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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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Contents

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Original Article

Surgical Approach to Paranasal Sinus Osteomas: Our Experience in 22 Cases

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ABSTRACT

Objective: Paranasal sinus (PNS) osteomas are rare, but the most common benign bone tumors of the paranasal region that can remain asymptomatic until reaching certain size are usually diagnosed incidentally. This study aimed to evaluate the factors that determine the surgical approach to PNS osteomas.

Methods: This retrospective study included 22 patients who underwent surgery for PNS osteoma between January 2012 and December 2018. Demographic characteristics, tumor location and size, symptoms, surgical techniques, and postoperative complications were analyzed retrospectively. The relationship between the location and size of the osteoma and the surgical approach was investigated.

Results: Of the 22 patients who underwent surgery for PNS osteoma, eight (36.3%) and 14 (63.7%) were women and men, respectively. The mean age of the patients was 39.1 years (range, 21–54 years). Based on their PNS location, osteomas were found in the ethmoid, frontal, maxillary, and both frontal and ethmoid sinuses in 10 patients (45.4%), eight patients (36.3%), three patients (13.6%), and one (4.5%) patient, respectively. The tumor was excised using the osteoplastic flap technique in five (22.7%) patients with frontal sinus osteomas larger than 2 cm in size. A combination of the Caldwell–Luc and transnasal endoscopic techniques was used in three (13.6%) patients with maxillary sinus osteomas. The tumor was excised using the lateral rhinotomy technique in one patient (4.5%) with a giant osteoma in the ethmoid sinus. Osteoma excision was performed using a transnasal endoscopic approach in the remaining 12 patients with ethmoid (n = 9) and frontal sinus (n = 3) involvement.

Conclusions: Although the tendency to perform minimally invasive and less morbid transnasal endoscopic approaches in PNS osteoma surgery is increasing, open surgical techniques and combined approaches should be preferred for ethmoid and frontal sinus osteomas with potential complications and which extend beyond the PNS boundaries. PNS osteoma size and localization, surgical equipment, endoscopic sinus surgery experience, and experience in open surgical techniques are the determinants for the surgical approach in PNS osteoma surgery.

Keywords: Osteoma, osteoplastic flap, paranasal sinus, transnasal endoscopic approach

INTRODUCTION

Osteomas are rare, slowly growing, and benign tumors of the paranasal region originating from bone tissue. Although it can be found in every age group, it is generally seen in the fourth and fifth decades and most frequently in men.[1] Paranasal sinus (PNS) osteomas, which are usually asymptomatic, are detected incidentally on radiographs or tomographies for other medical purposes. Although there is no consensus regarding the etiology of PNS osteomas, theories, such as infections, embryological developmental disorders, and trauma, have been proposed.[2,3] When PNS osteomas reach a certain size, they may cause various symptoms and findings depending on their location. Headache and facial pain are among the most common symptoms of PNS osteomas.[3–5] PNS osteomas can grow in the orbital structures and cause diplopia, proptosis, ptosis, and orbital pain. When they extend into the intracranial structures, life-threatening complications, such as cerebrospinal fluid (CSF) leakage, cerebral abscess, and meningitis, may occur.[4,6] Based on the histological types, osteomas are divided into three groups: (1) compact, (2) spongious, and (3) mixed types, and the most common form observed is the compact type.[7] Osteomas are most commonly located in the frontal sinus, and then, in the ethmoid, maxillary, and sphenoid sinuses with decreasing frequency.[6]

Although the definitive treatment for symptomatic PNS osteomas is surgical excision, follow-up is also recommended in asymptomatic cases.[7,8] Currently, there are two main approaches for the surgical treatment of PNS osteomas, open surgical techniques (osteoplastic flap, Caldwell–Luc, and lateral rhinotomy), and transnasal endoscopic techniques.[8–12] The authors aimed to present the clinical results in relation to patients who underwent surgery for PNS osteomas and to evaluate the factors that determine the surgical approach in the treatment of PNS osteomas.

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METHODS

This study included 22 patients with PNS osteoma in the Otorhinolaryngology Clinic of the Dr. Ersin Arslan Training and Research Hospital and the Otorhinolaryngology Department of the Faculty of Medicine of the University of Gaziantep between January 2012 and September 2018. The Gaziantep University local ethics committee approved the study protocol. A written informed consent was obtained from all patients. The medical records of the patients were analyzed retrospectively, including data such as age, sex, follow-up, localization, size of the osteoma, symptoms, surgical approach, and complications. Osteoma in all cases was diagnosed using computed tomography (CT) and confirmed by histopathological examination. Magnetic resonance imaging (MRI) was also used in certain cases where the osteoma had invaded the orbit and extended beyond the PNS. Preoperative CT images were examined, and a surgical approach was planned, depending on the location of the osteoma, its size, and whether it had spread beyond the PNS borders.

