxiety, post-traumatic stress symptoms, and insomnia.[9] A study conducted during the 2003 SARS pandemic showed that nurses and other healthcare professionals who had contact with SARS patients experienced more intense stress.[10] A study conducted in Spain showed that 71.6% of healthcare professionals working during the COVID-19 pandemic had anxiety symptoms, and 60.3% had depressive symptoms.[11] In a study conducted on nurses working in a university hospital at the beginning of the pandemic in Turkey, stress, depression, and anxiety levels were found to be significantly higher in nurses.[12]

Healthcare professionals working at critical points during the pandemic may have been professionally exposed to intense physical and psychological stress. For this reason, while the pandemic continues, it is thought that it will be important to determine nurses' psychological resilience and anxiety levels and develop supportive interventions in this regard. This study aimed to evaluate the vaccine hesitancy, psychological resilience, and anxiety levels of nurses during the COVID-19 pandemic.

Materials and Methods

Type, Place, and Time of Research

This survey-based cross-sectional study was conducted between September and October 2021 at Inönü University Turgut Özal Medical Center using the face-to-face interview technique with the staff working as a nurse. Before commencing the study, preliminary permission was obtained from the Director of İnönü University Turgut Özal Medical Center (approval date: August 24, 2021, and number: 77609). Each participant gave verbal consent before the questionnaire was distributed.

Main Points

- The COVID-19 pandemic is a public health problem that has affected the whole world in a short time and caused the death of millions of people.
- COVID-19 has caused high anxiety and burnout in all healthcare professionals, especially nurses.
- As the anxiety level increased, psychological resilience decreased dramatically, and this became even more evident throughout the pandemic.
- Fear of contracting COVID-19 infection caused other segments of society to stay away from healthcare workers, which caused health professionals to experience psychosocial problems.
- The effect of anti-vaccine news on social media and mass media caused a high rate of hesitancy against COVID-19 vaccination among nurses. Despite this, about 80% of the nurses were vaccinated.

Study Protocol and Ethics Committee Approval

This study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the İnönü University Institutional Review Board for non-interventional studies (approval date: August 24, 2021; number: 2416). Strengthening the reporting of observational studies in epidemiology (STROBE) guideline was utilized to assess the likelihood of bias and overall quality for this study.[13]

Study Population and Sample Size Calculation

About 900 nurses actively working in the hospital during the abovementioned study period were determined as the population of this study. After entering the confidence level (CL=95%), confidence interval (CI=2.5), and patient population (n=900) data to https://www.surveysystem.com/sscalc.htm to calculate a sample size that can represent this population, the number of samples calculated was determined as 674. A total of 680 nurses were interviewed face-to-face, and 676 nurses who answered all questions were included in this study.

Variables and Scales Used in the Study

Demographic and Social Characteristics Form

The questionnaire used in this study consists of 28 questions and 2 scales. The questions querying the sociodemographic characteristics of the study can be briefly defined as follows: variables such as age, gender, height, weight, marital status, number of children, education level, smoking, presence of chronic disease (diabetes mellitus, hypertension, asthma, chronic obstructive pulmonary disease, cardiovascular disease), presence of psychological disease requiring medication (anxiety, stress, depression), the unit he/she works in the hospital (ward, intensive care, operating room, polyclinics), working status in COVID-19 clinics during the pandemic, catching COVID-19 disease, use of antiviral drugs, hospitalization due to COVID-19 (service, intensive care, intubation), COVID-19 vaccination status (Sinovac, Biontech, both, none), vaccine dose (1, 2, 3, 4 doses), presence of hesitation about the COVID-19 vaccine (hesitant, no-hesitant), belief in the protection of the COVID-19 vaccine, thoughts on making the COVID-19 vaccine legally mandatory, ways to get information about COVID-19 (newspapers, books, magazines, television, social media platforms), post-vaccine COVID-19 disease, and situations causing worry during the COVID-19 process.

Coronavirus Anxiety Scale-Short Form

Coronavirus Anxiety Scale, which aims to determine the anxiety caused by the COVID-19 pandemic in society and the severity of this anxiety, was first defined by Lee in 2020.[14] The validity and reliability test of the Turkish version of this scale was performed by Bicer et al[15] in 2020 (Cronbach's alpha=0.832). The Coronavirus Anxiety Scale consists of 5 questions, and each question is scored between 0 and 4. In the CAS scale consisting of 5-point Likert-type questions, the scores are not at all (0 points), rare, less than a day or 2 (1 point), several days (2 points), more than 7 days (3 points), and nearly every day over the last 2 weeks (4 points). In this scale, where the lowest 0 points and the highest 20 points can be obtained, a score of 9 and above is considered as present with coronavirus anxiety.

Brief Resilience Scale

Smith et al[16] developed the Brief Resilience Scale in 2008 to measure the resilience level of individuals. Doğan[17] performed the validity and reliability test of the Turkish version of this scale in 2015. Brief Resilience Scale, which is a 6-item measurement tool, consists of 5 Likert-type questions, and the answers are listed as strongly disagree (1 point), disagree (2 points), neutral (3 points), agree (4 points), and strongly agree (5 points). Items 2, 4, and 6 on the scale are scored in reverse. Higher scores on the scale indicate higher psychological resilience. Cronbach alpha reliability and internal consistency coefficient of BRS were calculated as 0.830.

Statistical Analysis

Licensed version 22.0 of the International Business Machines' Statistical Package for Social Sciences Statistics software program was used for statistical analysis (IBM Corp., Armonk, NY, USA). Shapiro–Wilk test of normality was used to show whether the quantitative variables had normal distribution. Since the continuous variables were observed not to have normal distribution, the results were given as median, and interquartile range (IQR) and 95% CI for the median. Qualitative variables were given as numbers and percentages. Pearson chi-square test was used to compare 2 independent

groups. Non-parametric Spearman's rho correlation analysis was used to show whether there was any correlation between quantitative variables. The *P*-value less than .05 was accepted as significant.

Results

The median age of the nurses participating in the study was 31 years (IQR: 12; 95% CI: 30-32). 70.7% (n=478) of the nurses are women, 57.2% (n=387) are married, and 87.4% (n=591) have a degree from undergraduate schools. Of the study group, 51.6% (n=349) stated that they worked in the ward, and 79.6% (n=538) stated that they did not have a chronic disease. Forty-two percent of the nurses stated that they worked in COVID-19 clinics (ward and intensive care) at least once during the pandemic (Table 1).

A total of 41.4% (n=280) of the nurses in the study group stated that they had COVID-19, 2.7% (n=19) of them stated that they were treated in the hospital 1.9% (n=13) in the ward, 0.7% (n=5) in intensive care, 0.1% (n=1) in the ward and intensive care. None of the infected individuals were intubated. A total of 80.9% (n=547) of the nurses stated that they had the COVID-19 vaccine, 31.5% (n=213) had the Sinovac vaccine, 19.5% (n=132) had the BioNTech vaccine, and 29.9% (n=202) had both. A total of 12.2% (n=67) of the nurses stated that they had 1 dose of vaccine, 41% (n=224) of them had 2 doses of vaccine, 43.1% (n=236) of them had 3 doses of vaccine, 3.7% (n=20) had 4 doses of vaccine. A total of 68.6% (n=464) of the nurses participating in the study stated that they were hesitant about the COVID-19 vaccine, 50.0% (n=338) thought that this vaccine was protective, and 27.5% (n=186) were undecided about the protectiveness of the vaccine. A total of 51.2% (n=346) of the participants stated that they had read scientific articles about COVID-19 and vaccination. When asked about their sources of information on COVID-19 and vaccination, 63.2% (n=427) of nurses stated that the source of information was newspapers, books, magazines, or articles, 62.9% (n=425) stated that they obtained information from social media, 56.8% (n=384) from health programs on television, and 37.9% (n=256) from their relatives or neighbors who had the disease. When nurses were asked about the most worrisome situation(s) during the COVID-19 period, the highest response rates were 82.2% (n=556) for the parents' catching COVID-19 and 47.5% (n=321) for the unknowns about COVID-19 being high (Table 2).

Table 1. Distribution of Sociodemographic and Other Variables of the Nurses Participating in the Study

Variables of the Participants	n	%
Age groups (year)		
20-29	278	42.9
30-39	246	38.0
≥ 40	124	19.1
Gender		
Female	478	70.7
Male	198	29.3
Marital status		
Married	387	57.2
Single	289	42.8
Educational status		
High school/Assoc graduate	42	6.2
Bachelor's degree	591	87.4
Master's/Doctorate	43	6.4
Working unit		
Service (wards)	349	51.6
Intensive care	248	36.7
Emergency unit	13	1.9
Operating room	29	4.3
Outpatient clinic	37	5.5
Did you have chronic disease?		
Yes	138	20.4
No	538	79.6
Did you work in COVID-19 units?		
Yes	284	42.0
No	392	58.0
Exposure to the COVID-19		
Yes	280	41.4
No	396	58.6
Brief Resilience Scale Score		
Median (IQR)	19 (6)	
95% CI for median	19-20	
Coronavirus Anxiety Scale Score		
Median (IQR)	1 (3)	
95% CI for median	1-1	

IQR, interquartile range.

68.6% (n=464) of the participants stated they were hesitant about the COVID-19 vaccine. A significantly higher rate of hesitancy was detected in the age group of 20-29 years and 30-39 years, those who did not have COVID-19 vaccine, and those who did not think the

Table 2. Distribution of COVID-19 Vaccine Hesitancy and Various Variables of Nurses Participating in the Study

Variables of the Participants	n	%
Vaccinated against COVID-19?		
Yes	547	80.9
No	129	19.1
Number of COVID-19 vaccines		
1 dose	67	12.2
2 dose	224	41.0
3 doses	236	43.1
4 doses	20	3.7
Hesitancy against COVID-19 vaccine		
Hesitant	464	68.6
No-Hesitant	212	31.4
Do you think the COVID-19 vaccine is protective?		
Yes	338	50.0
No	152	22.5
No idea	186	27.5
Have you read scientific articles about COVID-19 and vaccine?		
Yes	346	51.2
No	152	22.5
Which is your source of information about COVID-19 and vaccination?		
From newspapers, books, magazines, or articles	427	63.2
Social media (Whatsapp, Facebook, Instagram, etc.)	425	62.9
Health programs on television	384	56.8
Relatives or neighbors who have had the disease	256	37.9
Other		
Which of the following worries you the most, during COVID-19 era durum/ durumlar		
My parents' exposure to COVID-19	556	82.2
Uncertainties about COVID-19	321	47.5
Individual exposure to COVID-19	223	33.0
Working in the COVID-19 intensive care unit	109	16.1
Working in the COVID-19 service	96	14.2
Should the COVID-19 vaccine be made mandatory by law?		
Yes	219	32.4
No	324	47.9
No idea	133	19.7

Table 3. Comparison of the COVID-19 Vaccine Hesitancy Status of the Nurses Participating in the Study According to Various Variables

	COVID-19 Vaccine Hesitancy Status				
	Hesitant (n=464)		No-Hesitant (n=212)		
Variables of the Participants	n	%	n	%	*P*
Age groups (year)					
20-29	202	72.7	76	27.3	**.035**
30-39	169	68.7	77	31.3	
≥40	74	59.7	50	40.3	
Gender					
Female	334	69.9	144	30.1	.282
Male	130	65.7	68	34.3	
Educational status					
High school/Assoc graduate	29	69.0	13	31.0	.835
Bachelor's degree	408	69.0	183	31.0	
Master's/Doctorate	26	63.4	15	36.6	
Do you think the COVID-19 vaccine is protective?					
Yes	182	53.8	156	46.2	**<.001**
No	132	86.8	20	13.2	
No idea	150	80.6	36	19.4	
Have you had the COVID-19 vaccine?					
Yes	347	63.4	200	36.6	**<.001**
No	117	90.7	12	9.3	

COVID-19 vaccine is protective ($P < .05$). There was no significant difference between COVID-19 vaccine hesitancy according to gender and education level ($P > .05$) (Table 3)

It was determined that 6.8% (n=46) of the nurses had COVID-19 anxiety. There was no significant difference between the presence of COVID-19 anxiety and gender and the presence of chronic disease ($P > .05$). A significantly higher rate of anxiety was detected in the age group of 40 years and older, those working in the emergency department, and those working in the COVID-19 unit during the pandemic period ($P < .05$). No significant difference was found between the presence of COVID-19 anxiety according to the COVID-19 status ($P = .546$) (Table 4).

The median BRS score of nurses is 19 (IQR=6). A negative, weak, and significant relationship was found between the BRS and the CAS scores. The CAS score decreases as the BRS score increases (Table 5).

Discussion

Half of the nurses participating in our study stated that the COVID-19 vaccine is protective, 27.5% are undecided about the vaccine's protection, 80.9% have the COVID-19 vaccine, and 68.6% are hesitant about the COVID-19 vaccine. In a study conducted on healthcare professionals in France, it was shown that 23.1% (n=453) of the participants were hesitant about COVID-19 vaccines, and 3.9% (n=76) were anti-COVID-19 vaccines.[18] In a study conducted among 1723 healthcare professionals in Italy, it was stated that 67% (n=1155) of the participants were willing to be vaccinated against COVID-19, 26% (n=443) were undecided, and 7% (n=125) refused to be vaccinated.[19] In a study conducted with healthcare professionals in Egypt, it was shown that 41.9 % (n=129) of the participants were undecided, 32.1% (n=99) refused, and 26% (n=80) were willing to COVID-19 vaccines.[20] A study conducted with healthcare professionals in Canada showed that 31.5% (n=84) of those who were hesitant about COVID-19 vaccines thought that the vaccine was not protective.[21] A study conducted with nurses in China in 2020 showed that 76.4% (n=360) of the participants had doubts about the efficacy or safety of the vaccine.[22] Healthcare professionals, who are the first group to be vaccinated, can be important role models for society, as they are generally the priority group around the world. Attitudes and behaviors of healthcare professionals about vaccination may affect the vaccination decisions of hesitant individuals. For this reason, it will be important to address the hesitations of healthcare professionals about vaccines and underlying causes and concerns, to conduct studies in this direction, and to provide more information about the safety and effectiveness of vaccines.