Depending on the location and size of the osteomas; transnasal endoscopic, lateral rhinotomy (external ethmoidectomy), Caldwell–Luc, and osteoplastic flap techniques were adopted. Combined surgical approaches using transnasal endoscopic and open surgical techniques were preferred in some cases where the osteoma could not be completely removed through the nasal cavity. All patients were operated under general anesthesia. In all patients, the tumor was removed without residues. In patients with giant osteomas in which the tumor could not be removed en bloc, the osteomas were fragmented using an otologic drill and then excised. In patients who underwent surgery using the transnasal endoscopic approach, the nasal mucosa and turbinates were decongested with 0.05% oxymetazoline hydrochloride-impregnated buffers preoperatively. Oxytetracycline hydrochloride pomade-mixed buffers were filled into the nasal cavity postoperatively. In patients with external skin incision, dressings were performed for 1 week, and the sutures were removed thereafter. In patients who underwent the Caldwell–Luc procedure, oral mucosal incisions were closed using absorbable sutures. All patients were administered postoperative prophylactic antibiotics and analgesics, if necessary. Nasal packs were removed on the third day, and the patients were called for a control examination at 3-day intervals in the first week, then once weekly for 2 weeks, followed by follow-ups at the end of the first month, sixth month, and 1 year. The mean postoperative follow-up was 15.8 months (minimum: 8 months and maximum: 27 months).

Main Points

- There are basically three different alternatives for paranasal osteomas: open and transnasal endoscopic approach and their combination.
- Appropriate approach should be determined according to the location and size of paranasal sinus (PNS) osteomas and the surgeon's experience.
- While surgical treatment is recommended for symptomatic PNS osteomas, incidentally detected PNS osteomas are followed.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis of the data. Descriptive and statistical analyses were performed. Results are presented as mean (±standard deviation), median (range), and per cent.

RESULTS

The medical records of 22 patients diagnosed with osteomas by postoperative histopathological examination were examined retrospectively. The most common types of osteomas were compact (n = 15), followed by mixed (n = 5) and spongious (n = 2) types. The clinical and demographic data of the patients are presented in Table 1. Of the 22 patients who underwent surgery for osteomas, eight (36.3%) and 14 (63.7%) were women and men, respectively. The mean age of the patients was 39.1 years (range, 21–54 years). Based on their location, osteomas were found in the ethmoid, frontal, maxillary, and both frontal and ethmoid sinuses in 10 patients (45.4%), eight patients (36.3%), three patients (13.6%), and one patient (4.5%), respectively. In one patient, ethmoid sinus osteoma had a retro-orbital invasion, causing diplopia and proptosis symptoms. Based on PNS CT measurements, osteoma sizes ranged from 0.5 to 7.5 cm, and the mean was 2.9 cm. The most common symptoms at the time of admission were headache (n = 14), followed by periorbital pain (n = 4), nasal obstruction (n = 2), proptosis and diplopia (n = 1), and facial pain (n = 1).

Osteomas were successfully excised completely using the transnasal endoscopic approach in 12 patients (54.5%), of which nine (40.9%) and one (13.6%) were located in the ethmoid and frontal sinuses, respectively. In patients who underwent transnasal endoscopic surgery, the mean osteoma size was 1.9 cm (range, 0.5–3.8 cm) and 1.5 cm (range, 0.5–2 cm) for ethmoid and frontal sinuses, respectively. The overall mean size of the osteomas removed using the transnasal endoscopic approach was 1.8 cm (range, 0.5–3.8 cm). Of the three cases of PNS osteomas removed using the transnasal endoscopic approach, two were in the frontal sinus inferior wall, and one was in the frontal sinus recess. In one case, a 3.8-cm ethmoid sinus osteoma, causing retro-orbital invasion and diplopia, was completely excised throughout the medial wall of the orbit by using the transnasal endoscopic approach (Figure 1). In the early postoperative period, proptosis and diplopia resolved rapidly without complications.

The osteoplastic flap technique was preferred in five (22.7%) patients with frontal sinus osteomas >2 cm. The mean size of frontal sinus osteomas excised using the osteoplastic flap approach was 3.9 cm (range, 2.3–5.5 cm). Of the five patients with excised using the osteoplastic flap approach, three had osteomas in the lateral wall of the frontal sinus, one had an osteoma on the posterior aspect of the frontal sinus, and one had an osteoma on the anterior wall of the frontal sinus. In three (13.6%) patients with maxillary sinus involvement, the osteomas originated from the maxillary sinus posterior wall in two patients and from the lateral wall in one patient. The Caldwell–Luc and transnasal endoscopic approaches were used in combination in three patients with maxillary sinus osteomas. A 4.5-cm ethmoid sinus osteoma was removed using the lateral

Table 1. Demographic and Clinical Characteristics of Patients with Paranasal Sinus Osteoma

Patients Number	Age (Years)	Gender	Osteoma Location	Size (cm)	Symptom	Surgical Approach	Follow-Up (Months)
1	21	Male	Ethmoid sinus	1.5	Headache	TE	12
2	37	Female	Ethmoid sinus	0.5	Nasal obstruction	TE	27
3	43	Male	Frontal sinus	2.3	Headache	OF	21
4	52	Male	Frontal sinus	2.5	Periorbital pain	OF	13
5	33	Female	Ethmoid sinus	2.5	Headache	TE	16
6	35	Female	Maxillary sinus	4.5	Headache	CL + TE	17
7	47	Male	Frontal sinus	2.5	Headache	OF	22
8	44	Male	Maxillary sinus	2.5	Nasal obstruction	CL + TE	8
9	38	Female	Ethmoid sinus	2.3	Headache	TE	11
10	37	Female	Maxillary sinus	4.5	Periorbital pain	CL + TE	21
11	54	Male	Frontal + ethmoid sinus	7.5	Headache	OF + TE	18
12	32	Female	Frontal sinus	2	Periorbital pain	TE	24
13	27	Male	Ethmoid sinus	2.5	Facial pain	TE	11
14	49	Female	Frontal sinus	0.5	Headache	TE	14
15	38	Male	Ethmoid sinus	4.5	Headache	LR	23
16	41	Male	Frontal sinus	6.5	Headache	OF	12
17	38	Male	Ethmoid sinus	1.5	Headache	TE	11
18	50	Male	Ethmoid sinus	1.2	Periorbital pain	TE	16
19	41	Male	Frontal sinus	2	Headache	TE	11
20	46	Female	Ethmoid sinus (retroorbital extension)	3.8	Propitozis + diplopia	TE	14
21	49	Male	Ethmoid sinus	1.5	Headache	TE	13
22	26	Male	Frontal sinus	5.5	Headache	OF	14

TE, transnasal endoscopic; CL, Caldwell–Luc; OF, osteoplastic flap; LR, lateral rhinotomy.

rhinotomy technique in one patient (4.5%). In one patient (4.5%), a 7.5-cm osteoma from the frontal and ethmoid sinuses was completely removed by fragments by using a combination of the osteoplastic flap and transnasal endoscopic techniques (Figure 2). Two patients who presented with nasal obstruction and diagnosed with PNS osteoma underwent both septoplasty and osteoma excision in the same session. The patients were hospitalized for 1 day postoperatively. Nasal tampons were removed after 48–72 hours, and the patients were followed-up by weekly controls every 3 days for the first week and thereafter for a month. Patients who underwent surgery using external approaches were advised to attend for controls every 2 days for dressing during the first week, then called for a weekly checkup for 1 month. Prophylactic oral penicillin was administered for 1 week postoperatively. None of the patients had intraoperative or early postoperative complications, such as CSF rhinorrhea, massive bleeding, periorbital hematoma, or PNS infection. In one patient who underwent surgery using the osteoplastic flap technique, a local soft tissue infection developed in the third postoperative month due to the titanium plate used for defect repair of the frontal sinus anterior wall. The local infection resolved with antibiotic treatment and did not recur during the 18-month follow-up period. One patient with frontal sinus osteoma resected using the osteoplastic flap approach had numbness in the forehead region.

DISCUSSION

Osteomas are asymptomatic until they reach a certain size; hence, small osteomas are generally diagnosed incidentally.

Figure 1. Osteoma surgery with orbital invasion by endonasal endoscopic approach. (a) Paranasal computed tomography (CT) image of the osteoma showing orbital invasion. (b) Paranasal CT image after osteoma excision with an endonasal endoscopic approach.

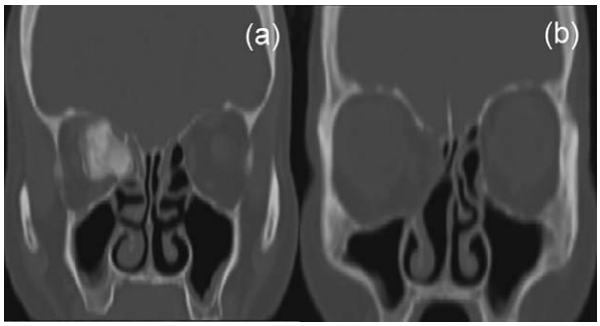
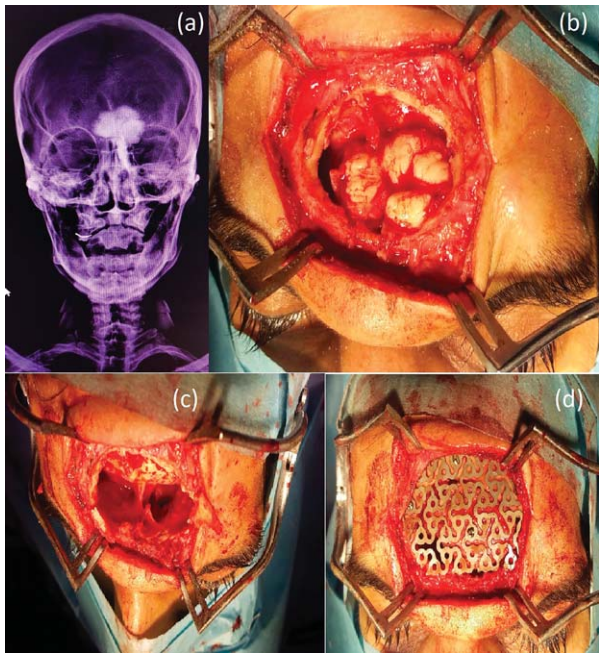