About 51.2% of the nurses participating in our study stated that they read scientific articles about COVID-19 and vaccination, and 63.2% stated that the source of information about COVID-19 and vaccination is in newspapers, books, magazines, or articles. A study conducted with healthcare professionals in Italy has shown that nurses use websites, social media, television, newspaper, family, and friend suggestions more as a source of information about COVID-19, and the rate of using scientific literature is lower.[23] A study conducted with healthcare professionals in Egypt has shown that 85% (n=68) of the participants who were willing to be vaccinated against COVID-19 used the websites of WHO and the Center for Disease Control and Prevention (CDC) as a source of information about the vaccine.[20] Healthcare professionals should have sufficient and up-to-date scientific knowledge about pandemics and vaccines. Considering the increasing vaccine rejection and hesitation in society, the information resources of healthcare professionals stand out. Therefore, it is important for nurses, who are healthcare personnel, to obtain the correct information from the right source.

It was stated that the most worrying situation for nurses during the COVID-19 period was parents catching COVID-19 and high uncertainty about COVID-19. Despite the highest protection measures, healthcare professionals may be at high risk of catching COVID-19 during the pandemic. For this reason, the high mortality and morbidity rates, especially in older parents, may have created this concern.

The vaccine hesitancy among nurses in this study was higher (68.6%) than expected. In another study, vaccine hesitancy rate was found to be 25.9% (n=531)[24] among healthcare workers, while 2 different studies done on the general public showed hesitancy rates of 36% (n=540)[25] and 35.9% (n=1098).[26] As anticipated, the vaccine hesitancy rates were lower among nurses who believed COVID-19 to be beneficial and those that had already received a vaccination.

The health belief model is a behavioral change model developed to explain the decision-making processes about human health and resulting behavioral changes. In this model, perceived sensitivity contributes to promoting decision-making based on various perceived stimulus

Table 4. Comparison of the Coronavirus Anxiety Status of the Nurses Participating in the Study According to Various Variables

	COVID-19 Anxiety Status				
	Presence (n=46)		Absence (n=630)		
Variables	n	%	n	%	*P*
Age groups (year)					
20-29	13	4.7	265	95.3	**.051**
30-39	17	6.9	229	93.1	
≥40	14	11.3	110	88.7	
Gender					
Female	35	7.3	443	92.7	.407
Male	11	5.6	187	94.4	
Did you have chronic disease?					
Yes	11	8.0	127	92.0	.542
No	35	6.5	503	93.5	
Working Unit					
Service (wards)	24	6.9	325	93.1	**.013**
Intensive care	15	6.0	233	94.0	
Emergency unit	4	30.8	9	69.2	
Operating room	1	3.4	28	96.6	
Outpatient clinic	2	5.4	35	94.6	
Did you work in COVID-19 Units?					
Yes	14	14.6	82	85.4	**.001**
No	32	5.5	548	94.5	
Have you been exposed to COVID-19?					
Yes	21	7.5	259	92.5	.546
No	25	6.3	371	93.2	

Presence (score ≥ 9 point), Absence (score < 9).

such as benefits and barriers.[27] Jain et al[28] stated that the perceived susceptibility to COVID-19 and the perceived benefits of vaccination had a crucial role in reducing hesitancy for COVID-19 vaccination. They stated that these findings match the health belief model. Similarly, in this study, the thought that the COVID-19 vaccines are safe and beneficial could have contributed to lower hesitancy rates among the vaccinated nurses who believed that the vaccines were protective.

Table 5. Correlation of the CAS and BRS Scores of the Nurses Participating in the Study

Brief Resilience Scale	Coronavirus Anxiety Scale
r	**−0.315**
P	**<.001**
n	**657**

BRS, Brief Resilience Scale; CAS, Coronavirus Anxiety Scale.

In our study, it was determined that 6.8% of the participants had COVID-19 anxiety, and a significantly higher rate of anxiety was detected in those working in the COVID-19 unit, in the group over the age of 40, and in the emergency room during the pandemic period. In a study conducted in Italy, it was shown that stress ($P=.013$), exhaustion ($P=.037$), anxiety ($P=.014$), and depression ($P=.013$) were higher in healthcare professionals dealing with COVID-19 patients.[29] In a study conducted in Oman, it was shown that anxiety (odds ratio (OR) = 1.557, $P=.004$), stress (OR = 1.506, $P=.016$), and insomnia (OR = 1.586, $P=.013$) states of healthcare professionals working on the front lines in the COVID-19 pandemic were 1.5 times more common than those in the other group.[30] In a study conducted on healthcare professionals in China, depression and anxiety were found in 50.4% (n = 634) and 44.6% (n = 560) of the participants, respectively, and similar to our study, it was shown that professionals working in the COVID-19 unit experienced more severe depression and anxiety.[31]

It was determined that the level of psychological resilience decreased as the COVID-19 anxiety level of the study group increased. In a study conducted with healthcare professionals in Spain during the first wave of the pandemic, it was shown that nurses and assistant nurses experienced mental disorders at a higher rate, and a positive trend was found in those whose parents, children, or partners were infected by COVID-19.[32] As shown in other studies similar to our study, in the healthcare professionals working on the front lines of the pandemic, higher levels of anxiety and depression were observed in the vaccine group of older age, with the thought that the age group increases the risk, and it is thought that taking precautions and interventions accordingly may have a healing effect in terms of mental health and work efficiency of healthcare professionals.

Considering that new pandemics may occur with new infectious agents in the coming years, urgent measures should be taken against anxiety, depression, and exhaustion in healthcare personnel. It is thought that additional interventions such as increasing personnel employment, arranging working shifts, and psychosocial support should be made.

Limitations

As in all other survey-based studies, this study has some limitations. It is very difficult to make a comment on the generalization of the results to the universe since the entire universe cannot be reached. Among the reasons for this situation are the shift work system, intensive working conditions, and the official leave of those with chronic diseases.

Conclusion

To sum up, necessary precautions should be taken to prevent anxiety, depression, and other psychological conditions that may occur in nurses who are active healthcare personnel during the pandemic period, and the awareness of healthcare personnel on this issue should be increased.

Data Availability Statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Ethics Committee Approval: Ethical committee approval was received from the Inonu University institutional Review oard (IRB) for non-interventional studies (2021/2416)

Informed Consent: Verbal informed consent was obtained from all participants who participated in this study.

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Anaesthesiology

Anesthesiologists' Perspective on the Use of Artificial Intelligence in Ultrasound-Guided Regional Anaesthesia in Terms of Medical Ethics and Medical Education: A Survey Study

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ABSTRACT

Objective: Controversy exists around the world as experts disagree on what artificial intelligence will imply for humanity in the future. Medical experts are starting to share perspectives on artificial intelligence with ethical and legal concerns appearing to prevail. The purpose of this study was to determine how anesthesiology and reanimation specialists in Turkey perceive the use of artificial intelligence in ultrasound-guided regional anesthetic applications in terms of medical ethics and education, as well as their perspectives on potential ethical issues.

Materials and Methods: This descriptive and cross-sectional survey was conducted across Turkey between July 1 and August 31. Data were collected through an online questionnaire distributed by national associations and social media platforms. The questionnaire included questions about the descriptive features of the participants and the possible ethical problems that may be encountered in the use of artificial intelligence in regional anesthesia and 20 statements that were requested to be evaluated.

Results: The average age of the 285 anesthesiologists who took part in the study was 42.00 ± 7.51, 144 of them were male, the average years spent in the field was 10.95 ± 7.15 years, 59.3% were involved in resident training, and 74.7% habitually used ultrasound guidance regional anesthetic applications. Of the participants, 80% thought artificial intelligence would benefit patients, 86.7% thought it would benefit resident training, 81.4% thought it would benefit post-graduate medical education, and 80.7% thought it would decrease complications in practice. There will be no ethical issues if sonographic data are captured anonymously, according to 78.25%, while 67% are concerned about who will be held accountable for inaccuracies.

Conclusion: The majority of anesthetists believe that using artificial intelligence in regional anesthetic applications will decrease complications. Although ethical concerns about privacy and data governance are low, participants do have ethical worries about "accountability for errors."

Keywords: Medical education, medical ethics, anesthesiology, ultrasonography

Introduction

Artificial intelligence (AI) or machine learning systems are computer systems that mimic human cognitive functions to execute tasks such as learning, problem-solving, and discrimination autonomously.[1] In recent years, AI has found its place in nearly all fields where technology is utilized, facilitating and alleviating challenges in human existence.[2] The most important advantages of AI technology are its ability to recognize structures and objects with high sensitivity and specificity, to provide fast reports attributed to programmed algorithms, and to achieve high consistency in results.[2] Initially, AI was employed for goals such as facilitating diagnosis from radiological images. Furthermore, it is currently employed in nearly all sub-branches of medicine, including diagnosis, treatment, drug development technology, and even improving the doctor–patient interaction.[3-7] Artificial intelligence is also being utilized to improve medical education.[8]

Artificial intelligence has been used in anesthesia for the estimation of adverse effects and mortality and the estimation of postoperative critical care requirements.[9-11] The use of AI in ultrasound-guided (USG) regional anesthesia (RA) has been addressed in a variety of ways, including increasing the safety of RA, decreasing the complication rate, as well as being used in education,

particularly as an innovation to assist in the identification of sono-anatomy for USG RA where it has been reported to be highly popular and motivating.[12-17]

In RA practice, AI is utilized in USG-guided RA applications. Artificial intelligence can identify all vital sono-anatomical structures, display the target, and help the practitioner to advance the needle tip to the correct target.[13,16] Every innovation is accompanied by unprecedented challenges. It appears that AI, as is the case in RA education, will break new ground in the world of education, with innovation as well as new concerns. Although there is growing consensus about the benefits and advantages of AI, ethical and legal concerns still remain. Prospective practitioners are at best to anticipate these benefits and potential problems.

The purpose of this survey is to ascertain the opinions of Turkish anesthesiology and reanimation specialists on the ethical implications of the use of AI in USG RA.

Materials and Methods

The study was approved by the local ethics committee. Surveys were sent to anesthesiology and reanimation specialists working in Turkey, between July 1 and August 31, 2022.

The study's questionnaire was originally written and applied in Turkish. A translation into English made by our English-native co-author (DTT) is included as a supplement (Table 1). All participants consented to participation, processing of data processing, and inclusion of their data in medical research, at the beginning of the survey. Those who did not consent were unable to access the questionnaire. There were a total of 5 descriptive items: age, gender, years of experience in the profession, participation in resident training, and routine use of USG in RA applications in the operating room.

All participants were given information about AI and its use in RA practice. Participants were asked to answer a total of 7 main questions with a total of 20 statements, all with regards to the use of AI in RA:

Table 1. Question Roots and Statements of Survey

	Agree	Neutral	Disagree
Q1. Use of artificial intelligence in regional anesthesia applications will benefit the patient.			
Q2. It will provide equal opportunity among residents studying in different institutions.			
Q3. The use of artificial intelligence in resident training in regional anesthesia applications;			
S1. It will be useful for residents			
S2. It will be useful for educators			
S3. It will positively affect trainer–trainee relationship			
S4. It may reduce the complications that could occur during the learning period			
Q4. When the introduction of artificial intelligence into regional anesthesia practice is evaluated in terms of continuing medical education after graduation;			
S1. It will be beneficial for the professional development of anesthesia and reanimation specialists.			
S2. It will be beneficial in terms of equal opportunity in education.			
S3. It may reduce the complications that could occur in regional anesthesia applications.			
Q5. In case of "a complication due to misidentification and orientation of the program" in artificial intelligence-supported applications in resident training;			
S1. The responsibility should be solely on the trainer.			
S2. Responsibility should not be only on the trainer, artificial intelligence can also be held responsible.			
S3. Responsibility should lie with the manufacturers or programmers of artificial intelligence.			
S4. Complications during training will create a problem about who will be responsible.			
Q6. In the case of "a complication due to misidentification and guidance of the program" in artificial intelligence-supported applications performed by anesthesiologists;			
S1. The responsibility should be solely on the trainer.			
S2. Responsibility should not be only on the trainer, artificial intelligence can also be held responsible.			
S3. Responsibility should lie with the manufacturers or programmers of artificial intelligence.			
S4. Complications during training will create a problem about who will be responsible.			
Q7. Artificial intelligence programs are currently guiding regional anesthesia by recognizing tissues through sono-anatomical images obtained with "ethics committee approval" and "patient consent." However, it is not plausible to obtain such approval/consent continuously as data from sequential applications lead to more data with increased sensitivity. Storage of sonographic images in the memory of artificial intelligence programs that processes these images in order to guide the practitioner better;			
S1. It is against privacy principles.			
S2. Since patients are recorded anonymously, it cannot be considered as a violation of privacy.			
S3. Patients should be able to withdraw their consent at any time.			
8. If you believe there are other ethical problems related to the use of artificial intelligence in regional anesthesia, please share your thoughts with us.			

Main Points

- The majority of anesthetists believe that using artificial intelligence (AI) in regional anesthetic applications will decrease complications.
- This survey found that the majority of anesthetists in Turkey believe that the use of AI in regional anesthetic applications will be advantageous for both resident training and post-graduate medical training.
- Using AI in regional anesthesia applications under ultrasound supervision would benefit the patient, resident training, and postgraduate continuing medical education, as well as lessen problems in both training stages.

Medical Ethics – Beneficence

In the first question (Q1), participants were asked to evaluate beneficence for patients in light of medical ethics principles.

Medical Ethics – Maleficence

In Q3/S4 and Q4/S3, participants were asked to evaluate the AI use in light of the medical ethics concept of "Maleficence."

Medical Education and Ethics – Beneficence

In Q3/S1-3 (resident training) and Q4-S1 (continuing medical education after graduation),

participants were asked to evaluate the use of AI in terms of the "beneficence" principle of medical ethics and education.

Medical Education – Equal Opportunity

In Q2 (resident training) and Q4/S2 (continuing medical education after graduation), participants were asked to evaluate the use of AI in terms of equal opportunity in education.

Ethical Concerns – Accountability for Errors

In Q5/S1-4 and Q6/S1-4, participants were asked to evaluate the use of AI in terms of "accountability for errors" in residency training and postgraduate continuing medical education, respectively.

Ethical Concerns – Data Governance and Privacy

In Q7/S1-4, participants were asked to evaluate AI in terms of "data governance and privacy."

On a 3-point Likert scale, participants evaluated a total of 20 judgments. In addition, participants were given the chance to share any ethical issues that were not addressed in the questionnaire in a final open-ended question. Table 1 provides an example of the questionnaire's English translation.