Figure 2. Fronto-ethmoid sinus osteoma resection via combination of osteoplastic flap and transnasal endoscopic technique. (a) X-ray view of the osteoma involving the frontal and ethmoid sinus, (b) intraoperative view of the giant osteoma, (c) appearance of the frontal sinus and frontal recess after osteoma removal, and (d) frontal sinus anterior wall reconstruction using titanium plate.



Symptoms and findings vary according to the location, size, and development rate, and direction of the osteomas.[6] Osteomas may cause diplopia, proptosis, and periorbital pain due to the involvement of orbital structures; meningitis, CSF rhinorrhea, and cerebral abscess due to intracranial spread; and chronic sinusitis and mucocele due to the disruption of drainage in the PNS.[8–10] Based on studies in the literature, the most commonly reported symptom of PNS osteomas is headache.[5,11,12] Nasal mucosal inflammation adjacent to the osteoma, chronic rhinosinusitis due to obstruction of the drainage pathways of the PNS, and compression effect on the structures around the osteoma are factors that may cause headache.[1,5] In our study, the most common symptom was pain in the head, face, and periorbital regions, which was consistent with the literature. Osteomas are generally diagnosed in the 40–50-year age group and are more common in men.[8] In this study, male predominance was determined, and age distribution was consistent with the literature. In terms of localization, PNS osteomas originate most frequently from the frontal sinus, followed by the ethmoid, maxillary, and sphenoid sinuses in decreasing frequency.[6,11,13] By contrast, in a prospective study with a large sample size, the authors argued that osteomas originate most frequently from the ethmoid sinus and then from the frontal, maxillary, and sphenoid sinus.[1] In our study, PNS osteomas were detected more frequently in the ethmoid sinus.

Although indications for the surgical treatment of PNS osteomas are controversial, there is a general consensus that surgical treatment should be performed for symptomatic patients and rapidly growing osteomas.[14,15] Savić and Djerić[8] suggested several indications for the surgical treatment of osteomas from the frontal and ethmoid sinuses, including osteomas extending beyond the frontal sinus boundaries, fast-growing osteomas, disruption of drainage of PNS, nasolacrimal duct involvement, and headache. Georgalas et al.[16] indicated that surgical treatment should be performed in cases where osteomas completely obstruct the frontal recess, cause orbital and neurological symptoms due to intraorbital and intracranial extensions, if the growing osteomas occupies >50% of the space in the frontal sinus. Although it is widely accepted that patients with asymptomatic PNS osteomas diagnosed incidentally should be followed-up because they show very slow growth characteristics, in the literature, studies advocating surgical treatment of asymptomatic PNS osteomas also exist as their increasing size may cause potential complications in the later stages of life.[14] In this study, surgical excision was performed in all symptomatic patients with PNS osteoma detected by PNS CT. PNS CT is the gold standard imaging modality for the diagnosis of osteomas. Compact osteomas appear as smooth, hyperdense, noncontrast-enhancing masses on CT. Spongious and mixed types of osteomas are denser than the surrounding bone tissue and appear as heterogeneous bone masses on a CT with partial contrast enhancement.[1] In addition, the most appropriate approach in the follow-up of asymptomatic patients who did not undergo surgery is a periodic evaluation with PNS CT. MRI is recommended to evaluate soft tissue in patients with orbital involvement and intracranial extension of osteomas.[10]

Surgical options for PNS osteomas can be classified into three main groups: open, closed (transnasal endoscopic), or a combination of these. Although the surgical approach is not standard for the surgical treatment of PNS osteomas, the surgical approach can be determined preoperatively according to the location and size of the tumor and the surgeon's experience with surgical techniques. Open surgical options include

alternative approaches, such as lateral rhinotomy and external ethmoidectomy for complicated osteomas located in the ethmoid sinus, Caldwell–Luc for osteomas located in the maxillary sinus, and osteoplastic flap or bicoronal flap techniques for osteomas >2 cm in the frontal sinus.[14] All large osteomas outside the frontal sinus can be safely removed in one piece or by fragmentation with the endonasal endoscopic approach.[15] Although open surgical approaches have advantages, such as better surgical vision, ability to use both hands simultaneously, and easier intervention for possible complications, such as bleeding and CSF rhinorrhea, they have several disadvantages compared with the transnasal endoscopic approach, such as being more invasive and resulting in visible scarring due to external surgical incisions, causing higher postoperative pain, resulting in prolonged hospital stays and high postoperative morbidity.[16]