The questionnaire, which was produced as a Google Form, was distributed on social media such as WhatsApp, Twitter, and Facebook to anesthesiologist groups and also via individual e-mails. Considering the size of the population (approximately 6500 specialists), a minimum sample size of 262 participants was calculated using a 90% confidence level and a 5% margin of error. Due to the possibility of data loss, a minimum of 300 participants were intended.

Statistical Analysis

Statistical Package for the Social Sciences 16 was used for data analysis (SPSS Inc., Chicago, IL, USA). Descriptive data were given as mean and standard deviation, and survey responses were given as frequency and percentage. *T*-test was used in the analysis of descriptive data. Categorical data were presented as counts and percentages and compared using Chi-square test or Fisher's exact test as appropriate, with post-hoc Bonferroni adjustments to determine where the difference between groups originated. Statistical significance was accepted as $P < .05$.

Results

A total of 305 participants completed our survey within the specified date range. Although the introduction section of our survey clearly stated that only specialists were invited to participate, we determined that 20 participants were residents continuing their training and thus they were excluded from the study. The female/male ratio of the participants in our study was 141/144. The mean age of participants was 42 ± 7.51 years. The mean length since completing training was 10.95 ± 7.15 years (range 0-30 years).

Of the participants, 59.3% took an active role in resident training, and 74.7% stated that they routinely used USG in RA practices. Descriptive data are presented in Table 2.

Of the participants, 80% agreed (Q1) that the use of AI in RA would be beneficial for the patient. The percentage of participants that stated AI would be beneficial in resident and postgraduate education (Q3-S1, Q3-S2) was 86.7% and 81.4%, respectively. Of the participants, 65.26% and 69.47% stated that the use of AI would lead to equal opportunity in education for both residents and in postgraduate education programs, respectively. Participants agreed that AI would lead to a decrease in complications for residents in training (Q3-S4, 81%) and for specialists too (Q4-S3, 80.7%).

There was no consensus over who would be accountable for a potential complication in AI-assisted practices. Of the respondents, 51% agreed that both the trainer/practitioner and AI should be held accountable for issues arising from the training of residents and the practice of specialist physicians. In all instances, nearly 67% of respondents agreed that the question of who will be accountable for complications if they occur would be problematic.

Only 9.47% of participants believed that it would be an invasion of privacy for AI to save the sonographic data of patients in their memory, while 78.25% thought that it would not be an issue to record this data anonymously. Of the participants, 67.7% stated that patients should be able to revoke their agreement for the use of their data at any time.

Participants were also asked for their additional opinions if any. We observed that reinforcing statements about the judgments presented in the survey statements were generally repeated. Participant feedback stating that sonographic data are not recorded in current AI applications was received. This was not in contraction to the root of our question. Figure 1 depicts the percentage of responses to all questions and statements.

Table 2. Demographic Characteristics of Participants

Variable	Result
Age (years)	42 ± 7.51
Sex (n, %)	
Female	141 (49.5%)
Male	144 (50.5%)
Active role as trainer? (n, %)	
Yes	169 (59.3%)
No	116 (40.7%)
Duration of experience as an anesthesiology specialist	
<10 years	113 (39.6%)
>10 years	172 (60.4%)
Using ultrasound in regional anesthesia: (n, %)	
Yes	213 (74.7%)
No	72 (25.3%)

When responses to survey questions were analyzed according to descriptive characteristics of participants such as age, gender, time spent in the profession, routine USG use, and active participation in assistant training, statistical significance was determined in only 3 judgments ($P > .05$). While 68.8% of those who actively participated in the training of residents agreed that the use of AI in RA would improve the relationship between the trainer and trainee, only 52.6% of those who did not participate in resident training agreed with this statement ($P = .02$). In Q6-S1, the statement that the responsibility will be solely on the practitioner in case of a complication during the use of AI was presented to the participants. Of the participants, 26.8% who routinely use USG in RA applications agreed with this statement, while 11.1% of the participants who do not use USG agreed. This difference was found to be statistically significant ($P = .02$) (Table 3).

Discussion

Our study found that the majority of participants believed that using AI in RA applications under ultrasound supervision would benefit the patient, resident training, and postgraduate continuing medical education, as well as lessen problems in both training stages. Furthermore, it was established that responsibility sharing would be a concern in the event of difficulties or complications that may emerge in AI-assisted RA applications during resident training and thereafter (about 70%). There was consensus that it was not against privacy to record data anonymously and to keep it in memory (75%). In addition, it was determined that the rate of agreement in the idea that AI programs keep

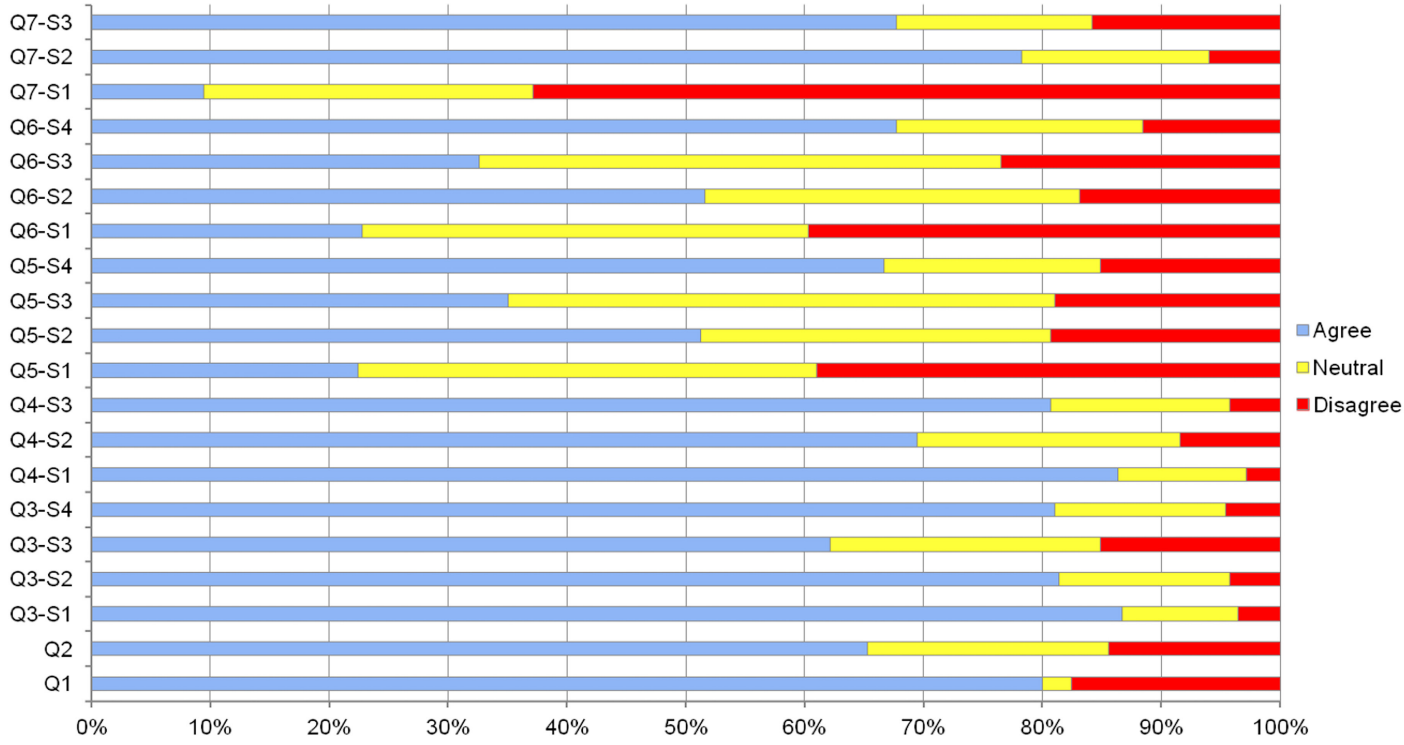

Figure 1. Distribution (percentage) of the answers given by the participants per question.

patient data in their memory is contrary to privacy is quite low (10%).

The use of AI in medicine has increased in popularity, particularly in the previous decade.[2] The USG applications in RA have grown in popularity in recent years. We asked participants in our study to rate the utility of AI help in RA training during resident training and postgraduate continuing education. In the near future, it appears that the use of AI in medical education will lead to a number of improvements similar to those in all areas of medicine. However, as the data fog grows with advances in technology, it becomes increasingly important to update and improve educational standards.[18] The long journey ahead requires the collaboration of medical science and data scientists. An evaluation paper on the application of AI in medicine predicts that it will have significant benefits in both decision-making in patient diagnosis and treatment, as well as in medical education.[19] Participants in our study believed that AI guidance in RA applications would be beneficial both in resident training and in continuing medical education after graduation. If we think of AI as a product in RA practice, we can see that the product's target audience is willing to use it and believes in its educational benefits.

Despite being used interchangeably in the literature, AI and machine learning are not synonymous.[20] Artificial intelligence uses machine learning algorithms such as reinforcement learning algorithms and deep learning neural networks are used. Machine learning, on the other hand, allows a computer system to generate predictions or make decisions based on past data without being explicitly programmed. Machine learning is based on an algorithm that learns on its own through the use of previous data. Artificial intelligence is a technology that allows machines to mimic human behavior. The goal of AI is to create a clever computer system that can solve complicated issues like humans. The purpose of machine learning is to enable machines to learn from data in order to provide correct output. Although we used the term AI in our work, the system currently being used in research is machine learning or deep machine learning systems.

Table 3. Assessment of Descriptive Items Regarding Questions/Statements

		Agree	Neutral	Disagree	
Question No		n (%)	n (%)	n (%)	*P*
Active role in residency education					
Q3-S3	Yes	116 (68.6%)*	33 (19.5%)	20 (11.8%)	.021
	No	61 (52.6%)	32 (27.6%)	23 (19.8%)	
Using US in regional anesthesia					
Q6-S1	Yes	57 (26.8%)	75 (35.2%)	81 (38%)	.023
	No	8 (11.1%)*	32 (44.4%)	32 (44.4%)	

No, number; Q, question; S, section; US, ultrasound.
Values are presented as number (%).
*Indicates the group leading to statistically significant difference.

To create a categorized summary, we found that a majority of anesthetists in Turkey (>80%) believe that employing AI in RA applications will benefit the patient, which is one of the core principles (*Beneficence*) of medical ethics.[21] We also addressed another major principle, nonmaleficence, in an indirect manner. More than 80% of our participants thought that AI assistance would help to lessen problems in RA training and practice. We believe that AI can help practitioners not only take action for the benefit of the patient but also avert potential harm.

When we evaluate the results of our survey in terms of medical education, we discovered that

the majority of participants (>80%) believed that incorporating AI into RA training will benefit trainers/trainees and practitioners. Again, we discovered that the vast majority (about 70%) believed AI will contribute to equal opportunity in medical education. What about equitableness? It should not be forgotten that medical education also has ethics and that the ethics of medical education cannot be treated separately from medical ethics.[22,23] It is necessary to conduct research to determine AI's role in RA teaching and its possible benefits. If it does indeed promote equal opportunity, its dissemination can help to resolve the dilemma of injustice in medical education, or alternatively it may pose further questions.[24,25]

According to an article, the primary ethical challenges that arise from using AI in surgery include human agency, accountability for errors, technical robustness, privacy and data governance, openness, diversity, non-discrimination, and justice.[26] In our study, we assessed anesthetists' perspectives on the accountability for errors item in question root 5 (applications in resident training) and question root 6 (applications performed by experts). In question root 7, we addressed privacy and data governance. Other ethical considerations can be addressed in future research with larger Delphi investigations.

Approximately two-thirds of the participants believed that the issue of "accountability for errors" in the employment of AI in RA training for residents would constitute an ethical concern. Half of the participants definitely believed that both AI and the trainer should be held accountable. It was found that the employment of AI in RA, like in other fields of medicine, will raise an ethical quandary in terms of "accountability for errors."[27] Although there have yet to be any legal ramifications (since there are no laws in this area), in the near future, if the systems utilized are updated from machine learning to sophisticated AI, the subject of who will be held accountable may spark heated debate.

Privacy and data governance are 2 other potential ethical issues. Systems developed for RA guidance, as is well known, are systems with recognition models that mark adjacent anatomical tissues and target tissue using a machine learning (or deep machine learning)-based processor that processes historical data (obtained in accordance with ethical guidelines) using certain algorithms. These programs are not involved in decision-making. They do not constantly collect data to better themselves as human intelligence does. However, as previously stated, AI is much more than machine learning. It solves problems by making decisions on its own and drawing new conclusions by analyzing the facts presented to it over time. When the process reaches this point, privacy and data governance may become of more ethical importance.

However, when we look at current practices, we observe that sonographic data from patients are neither regularly used in repetition nor stored in machine learning. However, the procedure will significantly differ from the continuous learning and guiding features of AI. Although there is currently no example, AI will analyze fresh data in each application, compare it to its previous "experiences," and achieve goals beyond what was envisaged. We asked participants in the seventh question of our questionnaire to evaluate – ethically, a circumstance that has not yet been experienced but that we may have to confront in the near future: storage of sonographic images in the memory of the AI. From an ethical standpoint, a relatively tiny number of the participants (10%) believed this would be an "infringement of privacy." Approximately 80% felt that recording sonographic data anonymously would not pose an ethical issue. When we conducted a literature review, we discovered studies that imply the advantages of AI's access to very large databases, as well as those that pose ethical concerns.[26,28,29] We believe that there is currently no cause for concern regarding AI in RA.

Is there a lack of standardization and norms for the use of AI in medicine, and what ethical problems must be addressed? As a future insight, we can argue that each branch of medicine will need to put forward their own worries regarding the use of AI in their field.[26] In the near future, professional associations, physicians, ethicists, law-makers, AI developers, and patient rights advocates will need to address problems and find consensus solutions regarding the medicolegal and ethical elements of AI.[30] Product developers should be more explicit about how data security is supplied in AI, and practitioners' concerns should be addressed. Of course, potential users' ethical concerns should also be resolved ahead of time by completing studies like ours. Given that AI is progressing from analyzing radiological imaging such as x-rays, mammography, and tomography to assessing and recognizing races, we must realize that these systems must be addressed from several perspectives (including hazards such as discrimination) and that we are only at the tip of the iceberg.[31]

Our study has some limitations. First, although we calculated the sample size, the study might have been strengthened by expanding the number of participants using a nationwide random sampling that takes into account variables such as age, gender, employer, and length of employment. We built the ethical concerns section of our study on the 3 primary ethical concerns that we anticipated. We could have, however, through a Delphi study, determined the major titles and their quantities in advance and thus conducted a more thorough examination.

This survey found that the majority of anesthetists in Turkey believe that the use of AI in RA applications will be advantageous for both resident training and post-graduate medical training and will reduce complications. We also determined that privacy and data governance pose few ethical concerns. The majority of respondents said that these activities would raise ethical problems around "error accountability."

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Samsun University (Approval No: 2022-3-9).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.T., Y.K.T.; Design – Y.K.T., G.Ç.N.; Supervision – M.D., S.T.; Materials – Y.K.T., H.C.K.; Data Collection and/or Processing – S.T., Y.K.T.; Analysis and/or Interpretation – S.T., Y.K.T., S.G.K.; Literature Review – S.T., D.T.T.; Writing – S.T., D.T.T.; Critical Review – S.T., H.C.K., Y.K.T.

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Randomized Assessor Blind Clinical Study

Mid-term Effect of Lumbar Sustained Natural Apophyseal Glides in Patients with Non-specific Chronic Low Back Pain: A Randomized Clinical Trial

Şule Şimşek[1], Nesrin Yağcı[2], Merve Bergin Korkmaz[3]

ABSTRACT

Objective: The objective of this study was to compare the standalone and combined mid-term effects of conventional physiotherapy and lumbar sustained natural apophyseal glides on pain, range of motion, fear avoidance belief, and functional status in patients with non-specific chronic low back pain.

Materials and Methods: This randomized clinical study was conducted in a state hospital. Fifty-five patients with non-specific chronic low back pain (mean age: 40.69 ± 6.27 years) were divided into 3 groups. Group I (n=18) received conventional physiotherapy (electrotherapy and heat application) 5 days a week for 3 weeks, group II (n=19) received lumbar sustained natural apophyseal glides 3 days a week for 3 weeks. Group III (n=18) received conventional physiotherapy plus lumbar sustained natural apophyseal glides. Pain (visual analog scale), flexion range of motion (back range of motion II), functional status (Roland–Morris Disability Questionnaire), and fear avoidance belief (Fear Avoidance Belief Questionnaire) were assessed at baseline, third week, and 6-month follow-up.

Results: After 3 weeks of intervention, all outcome measures improved in groups II and III. These improvements remained significant until 6-month follow-up ($P < .05$), except fear avoidance belief ($P=.06$) and flexion range of motion ($P=.764$) scores of group III. Flexion range of motion ($P=.001$), functional status ($P=.001$), and fear avoidance belief ($P=.03$) differed significantly between the 3 groups at 6-month follow-up; post-hoc analysis revealed that flexion range of motion ($P < .0001$), functional status ($P=.037$), and fear avoidance belief ($P=.002$) scores were significantly improved in group II compared to group I.

Conclusion: Compared with conventional physiotherapy, lumbar sustained natural apophyseal glides improved mid-term range of motion, functional status, and fear avoidance belief, but there was no difference in pain. Conventional physiotherapy added to lumbar sustained natural apophyseal glides provided no additional benefit.

Keywords: Functional status, kinesiophobia, low back pain, range of motion

This study has previously been presented in '7. Ulusal Fizyoterapi ve Rehabilitasyon Kongresi' at 18-20 April 2019, Ankara.

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Introduction

The point prevalence of low back pain (LBP) is 7.5% in 2017 according to the 2020 Global Burden of Disease data.[1] Low back pain is the leading cause of activity limitation and absenteeism from work[2] and results in a huge medical burden and economic cost.[3] The pain that lasts longer than 7-12 weeks or which recurs intermittently for a long time and the pathoanatomical cause of which cannot be determined is referred as non-specific chronic low back pain (NSCLBP).[4] Non-specific chronic low back pain represents 90%-95% of LBP cases.[5] Common symptoms of NSCLBP is pain, decreased range of motion (ROM), functionality, and quality of life.[4]

The main goals of rehabilitation for NSCLBP patients are to control pain, restore function, assure no future functional deficits occur, and preserve employment and productivity.[6] Conservative management approaches are preferred as a first treatment choice, but the most effective intervention is not clear, and most treatments have little or no effect.[7] Manual therapy techniques offer moderate- or high-level evidence in the treatment of NSCLBP.[8] Mulligan concept is essentially an articular technique with neuromuscular consequences. Sustained natural apophyseal glides (SNAGs) is the spine-specific technique of the Mulligan concept.[9] It is suggested that SNAGs can

decrease pain and improve ROM and disability (with moderate evidence) in patients with LBP.[10]

Fear of movement may have a central role in the development of LBP problems and is a strong predictor of self-reported disability in chronic LBP.[11] Although many studies showed that lumbar SNAGs could provide pain-free ROM, only 1 study has examined fear avoidance belief and reported that a single-session SNAG intervention does not provide any short-term improvement.[12] The studies in the literature generally focused on the immediate-[13-15] and short-term[12] benefits of lumbar SNAGs. Evidence on the mid-term effect of SNAGs is insufficient. Therefore, this study aimed to compare the standalone and combined mid-term effects of conventional physiotherapy (CP) and lumbar SNAGs on pain, ROM, fear avoidance belief, and functional status in patients with NSCLBP.

Materials and Methods

This randomized, assessor-blind clinical study was conducted in the Denizli State Hospital Outpatient Physical Therapy and Rehabilitation Clinic in Turkey. The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Pamukkale University Clinical Research and Ethics Committee (Date: November 15, 2016 No: 20). Informed consent was obtained from patients who participated in current study.

The study inclusion criteria were as follows: female gender, being diagnosed with NSCLBP, age between 20 and 50 years, pain duration >3 months, and pain intensity assessed using the visual analog scale (VAS) ranges from 3 to 6. The study exclusion criteria were as follows: low back-related conditions (e.g., spondylolisthesis and spinal stenosis), red flags indicating serious spinal pathology, neurological conditions (e.g., nerve root compromise, neurological signs, disc herniation, and radicular symptoms), rheumatologic or immunologic conditions, psychiatric disorder, cancer, had previous surgery related to the back, pregnancy, other current treatment, and participant's prior experience with a given treatment.

One hundred fifty patients were assessed for eligibility. Twenty-eight participants were excluded from the study because they did not meet the inclusion criteria (n=20) and did not want to participate in the study (n=8). Finally, 60 patients were randomly divided into 3 groups (20 patients in each group) using the closed envelope method (Figure 1).

Group I

Patients assigned to group I received CP for 5 days a week for 3 weeks. Conventional physiotherapy consists of hot pack (20 minutes), therapeutic ultrasound (frequency 1 MHz, intensity 1.5 w/cm^2, and duration 5 minutes), and transcutaneous electrical nerve stimulation (frequency 50 Hz with <150 microseconds pulse duration and current set in accordance with participant's sensations for 20 minutes).

Group II

Patients assigned to group II received lumbar SNAGs 3 times per week for 3 weeks. Lumbar SNAGs were performed by a physiotherapist who is trained in Brian Mulligan's concepts of Mobilization With Movement (certificated by the Mulligan Concept Teachers Association). The physiotherapist has more than 20 years of clinical experience in the treatment of musculoskeletal conditions. Before applying SNAGs, the patients were evaluated to determine the painful or restricted lumbar segment. The Mulligan concepts lumbar extension SNAGs in prone, SNAGs in lion position, and lumbar flexion SNAGs in sitting techniques were performed. The techniques were applied in 3 sets of 10 repetitions with a 60-second rest.

Lumbar Extension SNAGs in Prone: The participants were positioned in prone, and hands were placed close to the ribs at shoulder level. The therapist grasped the patient across the chest and was asked to perform extension. The therapist glided the predetermined painful or restricted facet joint cranially toward the eyeball. After holding this position for 10 seconds, the patient is asked to return to the initial position while the therapist maintained gliding.[16]

Main Points

- Activity pain, lumbar flexion range of motion, functional status, and fear avoidance belief were improved with lumbar sustained natural apophyseal glides (SNAGs) in patients with non-specific chronic low back pain (NSCLBP), and these achievements have been maintained at mid-term. However, conventional physiotherapy (CP) improved the functional status and fear avoidance belief only at short term, but these achievements were not maintained at mid-term.
- This made us think that lumbar SNAGs should be preferred instead of CP in patients with NSCLBP.
- The clinical advantages of the lumbar SNAGs are that it can be applied in a short time, it is an active pain-controlled treatment method, and improvements can be achieved immediately after the treatment session.
- The results of this study provided new insights into the effectiveness of manual therapy in patients with NSCLBP.

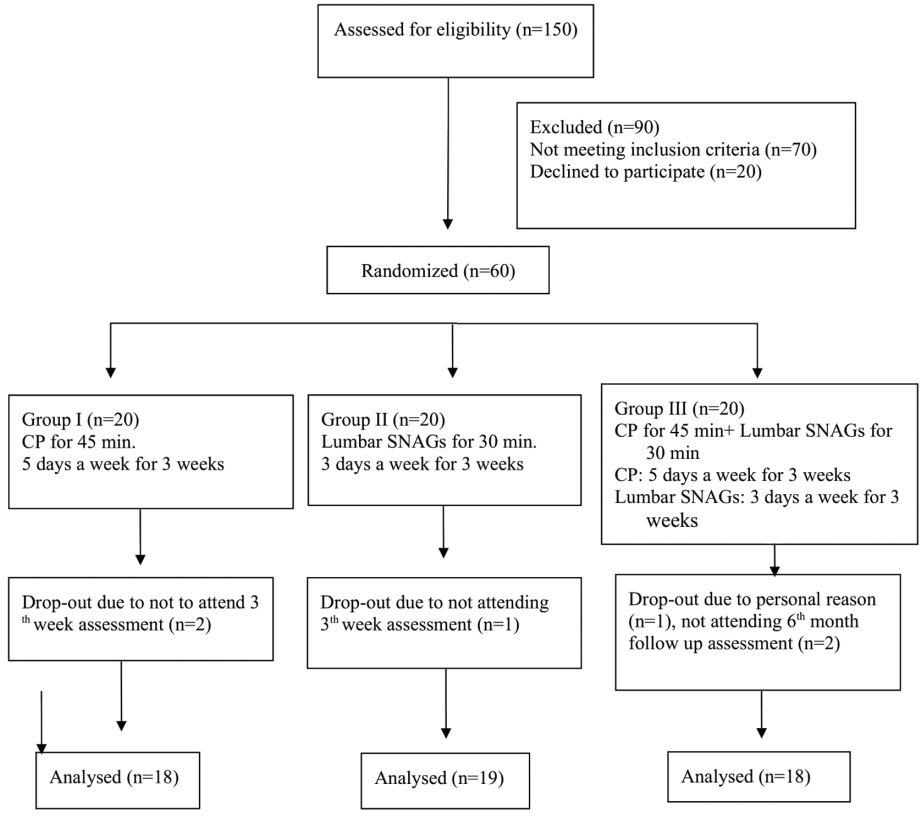

Figure 1. Flowchart of the study sample.

SNAGs in Lion Position: In the quadruped position, while patients were instructed to sit between the heels without changing the hand position, the therapist glided the predetermined painful or restricted segment in the lumbar spine. This position is held for 10 seconds and then the participant is asked to return to starting position while the therapist maintained mobilization. Holding for 10 seconds, the participant is asked to return to the initial position, while the therapist maintained the mobilization.[16]

Lumbar Flexion SNAGs in Sitting: The participant was asked to sit on the edge of the table, and stool was placed under the feet. The mobilization belt was secured around the patient's pelvis and around the therapist's gluteal folds. The therapist glided the predetermined painful or restricted facet joint by pushing it toward the eyeball. The patient was asked to perform the flexion movement and hold for a few seconds and return to the initial position while the therapist maintained gliding.[16]

Group III

Patients assigned to group III received CP for 5 days a week plus lumbar SNAGs for 3 days a week (first, third, and fifth days of every week) for 3 weeks.

The demographic data (age and body mass index) of the participants were recorded. Pain intensity, ROM, functional status, and fear avoidance belief were assessed. Outcomes were measured at baseline, at the third week (after the intervention), and at 6-month follow-up.

Visual analog scale was used to assess lumbar pain intensity during trunk flexion. Back Range of Motion II (BROM II) was used to assess lumbar flexion ROM. The device was fixed with Velcro at the symphysis pubis level of the patients, and the value on the unit was recorded. The participant was asked to touch the floor with his fingertip, and the value on the unit was recorded again. The difference between the 2 recordings constituted the flexion ROM.

The Roland–Morris Disability Questionnaire (RMDQ) was used to assess physical function. It consists of 24 items regarding activities of daily living that may be affected by back pain. Total score ranges from 0 to 24 points, with a higher score representing extremely severe disability.[17]

Fear Avoidance Belief Questionnaire (FABQ) was used to assess fear avoidance belief. Fear Avoidance Belief Questionnaire is a commonly used condition-specific health status measure for the assessment of fear of movement related to LBP. The score ranges from 0 to 96 points, with a higher score indicating great fear avoidance belief.[18,19]

Statistical Analysis

The sample size was estimated based on the primary endpoints, which were defined as the immediate effect of the intervention on the VAS and RMDQ scores. The overall effect size of the reference study was large with an index for RMDQ ($d=2.34$).[13] Therefore, we included a 3-group comparison with a large effect size ($f=0.44$). A 3-group comparison with a large size ($f=0.44$) was included in the study. Accordingly, when at least 54 people (at least 18 for each group) were included in the study that would result in 80% power with a 95% CI.

Obtained data were analyzed using Statistical Package of Social Sciences Statistics (Version 21; IBM, Armonk, NY, USA). Continuous variables were presented as mean ± SD, and maximum, minimum, and categorical variable values were presented as absolute frequency and percentages. The conformity of continuous variables with normal distribution was evaluated using the Shapiro–Wilk test. Paired samples *t*-test for parametric test assumptions and Wilcoxon signed-rank test (baseline to 3-week change in RMDQ scores of group II was not distributed normally) for non-parametric test assumptions were used for pairwise comparisons of within-group change scores. One-way ANOVA (post-hoc Tukey test) (baseline values of VAS and ROM, at third week value of FABQ and ROM, at 6-month value of RMDQ and ROM, baseline to 3-week change scores of VAS, and baseline to 6-month value of RMDQ were distributed normally) for parametric test assumptions and independent samples Kruskal–Wallis test (post-hoc Mann–Whitney *U* test with Bonferroni correction) for non-parametric test assumptions were used for intergroup difference among groups. Statistical significance was set at $P < .05$.