The osteoplastic flap and bicoronal flap techniques, which are commonly used, are open surgical methods that provide shorter operative times, wider areas for surgical intervention, and excellent surgical exposure for frontal sinus located osteomas >2 cm.[14,15] Open surgical approaches allow the complete removal of frontal sinus osteomas without residues; moreover, they provide easier repair of complications, such as defects in the posterior wall of the frontal sinus and CSF rhinorrhea.[15] Despite these advantages, pain and loss of sensation in the frontal region, scar on the skin due to surgical incisions, pain, and cosmetic deformity are among the most important disadvantages of open surgical techniques.[16] In our study, a titanium plate was used to repair the bone defect in the anterior wall of the frontal sinus in a patient who underwent osteoma excision with the osteoplastic flap approach, and a late postoperative soft tissue infection due to the presence of the titanium plate, which was treated with systemic oral antibiotics. In another patient who underwent excision of a frontal sinus osteoma with the osteoplastic technique, a transient temporary loss of sensation in the frontal region improved spontaneously within 6 months postoperatively.

The transnasal endoscopic approach, which offers minimally invasive surgery for the treatment of PNS osteomas, has been increasingly adopted in appropriate cases. Compared with open surgical techniques, the transnasal endoscopic approach results in scarless surgery, less pain, shorter hospital stays, low postoperative morbidity rates, and lower complication rates.[12,13] However, Rokade and Sama reported that the endoscopic transnasal approach is quite risky and challenging in patients with osteomas that fill >75% of the frontal sinus and erode the posterior wall of the frontal sinus or in patients with a history of meningitis and CSF rhinorrhea.[12] After endoscopic surgery, the anatomical structures of the nose and the drainage pathways of the sinuses were significantly preserved, and consequently, no deterioration of PNS function was observed. Castelnuovo et al.[17] reported that the transnasal endoscopic approach is not appropriate for the surgical treatment of patients with PNS osteomas, exceeding the ethmoidal sinus boundaries and showing orbital invasion, osteomas not arising from the inferior wall of the frontal sinus and frontal recess, or osteomas in the anterior or inferior maxillary sinus and >2 cm in size. In addition, the transnasal endoscopic approach is not an appropriate surgical technique for PNS osteomas that erode the posterior wall of the frontal sinus and show intracranial extension. By contrast, some studies suggest that transnasal endoscopic excision of large osteomas in the frontal sinus and osteomas in the upper medial wall of the maxillary sinus is feasible in suitable cases with large frontal recesses.[18] Seiberling et al.[19] reported that they successfully performed surgery in 23 patients with large frontal sinus osteomas with the transnasal endoscopic approach. Although the transnasal endoscopic technique has many advantages, it is not considered an appropriate option in intraorbital and intracranial extension osteomas due to the possibility of complications, such as intraorbital hemorrhage and CSF rhinorrhea. Although it is endoscopically possible to intervene in complications, such as CSF rhinorrhea and periorbital hemorrhage, it increases morbidity.[17,18] However, in our study, in a patient with a 3.8-cm osteoma with retro-orbital invasion exceeding the ethmoid sinus margins, the tumor was successfully removed completely using the transnasal endoscopic approach. Although the size and location of the osteoma have an impact on determining the surgical approach, the experience of the surgeon performing the surgery is also an important determining factor in choosing the surgical approach.

Finally, in this study, tumor excision was successfully performed using the transnasal endoscopic approach in patients with osteomas not exceeding 2 cm in size located in the frontal sinus inferior wall and recess. The tumor was excised using the osteoplastic flap approach in patients with osteomas >2.5 cm in size and located in the posterior and lateral regions of the frontal sinus. PNS osteoma was excised by using lateral rhinotomy in a patient with ethmoid sinus involvement and lateral extension. Serious major complications, such as periorbital hemorrhage, orbital injury, and CSF rhinorrhea, did not occur. In a patient who underwent open surgery for giant frontal sinus osteoma, soft tissue infection was developed in the third postoperative month due to the titanium plate used to defect repair and was treated with systemic oral antibiotics. During the follow-up period, no complications, such as reactions to a foreign body or explanation related to titanium plate use, were observed.