Results

A total of 60 patients were enrolled in this study. Two patients from group I, 1 patient from group II, and 2 patients from group III were excluded because of their unwillingness to come to the follow-up assessment, and so the final study sample consisted of 55 patients (Figure 1). Group I and group III consisted of 18 patients and group II consisted of 19 patients. The descriptive data of the participants are shown in Table 1.

Activity Pain

After 3 weeks of intervention, activity pain significantly decreased in group II ($P \leq .0001$) and group III ($P \leq .0001$), demonstrating 3.6 and 3.2 point improvements, respectively. However, the within-group scores were not significantly different in group I ($P=.206$). The between-group assessment demonstrated no significant differences at baseline ($P=.267$) but a significant difference at the third week ($P < .0001$). Mean change scores of activity pain differed significantly between the 3 groups at the third week ($P < .0001$); post-hoc analysis revealed that activity pain in group II ($P < .0001$) and group III ($P=.001$) was significantly improved compared to group I. Decreases in activity pain from baseline remained significant in group II ($P=.006$) and group III ($P=.003$) for 6 months. The within-group score of activity pain was statistically significant in group I at 6 months ($P=.022$). The between-group scores ($P=.119$) and mean change scores ($P=.077$) demonstrated no significant differences at 6-month follow-up (Table 2).

Flexion Range of Motion

After 3 weeks of intervention, flexion ROM significantly increased in both group II and group III ($P < .05$), with an average of 6.6 and 2.9 cm, respectively. However, the within-group scores were not significantly different in group I ($P=.597$). The between-group assessment demonstrated no significant differences at baseline ($P=.162$) and at 6 months ($P=.710$) but a

Table 1. Comparison of the Demographic Variables of Intervention Groups

	Group I	Group II	Group III	
Variables	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	*P*
Age (years)	39.44 ± 5.08 (40.5)	42 ± 7.51 (42)	40.56 ± 5.97 (42)	.171
BMI (kg/cm^2)	26.54 ± 4.29 (25.3)	25.68 ± 4.79 (25.3)	26.64 ± 3.57 (25.8)	.753
Employment status	**n (%)**	**n (%)**	**n (%)**	
White-collar jobs	7 (38.9)	13 (68.4)	8 (44.4)	
Blue-collar jobs	11 (61.1)	6 (31.6)	10 (55.6)	

BMI, body mass index.

Table 2. All Outcome Measures from Baseline to 6-Month Follow-Up

Variables	Group I Mean ± SD (95% CI)	$P_{intragroup}$	Group II Mean ± SD (95% CI)	$P_{intragroup}$	Group III Mean ± SD (95% CI)	$P_{intragroup}$	$P_{intergroup}$
VAS—Flexion							
Baseline	5.9 ± 1.6 (5.1-6.7)		5.4 ± 2.3 (4.3-6.5)		6.5 ± 1.7 (5.6-7.3)		.267
3W	5.5 ± 1.8 (4.6-6.3)		1.8 ± 1.6 (1.1-2.6)		3.3 ± 2.7 (2-4.6)		**<.0001**
3W-baseline change	–0.5 ± 1.5 (–0.3 to 1.2)	.206	–3.6 ± 2.1 (–4.6 to –2.6)	**<.0001**	–3.2 ± 2.6 (–4.5 to –1.9)	**<.0001**	**<.0001***,†
6M	5.1 ± 1.6 (4.3-4.8)		3.2 ± 2.6 (1.9-4.5)		3.6 ± 2.9 (2.1-5.1)		.119
6M-baseline change	–0.8 ± 1.6 (–1.7 to –0.1)	**.022**	–2.2 ± 3.1 (–3.8 to –0.7)	**.006**	–2.9 ± 3.5 (–4.6 to –1.1)	**.003**	.077
ROM—Flexion							
Baseline	15.8 ± 4.7 (13.5-18.2)		13.3 ± 5.9 (10.7-16.4)		16.9 ± 5.1 (14.3-19.5)		.162
3W	15.2 ± 5.1 (12.7-17.8)		20.21 ± 5.72 (17.5-23)		19.8 ± 6.2 (16.7-22.9)		**.019**
3W-baseline change	–0.6 ± 3.9 (–2.5 to 1.3)	.597	6.6 ± 4.2 (4.6-8.7)	**<.0001**	2.9 ± 5.4 (0.2-5.6)	**.035**	**<.0001***
6M	13.2 ± 4.3 (11.1-15.3)		18.95 ± 6.9 (15.6-22.3)		17.4 ± 6.3 (14.3-20.5)		.710
6M-baseline change	2.6 ± 4.2 (–4.7 to –0.5)	**.018**	5.4 ± 6.1 (2.5-8.3)	**.001**	0.5 ± 6.9 (–3 to 4)	.764	**.001***
RMDQ							
Baseline	14.2 ± 2.8 (12.8-15.6)		10.6 ± 4.8 (8.3-12.9)		12.7 ± 3.9 (10.8-14.7)		.056
3W	12.6 ± 4.1 (10.6-14.6)		6.4 ± 3.7 (4.6-8.2)		7.6 ± 3.5 (5.9-9.4)		**<.0001**
3W-baseline change	–1.6 ± 3 (–3.1 to –0.1)	**.043**	–4.2 ± 3.9 (–6.1 to –2.3)	**<.0001**	–5.1 ± 2.9 (–6.5 to –3.7)	**<.0001**	**.004**‡
6M	14.1 ± 3.5 (12.3-15.8)		6.8 ± 3.9 (4.9-8.7)		8.3 ± 4.9 (5.9-10.8)		**<.0001**
6M-baseline change	–0.1 ± 3.2 (–1.7 to 1.5)	.886	–3.8 ± 4.7 (–6.1 to –1.5)	**.002**	–4.4 ± 5.1 (–6.9 to –1.9)	**.002**	**.010***,†
FABQ							
Baseline	30.7 ± 5.2 (28.1-33.3)		28.6 ±9.2 (24.2-33)		35.5 ± 8.9 (31.1-39.9)		**.026**‡
3W	28.9 ± 5.8 (26.1-31.8)		24 ± 7.3 (20.5-27.5)		29.3 ± 7.1 (25.8-32.8)		**.031**
3W-baseline change	–1.8 ± 2.5 (–3.1 to –0.5)	**.008**	–4.6 ± 5.6 (–7.3 to –1.9)	**.002**	–6.2 ± 9.7 (–11 to –1.4)	**.005**	**.004***
6M	30.4 ± 5.3 (27.8-33)		22.2 ± 8.9 (17.9-26.5)		32.9 ± 8.1 (28.9-37)		**<.0001**
6M-baseline change	–0.3 ± 3.5 (–2.1-1.4)	.655	–6.4 ± 6.4 (–9.4 to –3.3)	**<.0001**	–2.6 ± 9.3 (–7.2 to 2.1)	.06	**.003***

FABQ, Fear Avoidance Belief Questionnaire; M, months; RMDQ, Roland–Morris Disability Questionnaire; ROM, range of motion; VAS, visual analog scale; W, week.Statistical significance: p<0.05.
*CP group vs. SNAG group.
†CP group vs. plus group.
‡SNAG group vs. plus group.

significant difference at the third week (P=.019). The mean change scores of flexion ROM significantly differed among the 3 groups at the third week (P < .0001) and at 6-month follow-up (P=.001); post-hoc analysis revealed that flexion ROM in group II (P < .0001) was significantly increased compared to group I (Table 2).

Functional Status

After 3 weeks of intervention, functional status significantly increased in all 3 groups (P < .05), demonstrating 1.6, 4.2, and 5.1 point improvements in group I, group II, and group III, respectively. However, the within-group scores were not significantly different in group I at 6-month follow-up (P=.886). The between-group assessment demonstrated no significant differences at baseline (P=.056) but a significant difference at third week and 6-month follow-up (P < .0001). The mean change scores of the RMDQ at the third week (P=.004) and 6-month follow-up (P=.01) were significantly different among all 3 groups; post-hoc analysis revealed that functional status improved significantly in group III than in the group I at the third week (P=.003) and in group II (P=.037) and group III (P=.014) compared to group I at 6-month follow-up (Table 2).

Fear Avoidance Belief

After 3 weeks of intervention, fear avoidance belief significantly decreased in all 3 groups (P < .05), demonstrating 1.8, 4.6, and 6.2 point improvements in group I, group II, and group III, respectively. The between-group assessment demonstrated statistically significant differences at baseline (P=.026) and at the third week (P=.031). The mean change scores of FABQ significantly differed among the 3 groups at the third week (P=.004); post-hoc analysis revealed that fear avoidance belief in group II was significantly improved compared to group I (P=.003). The within-group score was statistically significant in group II at 6-month follow-up ($P \leq .0001$). The between-group assessment demonstrated statistically significant differences at 6-month follow-up (P < .0001). The mean change scores of FABQ significantly differed among the 3 groups at 6-month follow-up (P=.003); post-hoc analysis revealed that fear avoidance belief was significantly improved in group II compared to group I (Table 2).

Discussion

The aim of this study was to compare the standalone and combined mid-term effects of CP and lumbar SNAGs on pain, ROM, fear avoidance belief, and functional status in patients with NSCLBP. The results of this study showed that pain, ROM, functional status, and fear avoidance

belief improved after 3 weeks of lumbar SNAGs, and these achievements were maintained up to the mid-term. In contrast, the achieved improvements in functional status and fear avoidance belief with CP did not maintain up to the mid-term. The mid-term improvements in ROM, functional status, and fear avoidance belief with lumbar SNAGs were significantly better than with the CP. Conventional physiotherapy added to lumbar SNAGs provided no additional benefit at any measurement time.

The mechanisms by which Mulligan concept exerts its curative effect in clinical practice still remain mysterious. It has been suggested that the immediate pain relief achieved with SNAGs may be due to non-opioid endogenous pain inhibition pathways or to restoring muscle balance due to correction of positional fault.[20] Some studies focused on the effect of SNAGs on VAS resting pain score,[13,20] while others focused on pain activity score.[12,22] Reduction in pain during flexion was achieved with lumbar SNAGs compared to the control subjects[21] and sham SNAGs.[12,14] In the current study, after 3 weeks of intervention, pain during flexion was significantly reduced in the SNAG-administered patients. Patients treated with standalone and combined lumbar SNAGs showed improvement in VAS activity score of 3.6 and 3.2 points, respectively. The minimal clinically important difference (MCID) of VAS pain score in chronic LBP has been reported as 20 mm.[22] According to the reported MCID score, these improvements may be both considered clinically important and statistically significant after 3 weeks of intervention. At mid-term, pain during trunk flexion was significantly decreased in all intervention groups. While this decrease was 0.8 points in patients who received CP, it was 2.2 and 2.9 points in patients who received standalone and combined SNAGs, respectively. However, the improvement in terms of activity pain achieved with CP intervention is statistically significant but may not be clinically important. Pain during activity has a greater association with decreased physical function and quality of life than pain at rest.[23] Therefore, we chose to evaluate pain during activity. We think that activity pain is decreased because mobilization is applied in the direction of painful movement. Conventional physiotherapy intervention, which is one of the passive treatment methods, was insufficient to reduce pain during activity. Therefore, adding CP to lumbar SNAGs provided no additional benefit.

Applying SNAGs to mobilize the affected facet joints may release capsular strain, resulting in ROM improvement.[20] However, studies have focused on the immediate- and short-term effects of SNAGs on ROM[12,14]. Studies have shown that lumbar SNAGs provide pain-free ROM. However, no studies were found examining the mid-term effect of SNAGs. According to the current study results, flexion ROM was significantly increased in the SNAG-administered groups after 3 weeks of intervention, but this improvement was maintained at mid-term only in in patients who were administered standalone lumbar SNAGs. Lumbar SNAGs which was applied in the direction of painful or restricted motion were able to increase ROM in the short term because of provided positive feedback. Thus, patients may be able to repeat painful or restricted movements they have experienced before without fear, and these repeated movements may have increased ROM. The improvement in ROM may not have been maintained in the mid-term because of the high baseline FABQ score of patients who were administered CP plus lumbar SNAGs intervention. In addition, since the patients were not supported with a self-exercise program after all interventions, the improvements may not have been maintained at mid-term.

In current study, after 3 weeks of intervention, the functional status score was significantly decreased in all intervention groups. While this decrease was 1.6 points in patients who received CP, it was 4.2 and 5.1 points in patients who received standalone and combined SNAGs, respectively. The MCID of functional status RMDQ score has been reported as 3.5 points.[22] The improvement achieved with CP intervention was statistically significant but may not be clinically important. The improvement in the functional status score was maintained up to mid-term in the SNAG-administered patients. Trunk flexion is known as the most painful movement in patients with LBP. Restriction of trunk flexion may have a major impact on high level of disability in patients with chronic LBP.[23] In the current study, the achievement of pain-free flexion ROM with lumbar SNAG intervention may lead to an increase in functional status in the SNAG-administered patients.

In the treatment of chronic LBP, it is recommended to avoid long-term inactivity and increase physical activity level gradually.[24] However, these recommendations might not be followed by the patients who have greater fear avoidance beliefs.[25] Therefore, it is important to eliminate it. While a previous study had reported that lumbar SNAGs have a short-term favorable effect on fear avoidance belief,[12] we found that lumbar SNAGs were more effective in reducing fear avoidance belief after 3 weeks of intervention and at mid-term. The mobilization is performed in the direction of previously experienced painful or restricted movement with the SNAGs intervention; therefore, the patient may have gained a positive experience with the painful/restricted movement they had before. And the belief in fear avoidance may have decreased as a result of this. They applied 1 session of SNAGs, whereas we applied 9 sessions. Most probably, this is the reason why we achieved mid-term improvements.

Limitations

The re-evaluation schedule of primary outcome measures in the current study was at third week and 6-month follow-up. The follow-up period after treatment was relatively long. An interim evaluation during this process could have helped us better interpret the intervention effects. We have chosen the flexion ROM as one of the outcome measures. According to Atya, lumbar flexion cannot be used separately as a collective score or index for disability.[23] In future studies, rotation and extension ROM and pain during extension and rotation could be included. However, the current study is the first to investigate the standalone effects of the interventions that make up combined intervention and to have mid-term follow-up.