CONCLUSION

Open, transnasal endoscopic, and combined approaches for PNS osteomas have been described, and the decision regarding the surgical approach is determined based on the tumor location, size, and invasion to adjacent structures. Although there has been an increased tendency to apply the transnasal endoscopic approach in PNS osteoma surgery in recent years, open surgical techniques and combined approaches should be preferred for ethmoid and frontal sinus osteomas exceeding the PNS boundaries and have a potential for complications. In selecting the surgical approach, size and localization of the osteoma, surgical equipment, and surgeon's experience in endoscopic sinus surgery and open surgical techniques are also determinant factors.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University.(Approval date/number : 27.03.2017/88)

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.M., S.G.; Design - S.G., A.T.; Supervision - S.M., S.G.; Resources - A.T., S.G.; Materials - S.G., A.T.; Data Collection and/or Processing - S.G., A.T.; Analysis and/or Interpretation - S.G., A.T.; Literature Search - S.G., A.T.; Writing Manuscript - S.G., A.T., S.M.; Critical Review - S.M., S.G.; Other - S.G., A.T., S.M.

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Original Article

Can Chemotherapy Induced Cardiomyopathy Be Detected from Pretreatment Platelets to Lymphocytes Ratio?

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ABSTRACT

Objective: In this study, we aimed to identify patients at risk of chemotherapy-induced cardiotoxicity with a simple method like platelet-to-lymphocyte ratio (PLR) before starting therapy.

Method: A total of 65 breast cancer patients who completed anthracycline or adjuvant trastuzumab treatment were evaluated retrospectively. Serial PLR calculations, echocardiographic examinations, and cardiac markers before treatment and after follow-up period were analyzed. Cardiotoxicity was determined according to Cardiac Review and Evaluation Committee Criteria.

Results: Patients were divided into two groups according to their baseline PLR levels as Group C—PLR $<$ 119 and Group D—PLR $\geq$ 120. The median follow-up of the study was 22.23 (12-42) months. Concomitant disease and baseline characteristics were similar in both groups. Symptomatic cardiotoxicity was not observed in both groups. Cardiotoxicity was occurred in one patient (2.3%) in Group C and in four patients (9.5%) in Group D ($P = .005$). Average mean left ventricular ejection fraction loss from baseline was 10.7 $\pm$ 7.0% in Group D vs 2.3 $\pm$ 6.4% in Group C ($P = .008$). Interpretation of cardiac markers that were present in nearly half of the patients revealed that serum hs-c-reactive protein and pro-brain natriüretic peptide levels were significantly higher in patients who developed cardiotoxicity compared to who did not develop cardiotoxicity. PLR $\geq$ 120 had 99% sensitivity and 85% specificity in predicting cardiotoxicity.

Conclusion: This study's results showed that high PLR levels were associated with chemotherapy-induced cardiotoxicity. To our best knowledge, this is the first study, examining the impact of whole blood test on chemotherapy-induced cardiotoxicity before starting the therapy and allowing doctors plot a route for these risky patients.

Keywords: Breast cancer, cardiotoxicity, chemotherapy, platelets-to-lymphocytes ratio

INTRODUCTION

Aged people are increasing as a consequence of better living conditions and improved technological development in our country as in the world. The incidence of malignancy especially breast cancer in women and, hence, the chemotherapy-treated patients is increasing with ages.[1] Apparently in the near future, cancer patients and also chemotherapy-treated patients will increase. The anthracycline and trasthuzumab therapy has been shown to improve survival in breast cancer patients.[2] According to the large retrospective studies, apparent reductions were recorded in mortality with these chemotherapeutic agents.[3–5] Although the drugs are highly effective in treatment, silent and severe cardiac side effects make to stop the therapy and limit the therapy effectiveness.[6,7] An effective parameter is not currently available to detect the cardiotoxicity.

PLR is a novel biomarker showing inflammation in cardiac and noncardiac patients. T and B lymphocytes and platelets secrete proinflammatory substances such as chemokines and cytokines are suggested to play a prominent role in the development and progression of many cancer types. PLR is a fast, simple, and cheap biomarker, showing inflammation in cardiac and noncardiac patients and widely studied in many subjects and found as an independent predictor for cardiac complications and prognosis.[8–15] In this study, we planned to find out patients with the risk of cardiotoxicity before starting the therapy with a simple whole blood test.

METHODS

Consent was obtained from the patients in accordance with the Declaration of Helsinki for participation. This study was approved by the Ankara Numune Education and Research Hospital Ethics Committee on March 5, 2017 (study number 2017E- 18)

The demographic characteristics including age, gender, history of arterial hypertension, diabetes mellitus, tobacco use, body mass index, past medications menopausal history, treatment history, beginning and ending time of treatments, timing of