In conclusion, improvements in pain, flexion ROM, functional status, and fear avoidance belief were achieved with lumbar SNAGs. These achievements have been maintained at mid-term. On the other hand, CP reduced the functional status and fear avoidance belief only at short term, but these achievements were not maintained at mid-term. This made us think that lumbar SNAGs should be preferred instead of CP in patients with NSCLBP. The clinical advantages of the lumbar SNAGs are that it can be applied in a short time, it is an active pain-controlled treatment method, and improvements can be achieved immediately after the treatment session. The results of this study provided new information regarding the effectiveness of manual therapy in the treatment of patients with NSCLBP.

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Informed Consent: Informed consent was obtained from the participants.

Peer-review: Externally peer-reviewed.

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Materials – Ş.Ş., M.B.K.; Data Collection and/or Processing – Ş.Ş., M.B.K.; Analysis and/or Interpretation – N.Y., Ş.Ş., M.B.K.; Literature Review – Ş.Ş., N.Y.; Writing – Ş.Ş., M.B.K.; Critical Review – Ş.Ş., N.Y.

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Dermatology

The Frequency of Association of Nail Involvement and Psoriatic Arthritis in Psoriasis Patients

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ABSTRACT

Objective: While the relationship between psoriatic arthritis and skin findings is well-known in patients with psoriasis, the relationship between psoriatic arthritis and nail involvement is less known. In this study, it was aimed to examine the frequency of association between nail involvement and psoriatic arthritis in patients with psoriasis.

Materials and Methods: Our study is a retrospective observational study. It was conducted with 250 registered patients who applied to the dermatology polyclinic and clinic of our university hospital. The follow-up forms of the patients were scanned retrospectively and the findings were recorded.

Results: The average age of the 250 patients evaluated in this study was 39.62 ± 9.30, and 133 (53.2%) of them were women. The frequency of nail involvement in psoriasis patients was determined to be 36.8% (n=92) and the frequency of arthritis was determined to be 8.8% (n=22). Nail involvement was statistically significantly more common in those with arthritis, and nail involvement was present in all of those with arthritis ($P < .001$). Nail involvement was significantly more common in those with only arthralgia ($P < .001$). A significantly higher average of nail psoriasis severity index was found in those with both joint and nail involvement compared to those with only nail involvement ($P < .001$). There was no statistically significant difference in terms of psoriasis area severity index average ($P=.235$). Proximal and distal interphalangeal arthralgia and sacroiliac arthralgia were found significantly more frequently in those with nail involvement than in those without nail involvement (respectively $P=.007$ and $P < .001$). There was no statistically significant relationship between nail involvement with the presence of arthritis and the clinical type (respectively $P=.288$ and $P=.955$).

Conclusion: Joint involvement and nail involvement in patients with psoriasis are closely related, and we think that nail and joint involvement in psoriasis patients should be evaluated together.

Keywords: Psoriasis, psoriatic arthritis, nails, severity of illness index

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Introduction

Psoriasis is a systemic inflammatory, chronic and recurrent disease that might affect the skin, joints, and nails, with the frequency of 1%-3% in the population. Although immunological, autoimmune, and genetic factors are considered to be effective in the pathogenesis of the disease, it has not been fully clarified yet. Nail involvement is a common condition in patients with Ps. Although the normal frequency of nail involvement in psoriasis is 40%, this rate might increase up to 80% in cases with psoriatic arthritis (PsA).[1] Psoriatic arthritis is a chronic immune-mediated spondyloarthropathy that may occur in 20-30% of patients with psoriasis and may lead to devastating and permanent joint damage. Peripheral arthritis, axial disease, dactylitis, enthesitis, and skin and nail psoriasis may also develop in PsA.[2] Recently, it has been suggested that nail involvement in patients with psoriasis may be a marker of PsA development.[3] Nail changes may occur 1-2 years before arthritis in patients with psoriasis.[4] The relationship between nail involvement and distal interphalangeal (DIP) joint involvement is well known. It is believed that this close relationship occurs with the progression of the inflammation that starts in the nail and then progresses to the DIP joint due to the anatomical proximity of the nail bed and its matrix to this joint.[5] Nail psoriasis is a condition that leads to a decrease in the self-confidence of individuals due

to its disfiguring feature, along with an increase in the frequency of depression and anxiety. Likewise, PsA patients have deterioration in the quality of life, reduced functional capacity and loss of work force. Because of this, PsA results in negative consequences for the individual and society physically, psychologically, and economically. There is a need to establish a clinical indicator to detect the risk and early diagnosis of PsA.[3] In the literature, studies on the frequency of association of PsA and nail involvement are very few. Therefore, in this study, we aimed to examine the frequency of nail involvement and PsA association in patients with psoriasis and how this association affects the nail psoriasis severity index (NAPSI) in patients.

Materials and Methods

The study is a retrospective cross-sectional study. Recorded patients, who were admitted to the Dermatology Polyclinic and Clinic between January 2018 and December 2022 and who were clinically and histopathologically diagnosed with psoriasis, were included in the study. The study was performed in accordance with the principles of the Declaration of Helsinki following receipt of approval from the local ethical committee (Date:December 29, 2022, No: 4).

Data Collection and Study Design

A total of 250 patients aged between 18 and 70 who were diagnosed with psoriasis clinically and histopathologically were included in the study. Pregnant and lactating women and people with another known inflammatory skin or systemic disease were excluded from the study. The demographic characteristics of the patients, duration of the disease, smoking and alcohol use, psoriasis clinical types, whether the patient has joint complaints, nail examination findings, medication use history, and body mass index (BMI) of the patients were retrospectively scanned and recorded in the registered files of the patients. Psoriasis area severity index (PASI) scores in patients were calculated and recorded according to the distribution areas of the lesions. According to the PASI results, those below 10 were considered mild, those between 10 and 15 were considered moderate, and those above 15 were considered severe diseases. Nail psoriasis severity index scores were calculated and recorded according to the nail examination findings and the number of nails involved. Whether those with joint complaints have swelling in the joints, joint stiffness when waking up in the morning, recurring pain in the tendons, pain and swelling in the fingers, how many joints and in which joint they have complaints were recorded according to the anamnesis files. In patients with joint complaints, the consultation notes requested from the Rheumatology Department of our hospital were examined using the electronic record system. According to the rheumatology note, patients who met the Classification Criteria for Psoriatic Arthritis (CASPAR) were considered to have arthritis. In the evaluation of the laboratory tests performed, the laboratory values of our hospital were taken into account for the reference values of the test results. In this context, as normal values; values of white blood cell (WBC) 4.000-11.000/μL, hemoglobin >12 g/dL, C-reactive protein (CRP) <5 mg/L, erythrocyte sedimentation rate 0-20 mm/h, rheumatoid factor (RF) 0-16 IU/mm were considered as normal values.

Main Points

- Joint involvement and nail involvement in patients with psoriasis are closely related.
- Nail involvement was statistically significantly more common in those with arthritis.
- Concomitant arthritis in psoriasis may increase the nail psoriasis severity index score in patients.
- Distal interphalangeal joint complaints were more common in patients with nail findings in psoriasis.

Statistical Analysis

All tests were analyzed using the statistical package SPSS, version 21.0 (IBM Comp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to check the suitability of continuous variables to a normal distribution. In the comparison of 2 independent groups, the Mann–Whitney *U*-test was used for variables that do not have a normal distribution, and the Student's *t*-test was used for variables that have a normal distribution. The relationships between categorical variables were tested by the chi-square test. It was accepted as $P < .001$ for statistical significance.

Results

Demographic and Clinical Characteristics

The average age of the 250 patients evaluated in this study was 39.62 ± 9.30 (youngest–eldest; 20-67) and 133 (53.2%) were women. The demographic and clinical characteristics of the patients were presented in Table 1. The frequency of nail involvement in psoriasis patients was determined to be 36.8% (n=92) and the frequency of arthritis was determined to be 8.8% (n=22).

Nail and Joint Involvement

A total of 67 of the patients with nail involvement (72.8%) had only fingernail involvement, 1 of them (0.4%) had only toenail involvement, and 24 of them (9.6%) had both fingernail and toenail involvement. The average of nail involvement number was 5.73 ± 2.23. Psoriatic hand and toenail findings in patients were presented in Table 2. Accordingly, the most common findings detected only on the fingernail and on both the toenail and the hand were pitting, onycholysis, and subungual hyperkeratosis while onycholysis, leukonychia, and subungual hyperkeratosis were detected on only the toenail of 1 patient. Pitting and onycholysis in 17 (18.5%) patients, pitting in 15 (16.3%) patients, and pitting, onycholysis, and subungual hyperkeratosis in 12 (13.0%) patients were detected.

The relationship between nail involvement, arthritis, and arthralgia is presented in Figure 1. Nail involvement was statistically significantly more common in those with arthritis, and nail involvement was present in all of those who developed arthritis ($P < .001$). Nail involvement was significantly more common in those with arthralgia ($P < .001$). Arthralgia and nail involvement were present in all 22 (8.8%) patients with arthritis. While 18 (7.89%) of 38 (16.6%) patients with arthralgia and no arthritis had nail involvement, 20 (8.77%) did not. A total of 138 (60.53%) patients did not have arthritis, arthralgia, or nail involvement.

Psoriasis area severity index and NAPSI values according to nail and joint involvement were presented in Figure 2. A significantly higher average of NAPSI was found in those with both joint and nail involvement compared to those with only nail involvement ($P < .001$). There was no statistically significant difference in terms of PASI average ($P=.235$).

The distribution of nail involvement according to the localization of joint pain is presented in Table 3. Proximal and DIP arthralgia and sacroiliac arthralgia were found significantly more frequently in those with nail involvement than in those without nail involvement (respectively $P=.007$ and $P < .001$).

The distribution of demographic, clinical, and laboratory characteristics according to the incidence of joint and nail involvement in psoriasis was evaluated in Table 4. The average RF was significantly higher in the presence of nail involvement ($P < .001$). Only one of the patients with arthritis was RF (4.5%) positive. Those with arthritis were found to be significantly older, with longer disease duration, and with higher BMI than those without arthritis (respectively $P=.006$, $P=.004$, and $P=.009$). Significantly higher CRP, sedimentation, and significantly lower hemoglobin were detected in those with arthritis (respectively $P < .001$ and $P=.007$).

Table 1. Demographic and Clinical Characteristics of Patients

Variables		
Age, average ± SD		39.62 ± 9.30
Sex, n (%)	Male	117 (46.8)
	Female	133 (53.2)
Age of onset of the disease, average ± SD		27.42 ± 11.20
Duration of disease (month), average ± SD		143.04 ± 111.60
Body mass index, average ± SD		26.77 ± 4.22
Habits		
Presence of smoking, n (%)		96 (38.4)
Smoking (pack-year), average ± SD		14.13 ± 13.57
Presence of alcohol use, n (%)		4 (1.6)
Nail involvement, n (%)		92 (36.8)
	Hand	67 (72.8)
	Foot	1 (0.4)
	Hand–foot	24 (9.6)
Number of nail involvement, average ± SD		5.73 ± 2.23
Presence of arthritis, n (%)		22 (8.8)
	Monoarthritis	11 (50.0)
	Oligoarthritis	2 (9.1)
	Polyarthritis	9 (40.9)
Presence of arthralgia, n (%)		60 (24.0)
	Active	18 (30.0)
	Inactive	42 (70.0)
Duration of arthralgia (month), average ± SD		33.08 ± 28.26
NAPSI score, average ± SD		8.32 ± 13.72
PASI score, average ± SD		7.71 ± 5.87

NAPSI, nail psoriasis severity index; PASI, psoriasis area severity index.

The distribution of clinical types according to the presence of nail and joint involvement in psoriasis is shown in Figure 3. The most common clinical types of limited plaque, diffuse plaque, and palmoplantar plaque were detected in those with nail involvement. There was no statistically significant relationship between the presence of nail involvement and the clinical type (P=.288). Limited plaque, diffuse plaque, and palmoplantar plaque types were commonly observed in those with arthritis. There was no statistically significant relationship between the presence of arthritis and the clinical type (P=.955).

Discussion

Psoriasis is a systemic inflammatory chronic and recurrent disease that affects the skin, nails, and joints and that might be accompanied by many comorbidities. Although the relationship between skin manifestations and joint findings in psoriasis is well known, there are fewer studies in the literature on the relationship between joint findings and nail findings. In psoriasis, both nail involvement and joint involvement impair the quality of life, working life, sleep quality, and general health status of patients, and create a great burden to both the individual and the society, physically, psychologically, and economically.[6,7] There are opinions that the presence of nail involvement in patients with psoriasis may be a marker of PsA development. In this way, it is stated that the subclinical state of PsA might be detected early and its clinical progression might be prevented.[3] Therefore, in this study, we aimed to examine the frequency of nail involvement and PsA association in patients with psoriasis and how this association affects the NAPSI in patients with PsA.

Table 2. Psoriatic Hand and Toe Nail Findings in Patients

Findings, n (%)	Hand Nail (n=67)	Foot Toe (n=1)	Hand–Toe Nail (n=24)
Pitting	58 (86.6)	–	21 (87.5)
Onycholysis	45 (67.2)	1 (100)	21 (87.5)
Subungual hyperkeratosis	25 (37.3)	1 (100)	14 (58.3)
Leukonychia	8 (11.9)	1 (100)	6 (25.0)
Breaking quickly	10 (14.9)	–	1 (4.2)
Splinter hemorrhage	6 (9.0)	–	8 (33.3)
Red lunula	–	–	–

Psoriatic arthritis is a chronic, immune-mediated spondyloarthropathy that can be observed in patients with psoriasis. The incidence of PsA in patients with psoriasis varies between 7 and 40%.[8] Symptoms such as inflammatory pain, diffuse arthralgia, arthritis, dactylitis, enthesitis, uveitis, peripheral edema, and nail involvement might be observed in the PsA clinic. Psoriatic arthritis might be seen clinically as polyarthritis, oligoarthritis, monoarthritis, DIP, spondylitis, and arthritis mutilans, involving the peripheral joint, spine, and enthesis region.[9] In our patients, PsA was accompanied by a rate of 8.8% (n=22) in 250 psoriasis patients in accordance with the literature. In our patients who were diagnosed with PsA, 50% (n=11) monoarthritis, 9.1% (n=2) oligoarthritis, 40.9% values were recorded. We can change the sentence like this. Despite this, although 24% (n=60) of our patients have arthralgia complaints in one or several joints, it could not be decided whether PsA was present in these patients according to CASPAR criteria since the study was conducted retrospectively. In a study, it is stated that the average duration of arthralgia in patients with psoriasis is 35 months. Again in this study, it is stated that the long duration of psoriasis and the female gender increase the incidence of PsA.[10] In our study, in accordance with the literature, it is found that the average duration of arthralgia was 33 months, the average duration of psoriasis was 12 years, and the frequency of female gender was higher in our patients. Those with arthritis were found to be significantly older, with longer disease duration, and with higher BMI than those without arthritis (respectively P=.006, P=.004, and P=.009). In our study, when the complaints of pain in the joint regions of the patients were evaluated, arthralgia was most common in the DIP and sacroiliac joints. Rheumatoid factor is

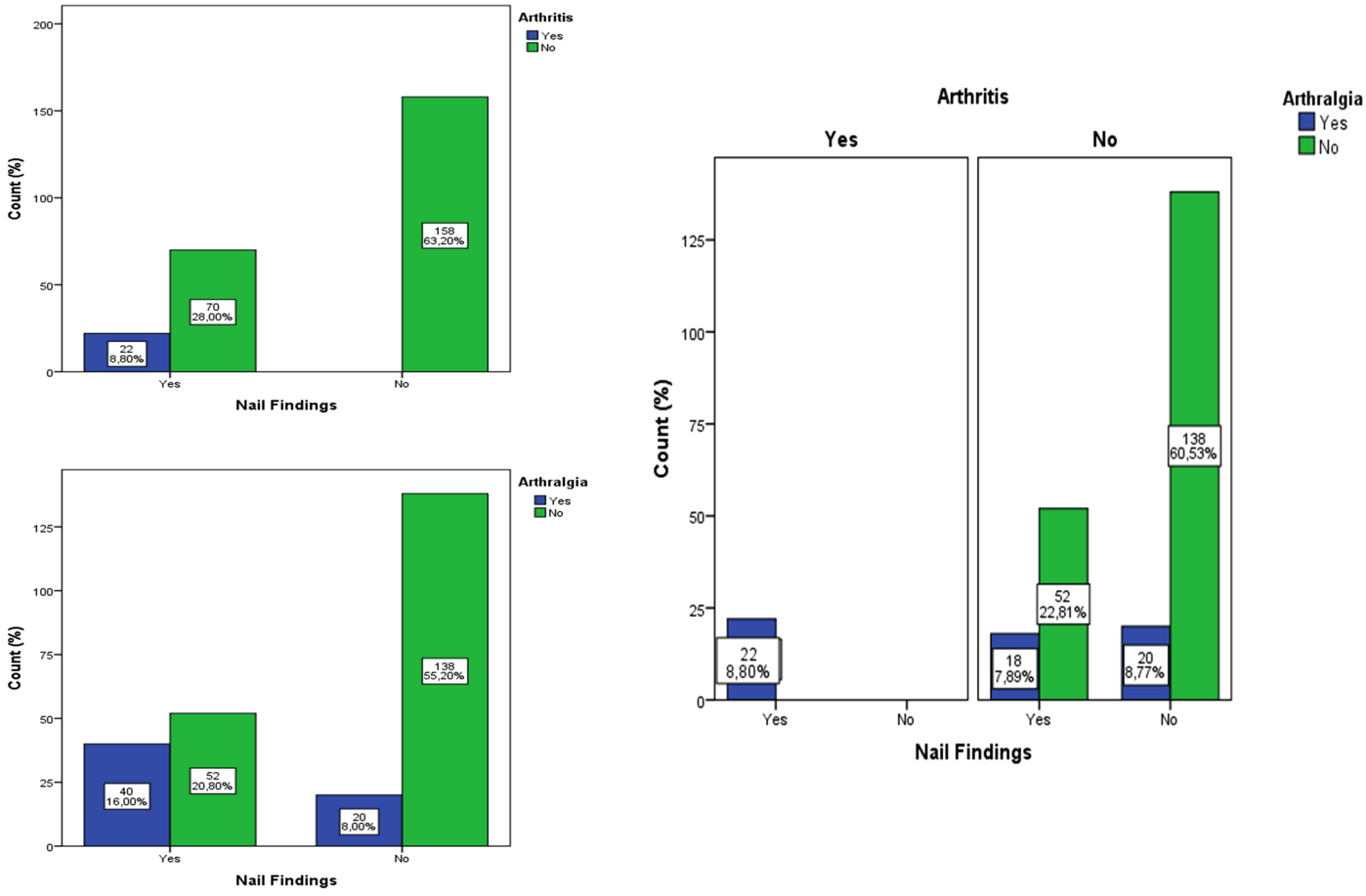

Figure 1. The relationship between nail involvement and arthritis and arthralgia.

very important in the separation of PsA and rheumatoid arthritis. Rheumatoid factor is positive in approximately 80% of patients with rheumatoid arthritis, while it is positive in 13% of patients with PSA.[4] In this study, only 4.5% (n=1) of 22 patients with arthritis were RF positive.

Psoriasis is a disease that can also affect the nails. While nail involvement is mostly associated with skin manifestations, it might also be seen in the form of only nail involvement without skin manifestations in 5% of cases.[11] There were no psoriasis patients with only nail findings in our study. All of our patients were accompanied with skin manifestations. Sometimes, only nail and joint involvement can be together. Nail involvement is observed in about 40% of patients with psoriasis, while this rate may be up to 80% if there is also joint involvement.[1] In psoriasis, the fingernails are more often affected than the toenails. As there may be involvement in a single nail, there

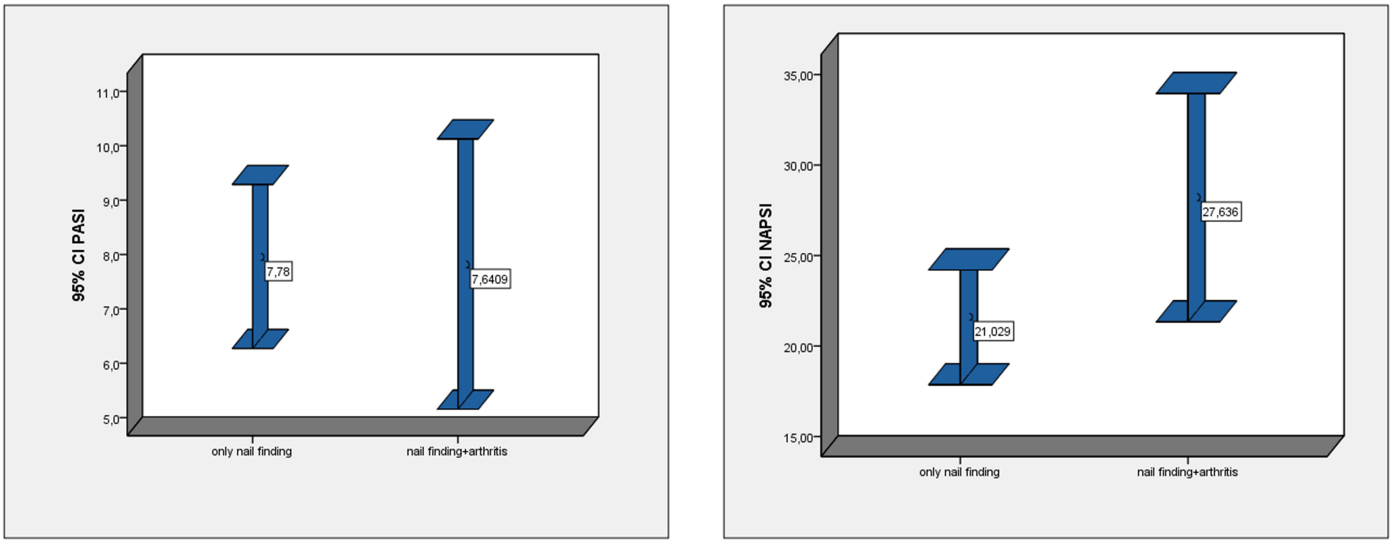

Figure 2. Average values of PASI and NAPSI according to nail and joint involvement.

Table 3. Distribution of Nail Involvement According to Localization of Joint Pain

	Nail Finding		
	Yes (n=92)	No (n=158)	*P*
Cervical arthralgia	–	2 (1.3%)	.398
Shoulder arthralgia	–	1 (0.6%)	.632
Elbow arthralgia	1 (1.1%)	2 (1.3%)	.694
Wrist arthralgia	8 (8.7%)	6 (3.8%)	.102
Proximal interphalangeal arthralgia	9 (9.8%)	3 (1.9%)	**.007**
Distal interphalangeal arthralgia	20 (21.7%)	5 (3.2%)	**<.001**
Thoracic arthralgia	–	–	–
Lumbar arthralgia	7 (7.6%)	5 (3.2%)	.113
Sacroiliac arthralgia	20 (21.7%)	8 (5.1%)	**<.001**
Knee arthralgia	4 (4.3%)	1 (0.6%)	.063
Ankle arthralgia	3 (3.3%)	–	.050

is often involvement in more than 1 nail.[12] In our study, nail involvement was detected in 36.8% (n=92) of the patients and, in accordance with the literature, the fingernails of the patients were most commonly involved. The average of nails involvement number in our patients was found 5.73 nails. Psoriatic nail findings can vary considerably between studies. In one study, the most common nail findings were reported as onycholysis and subungual hyperkeratosis.[13] In our study, pitting and onycholysis were detected as the most frequent. This shows that both the nail matrix and the nail bed are often affected in our patients.

Table 4. Distribution of Demographic, Clinical, and Laboratory Characteristics According to the Incidence of Joint and Nail Involvement in Psoriasis

	Nail			Arthritis		
	Yes	No	*P*	Yes	No	*P*
Age, average ± SD	40.57 ± 9.15	39.08 ± 9.37	.231	45.05 ± 7.97	39.10 ± 9.27	**.006**
Sex, n (%) female	42 (31.6%)	91 (68.4%)	.068	15 (68.2%)	118 (51.8%)	.140
Male	50 (42.7%)	67 (57.3%)		7 (31.8%)	110 (48.2%)	
Age of onset of the disease, average ± SD	27.01 ± 11.06	27.67 ± 11.32	.657	27.13 ± 9.15	27.45 ± 11.40	.984
Duration of disease (month), average ± SD	169 ± 127	134 ± 105	.180	210 ± 133	137 ± 107	**.004**
Body mass index, average ± SD	26.68 ± 3.90	26.82 ± 4.41	.980	29.10 ± 4.37	26.54 ± 4.15	**.009**
Habits						
Presence of smoking, n (%)	42 (43.8%)	54 (56.3%)	.072	8 (8.3%)	88 (91.7%)	.837
Smoking (pack-year), average ± SD	12.62 ± 8.61	14.54 ± 14.66	.392	7.91 ± 3.53	14.76 ± 14.06	.183
Presence of alcohol use, n (%)	2 (50.0%)	2 (50.0%)	.469	–	4 (100%)	.690
Laboratory, average ± SD						
C-reactive protein	6.89 ± 8.06	4.65 ± 4.65	.111	10.55 ± 7.76	4.99 ± 5.83	**<.001**
Sedimentation	13.28 ± 14.9	10.34 ± 10.27	.901	30.86 ± 19.60	9.55 ± 9.40	**<.001**
Rheumatoid factor	5.86 ± 3.05	4.27 ± 2.20	**<.001**	7.95 ± 4.01	4.56 ± 2.29	**<.001**
White blood cell	8.06 ± 2.11	8.14 ± 2.26	.965	8.23 ± 2.64	8.10 ± 2.29	.785
Hemoglobin	14.60 ± 2.04	14.54 ± 1.71	.587	13.47 ± 1.91	14.67 ± 1.79	**.007**
Thrombocyte count	289 ± 80	280 ± 66	.478	319 ± 106	278 ± 65	.065

The results of studies conducted on the frequency of nail involvement and PsA association in patients with psoriasis vary. It has been stated that the frequency of this association in some studies varies between 40% and 80%. In one study, it was reported that nail involvement was present in 64.4% of patients with DIP joint arthritis.[14] In another study that nail involvement is examined according to PsA onset time, it is determined that the frequency of nail involvement in patients with early onset PSA was 77%, and the association of nail involvement in patients with late onset PSA was 74%.[15] In this study, nail involvement was present in all of our patients with arthritis. However, nail involvement was again accompanied in 18 (7.89%) of the 38 (16.6%) patients who did not have arthritis, but had arthralgia and could not be diagnosed with PsA according to CASPAR criteria. Nail involvement was statistically significantly more common in those with arthritis, and nail involvement was present in all of those who developed arthritis. Nail involvement was significantly more common in those with arthralgia. Proximal and DIP arthralgia and sacroiliac arthralgia were found significantly more frequently in those with nail involvement than in those without nail involvement (respectively $P=.007$ and $P<.001$). C-reactive protein and sedimentation rate, which are indicators of inflammation, were statistically higher in patients with arthritis than in those without.