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hormonal and chemotherapeutic treatments, and history of comorbid disease are presented in Table 1, and serum levels of fasting blood glucose, hemogram, c-reactive protein (CRP), and a lipid panel including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels are all evaluated and shown in Table 2. Baseline and control echocardiographic left ventricular ejection fraction (LVEF) measurements and echocardiographic data are presented in Table 3. All data were analyzed retrospectively. Patients with heart failure, significant valvular disease, cardiomyopathy, uncontrolled hypertension, abnormal hepatic and renal functions, active infection, chronic inflammatory disease, chronic obstructive pulmonary disease, other malignancies, previous use of chemotherapy, and radiotherapy and immunotherapy patients were excluded. Recurrent or metastatic patients and severely ill patients were also excluded from the study. The PLR was calculated before and after 6 months of treatment. Institutional ethics committee approval was obtained. Cardiotoxicity was defined according to Cardiac Review and Evaluation Committee definition as an absolute decline of LVEF of 5% to <55% with symptoms of HF or an asymptomatic reduction of LVEF of 10% to <55%.[16]

The long and short axis parasternal and apical views, two-dimensional, M-mode, pulsed, and color flow Doppler echocardiographic examinations in the left lateral decubitus position were done using a Vivid 5, GE Vingmed, Horten, Norway, 2–4 mHz phased array transducer. Left ventricle end-diastolic (LVEDD), left ventricle end-systolic (LVESD), LVEF, mitral inflow indices as the peak early filling (E peak) and late diastolic filling (A peak) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the isovolumic relaxation time (IVRT) were present in echocardiography reports.

An automated blood cell counter (ADVIA 2120i Hematology System, Siemens Healthcare Diagnostics, Deerfield, IL) was used in hematology laboratory. A Cobas E-601 analyzer (Roche Diagnostics, Mannheim, Germany) using electrochemiluminescence immunoassay was used in vitro CK-MB, pro-brain natriüretic peptide (BNP), and Troponin I and high-sensitive (hs) Troponin T analyses. A Hitachi Modular P800 analyzer (Roche Diagnostics, Mannheim, Germany) was used to measure the hs-CRP.

Main Points

- We aimed to identify patients at risk of chemotherapy-induced cardiotoxicity with a simple method like platelet-to-lymphocyte ratio (PLR) before starting therapy. Because cardiotoxicity is a therapy limiting factor in cardio-oncology.
- We planned this study to find out any possible association between PLR and cardiac complications.
- For the first time, the study results showed a possible correlation between PLR and cardiotoxicity.
- With this knowledge, we can predict the patients at cardiotoxicity risk and change if possible the chemotherapeutic agent or lower the dose.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Variables were analyzed using the Kolmogorov–Smirnov test. Categorical variables were presented as percentages, and parametric variables were presented as mean ± standard deviation. Nonparametric variables were expressed as median (minimum – maximum). The normally distributed numeric variables were analyzed using the Student's t-test, and non-normally distributed variables were evaluated by the Mann–Whitney U test variance analysis. The categorical variables were compared with Chi-square test. P value $< .05$ was accepted as statistically significant.

RESULTS

This study was consisted of a total of 65 patients with breast cancer completed at least ≥6 months an anthracycline-containing regimen setting weekly doxorubicin (24 mg m^{-2} IV) with daily oral cyclophosphamide (60 mg m^{-2} PO) for 12 weeks, and in 11 of 65 patients, taxanes were added to the regimen. Patients' demographic characteristics were listed in Table 1. The median follow-up of the study was 22.23 (12-42) months and was not significant between two groups ($P = .34$). Of the enrolled patients, 29 (28.57%) patients were PLR < 119 in Group C and 36 (47. 61%) patients were PLR ≥ 120 in Group D. The median age was 48.1 ± 7.7 years (35-69) for Group D, whereas it was 46.2 ± 8.6 years (32-67) for Group C ($P = .47$). These accompanying chronic diseases were similar in both treatment groups. Histology of the primary tumor, lymphovascular invasion, perineural invasion, extracapsular extension, and histological grade and type of surgery were similar and not statistically significant in both groups.

Baseline LVEF values were 65.5 ± 3.4% and 67.1 ± 4. 5% in Group C and Group D, respectively ($P = .13$). Symptomatic heart failure was not observed during treatment in both groups. All echocardiographic results were presented in Table 2. Asymptomatic LVEF decline was observed in one (2.3%) and four (9.5%) patients in Group C and Group D, respectively ($P = .005$). The incidence of LVEF decline was significantly higher in Group D ($P < .001$). The lowest LVEF values during treatment were 64.3 ± 3.9% and 58.6 ± 6.7% in Group C and Group D, respectively ($P = .01$). Mean LVEF values decreased below 50% for two patients in Group D, and all of them had been treated with heart failure medications. In the subgroup analyses, no association was found between cardiotoxicity and hypertension ($P = .54$), hyperlipidemia ($P = .69$), diabetes ($P = .59$), obesity ($P = .79$), total anthracycline dose ($P = .68$), and family history of coronary artery disease ($P = .68$). Despite the risk of cardiotoxicity was increased with advanced age >60 years ($P = .08$) and with a combination of taxane and anthracycline regimens ($P = .07$), this risk was not significant. Baseline mean LVEF values were similar in Group C and Group D. Mean LVEF was 64.3 ± 2.7% and 63.8 ± 3.2% in Group C and Group D ($P = .29$), respectively. Average mean LVEF loss from baseline was significantly higher in Group D than Group C (10.7 ± 7.0% vs 2.3 ± 6.4%, HR: 1.46; 95% CI: 1.17 to 1.73; $P = .008$). As shown in Figure 1, patients with cardiotoxicity had significantly higher PLR values lower lymphocyte counts than those with cardiotoxicity not observed group. In the subgroup