The NAPSI is often used to determine the severity of nail involvement in patients with psoriasis. While pitting finding is scored according to the number of pitting in modified NAPSI (mNAPSI), other findings are scored according to the percentage of involvement. We used NAPSI scoring in our study. Palmou et al[16] found no statistically significant difference in mNAPSI scores between psoriasis patients with and without PsA in a study. In another study, it was found that the mNAPSI score was higher in patients with DIP joint arthritis than in the control group.[17] In our study, a statistically significant difference was found in terms of NAPSI between psoriasis patients with PsA and nail findings and patients with nail involvement without PsA. Nail involvement was more severe in those accompanied by PsA. Again, when the relationship between PsA and PASI in patients with psoriasis was examined in the literature, a significantly higher PASI score was observed in those with PsA.[18] In this study, there was no statistically significant difference in terms of PASI score between patients with psoriasis with only nail findings and patients with nail involvement and joint involvement. There was no statistically significant relationship between clinical type in patients with only nail involvement and patients with nail involvement and

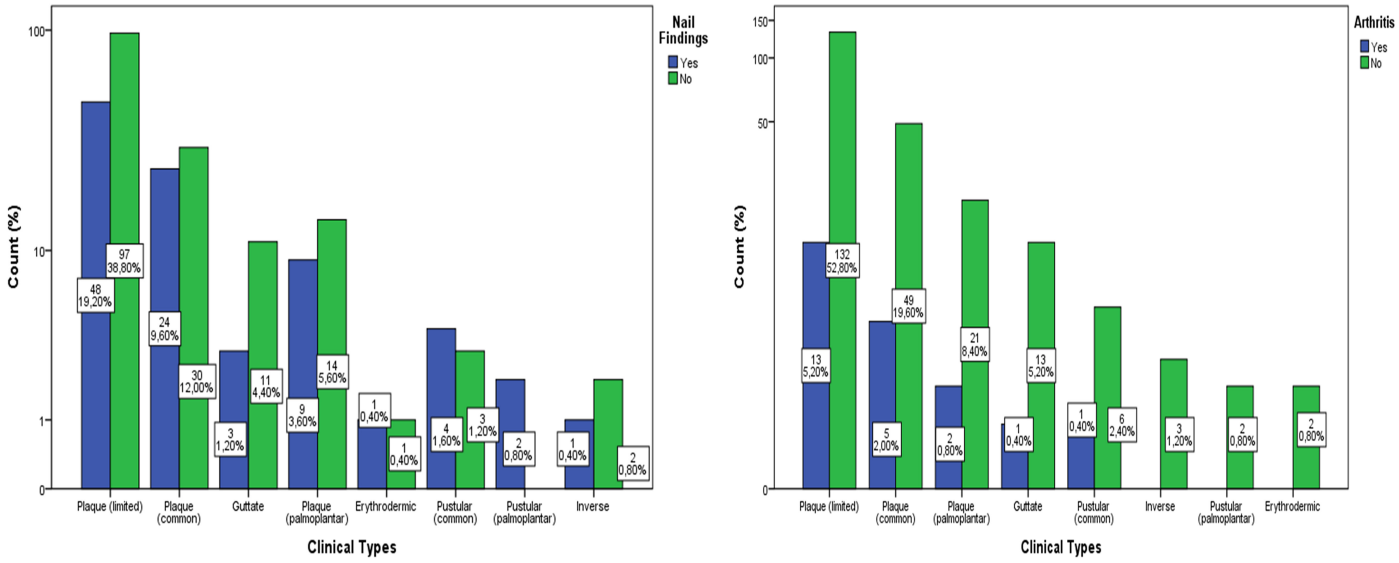

Figure 3. The distribution of clinical types according to the presence of nail and joint involvement in psoriasis.

joint involvement. The most common clinical types in patients with both only nail involvement and joint involvement along with nail involvement were determined as limited plaque, diffuse plaque, and palmoplantar plaque.

Limitations

There are some limitations to the study. First, the study was conducted retrospectively in a single center. Second, the fact that we could not compare it with the control group is another limitation of the study. Third, since we did not have access to the retrospective rheumatology consultation notes and rheumatology examination findings of all patients with arthralgia complaints in the patient registration forms, the decision on arthritis according to CASPAR criteria could not be made fully in these patients. This has created a limitation in terms of fully reflecting the frequency of arthritis in our patients. Fourth, the fact that we could not reach the records about the onset of nail findings in patients with and without arthritis constitutes a limitation. This constitutes a limitation in evaluating nail involvement as a predictor for PsA development. Therefore, we think that there is a need for prospective studies comparing a larger number of patients and control groups.

As a result, the frequency of nail involvement was found to be higher in patients with arthritis than in those without in this study. And again, it was found that the severity of nail involvement was higher in patients with joint involvement. While nail involvement can distinguish PsA from other causes of arthritis, it is also an important finding in predicting the development of PsA. Therefore, psoriasis patients, especially those who admit with nail involvement, should be closely monitored in terms of PsA development, and we think that rheumatologists should pay attention to nail examination with a multidisciplinary approach to such patients.

Ethics Committee Approval: The study was conducted in compliance with the principles of the Declaration of Helsinki following receipt of approval from the Atatürk University, Faculty of Medicine Ethical Committee (Date:December 29, 2022, No: 4).

Informed Consent: Informed consent was not obtained from the patients since the study was conducted retrospectively and was designed as an archive scan of all patient files. N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.P.; Design – M.M.; Supervision – E.P.; Resources – E.P.; Materials – M.A.M.; Data Collection and/or Processing – E.P.; Analysis and/or Interpretation – Ö.K.; Literature Search – E.P.; Writing Manuscript – E.P.; Critical Review – M.A.M.

Declaration of Interests: The authors declare that they have no competing interest.

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Pediatric Intensive Care

Atypical Cardiac Compression Technique on a Seriously Skeletal Deformity Child

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To the Editor

The cardiac compression techniques were explained in the past by Pediatric Basic and Advanced Life Support 2020 American Heart Association Guidelines.[1] In addition, Jung et al[2] described the "Knocking-fingers" technique that was not in this guide. After reading this article with interest, we also experienced that this technique is effective in infant cardiac arrests. We could not find in the literature the chest compression technique we had to apply to a patient in our tertiary pediatric intensive care unit. This previously diagnosed Spinal Muscular

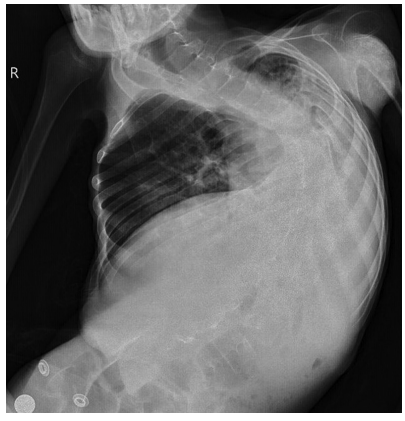

Figure 1. X-ray findings show serious skeletal deformities.

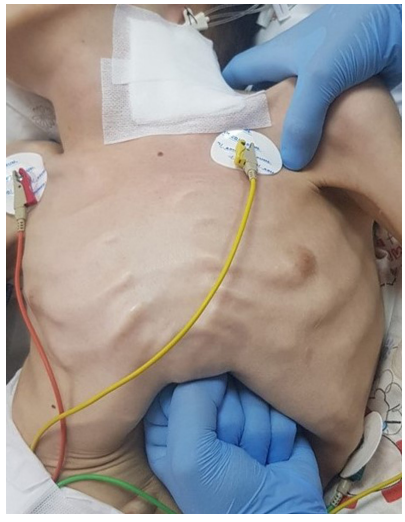

Figure 2. A new cardiac compression technique was applied to the patient by a rescuer.

Atrophy type 2 and a glial tumor 13-year-old boy developed cardiac arrest. It was impossible to apply effective cardiac compression with known techniques for him because of his serious skeletal deformities (Figure 1). For this reason, we applied to the patient a cardiac compression technique we developed spontaneously at that time (Figure 2). The patient was gotten in a semi-sitting position (30-45°). The rescuer fixed the patient's right shoulder with her right hand. She made a fist with her left hand. She applied the periodic pressures perpendicularly to the diaphragm under the left costal arch with her fist, just like in the Heimlich maneuver. The resuscitation response was performed with 10-second ultrasound assessments every 2 minutes. The process was successful after the cardiac compression and the third dose of adrenaline administration, which can be done with this technique. This technique may be an alternative to the traditional method for cardiac compressions in patients with severe skeletal deformities.

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Psychiatry - General

Coexistence of Schizophrenia, Epilepsy, and Polyglandular Autoimmune Syndrome

Halil Özcan

Dear editor,

Polyglandular autoimmune syndrome (PAS) is a group of disorders identified by the association of endocrine and nonendocrine organ involvement. There are 4 subtypes. Type I is characterized by comorbidities of hypoparathyroidism, Addison disease, and mucocutaneous candidiasis. Type II; Addison disease, insulin-dependent diabetes mellitus, and/or autoimmune thyroid disease. Type III; insulin-dependent diabetes mellitus and autoimmune thyroid disease without Addison disease.[1] Type IV is a combination of endocrine and autoimmune diseases including insulin-dependent diabetes mellitus, pernicious anemia, alopecia, vitiligo or neuromuscular junction disorder, thyroid disease, or hypoparathyroidism without Addison disease.[2] There are case reports representing comorbidities of PAS and neuropsychiatric disorders such as anorexia nervosa, paranoid schizophrenia, obsessive-compulsive disorder, narcolepsy, Munchausen syndrome, myopathy, dystonia, etc.[2-7] According to our knowledge, this is the first case with type IV PAS having type I insulin-dependent diabetes mellitus, pernicious anemia, and generalized vitiligo with the coexistence of schizophrenia and epilepsy.

Twenty-four-year-old male college student, with previous diagnoses of type I diabetes mellitus, pernicious anemia, and generalized vitiligo had been hospitalized at the internal medicine inpatient department due to unregulated blood glucose levels. During clinical follow-up, he had been consulted with the psychiatry department because of noncompliance to treatment regimens, irritability, and aggressive behaviors toward other people. In psychiatric anamnesis, his parents declared that for 2 years, they had noticed some odd behaviors in their son, such as talking to himself, suspiciousness of others, aggressiveness, social isolation, etc. Also, he had been noncompliant with his insulin treatment during this 2-year period. His psychiatric symptoms have been continuing during this 2-year period. On admission to the psychiatric unit of another hospital with the insistence of his parents to admit 3 months before, he had been diagnosed with schizophrenia and an atypical antipsychotic (aripiprazole 15 mg/day) and a benzodiazepine (lorazepam 2 mg/day) had started. He had been discharged on the fourth day of hospitalization due to his inconvenient behaviors such as verbal and physical assault on clinical staff and damaging the hospital equipment. After 10 days of usage, he stopped taking aripiprazole and lorazepam without medical advice as his psychotic symptoms were partially alleviated. Three months later, he was rehospitalized to our inpatient clinic because of the exacerbation of psychotic symptoms. On physical examination, generalized vitiligo (nearly involving 70% of his full body skin) was detected. His mental state examination revealed that he was fully conscious, his appearance was compatible with his socio-cultural level, his speech was clear, and his orientation to time, place, and person was intact. Immediate, recent, and remote memory was normal. His affect was irritable, and his mood was euthymic. No pathology was defined in thought structure and process. In thought content, paranoid and persecutory delusions, and in perception examination, possible visual hallucinations were detected. Aggressive behaviors toward other people and odd behaviors such as talking to himself were seen. His family history of psychiatric disorders was unremarkable. On laboratory examinations, his blood glucose levels were generally found as higher than normal (varying between 300 mg/dL and 850 mg/dL, normal ranges 70-100 mg/

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dL). His serum vitamin B12 level was 112 pg/mL (normal ranges 200-900 pg/mL). The mean corpuscular volume of red blood cells was 122 femtoliters (fL) (normal ranges 80-100 fL). Folic acid level, thyroid, parathyroid, kidney and liver functions, and serum electrolyte levels except sodium were within normal ranges. Sodium level was 123 (normal ranges 135-147 milliequivalents), and it was thought as related to the high blood glucose level. Aripiprazole 15 mg/day was started due to a diagnosis of schizophrenia. Three days later, he was transferred to the internal medicine inpatient clinic due to the occurrence of diabetic ketoacidosis. Five days later, a significant decrease in psychotic symptoms was observed and he was transferred to the psychiatry inpatient clinic. During hospitalization in our inpatient clinic, his mother mentioned about the seizures that the patient has for the first time, as contractions starting on the right hand and spreading to all extremities causing him to fall and leading to loss of consciousness. These seizures started nearly 4 years ago, at first they had been occurring once in a few months but nowadays they had been occurring more often nearly 3 times a month. One of his aunts and cousins had been on an antiepileptic treatment due to a diagnosis of epilepsy. His neurologic examination was unremarkable. His brain magnetic resonance imaging showed no pathology. Electroencephalography revealed sharp waves on the left frontal area. He was diagnosed with complex partial epilepsy and levetiracetam 1000 mg/day was started. A brief psychiatric rating scale (BPRS) was applied for identifying and measuring the severity of psychotic symptoms. The BPRS score on the first day of hospitalization was 71 and on his 15th day of hospitalization at discharge from the psychiatry inpatient clinic dropped to 21 points. Clinical follow-up was recommended. On his mental and neurologic examination on the third month of discharge, no psychotic symptoms and/or seizures have been observed and/or declared by him and/or his parents. His blood glucose levels were generally measured in normal ranges. Also, his mother declared that he had never been better during these 2 years, and his functionality significantly increased (achieved success in school, had social activities with his friends, etc.). We think that successful treatment of schizophrenia and epilepsy increased his adherence to diabetes mellitus treatment.

Cases with PAS type II and schizophrenia, a well-known psychotic disorder, exist in the literature.[5] A genetic relationship between PAS, progressive myoclonic epilepsy, and holoprosencephaly-1 is reported.[8] It is also known that there is a genetic link between holoprosencephaly and schizophrenia.[9] In our case, the patient was diagnosed with PAS type IV and secondary generalized epilepsy. There may be a common genetic background between type 1 diabetes mellitus and epilepsy, also hypoglycemia and hyperglycemia may cause epileptic seizures.[10] We excluded the effects of blood glucose dysregulation on seizures with the data of his blood glucose levels which were measured by his parents as in normal ranges or mildly high following the seizures. Epilepsy, especially temporal lobe epilepsy, and postictal or interictal psychosis may co-occur in autoimmune diseases.[11] Studies have demonstrated the presence of antibodies directed against synaptic autoantigens in approximately 10% of cases of sporadic epilepsy.[12] These antibodies may be associated with a purely psychiatric phenotype. Patients with postictal psychosis show higher levels of synaptic autoantibodies in serum than patients with epilepsy without psychosis.[12] Also vitamin B12 deficiency has been related to many neuropsychiatric symptoms such as psychosis, mania, depression, cognitive impairment, delirium, etc.[13,14] In our patient, psychotic symptoms alone may be related to schizophrenia diagnosis on its own, because psychotic symptoms alleviated in a short time with an antipsychotic regimen before antiepileptic and vitamin B12 treatments, and also might be associated or augmented with epilepsy and/or vitamin B12 deficiency. In addition in a scientific paper, PAS is disguised as a mental illness.[15] We also think that PAS, psychosis and/or schizophrenia, epilepsy, vitiligo, and pernicious anemia may all be a part of genetic autoimmune syndrome. In this case, we were unable to make a genetic analysis. We think further research on this topic may lead to new biological perspectives on the biology of schizophrenia as a psychotic disorder, epilepsy, and PAS.

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