Table 1. Baseline Demographic Characteristics of the Study Population

Variables	Group C, n (%); 29 (44.61%)	Group D, n (%); 36 (55.38%)	*P*
Age, years; median	48.1 ± 7.7 (35-69)	46.2 ± 8.6 (32-67)	.47
Diabetes mellitus, n (%)	5 (7.65)	7 (10.7)	.24
Hypertension, n (%)	17 (26.15)	19 (29.23)	.19
Hyperlipidemia, n (%)	5 (7.69)	6 (9.03)	.23
Family history with cancer, n (%)	14 (21.53)	13 (20.0)	.32
Grade, n (%)			
I	4 (6.15)	3 (4.61)	.67
II	8 (12.30)	13 (20.0)	.48
III	17 (26.10)	20 (30.70)	.56
T-Stage at diagnosis, n (%)			
T1	2 (3.07)	3 (4.61)	.56
T2	15 (23.07)	17 (26.15)	.67
T3	7 (10.7)	13 (20.20)	.65
T4	5 (7.65)	3 (14.61)	.54
Chemotherapy, n (%)			
Anthracycline	18 (27.69)	24 (36.9)	.65
Anthracycline + taxanes	11 (16.9)	13 (20.0)	.47
Hormonal treatment, n (%)			
No	9 (13.8)	13 (20.0)	.23
Yes	20 (30.7)	23 (36.38)	.45
Prior medication, n (%)			
Beta-blocker, ACE inhibitor	4 (6.67)	7 (10.7)	.32
ARB	5 (7.69)	4 (6.67)	.65
Calcium-channel blocker	2 (3.07)	3 (4.61)	.56
Statin	1 (1.65)	2 (3.07)	.67
	4 (6.67)	3 (4.61)	.45

Data are expressed as mean ± standard deviation (SD) for continuous variables and as percentages for dichotomous variables. P-values denote overall differences between groups.

analyses, mean LVEF was significantly lower in patients who developed cardiotoxicity during treatment compared to who did not develop (61.9 ± 3.6% vs 64.4 ± 2.6%, $P = .01$). Baseline LVEF values were significantly higher in patients who developed cardiotoxicity compared to who did not develop cardiotoxicity (69.0 ± 5.5% vs 65.6 ± 3.3%, $P = .01$). No significant differences were found in other echocardiographic measurements between both groups. Cardiac biomarkers such as hs-CRP, CK-MB, troponin I, troponin T, and pro-BNP were present in nearly half of the patients, and levels were shown in Table 4. Serum hs-CRP and pro-BNP levels were significantly higher in patients who developed cardiotoxicity compared to who did not develop cardiotoxicity (HR: 1.58; 95% CI: 1. 25 to 2. 01; $P = .001$) as shown in Figure 2.

Table 2. Biochemical and Hematological Measurements of the Study Population

Variables	Group C (n = 29)	Group D (n = 36)	*P*
Hemoglobin (g dL^{-1}) median (IQR)	14.3 (12.7–15.8)	13.9 (12.1–16)	.184
WBC ($\times 10^3$ μL^{-1}), mean ± SD	8.4 ± 3.9	7.2 ± 3.7	.062
Lymphocyte ($\times 10^3$ μL^{-1}), mean ± SD	2.0 ± 1.1	1.7 ± 1.2	.035
Platelet ($\times 10^3$ μL^{-1}), mean ± SD*	213 ± 65	254 ± 59	.001
PLR, median (IQR)	100 (86–119)	129 (120–154)	<.001
Creatinine (mg dL^{-1}), mean ± SD	1.1 ± 0.4	1.1 ± 0.3	.655

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
IQR, interquartile range; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; TG, triglyceride; WBC, white blood cell.

Table 3. Comparison Echocardiographic Findings between Group C and Group D

Characteristics	Group C (n = 29)	Group D (n = 36)	*P*
LVEDD (3.5–5.8 cm)	4.2 ± 0.4	4.0 ± 0.4	.87
LVESD (2.45–4.1 cm)	2. 7 ± 0.3	2.9 ± 0.3	.26
Baseline LVEF (%)	65.5 ± 3. 4	67.1 ± 4.5	.13
Control LVEF (%)	65.3 ± 3. 1	62.8 ± 3. 2	.29
Average LVEF loss (%)	2.3 ± 6.4	10.7 ± 7.0	.008
E peak velocity (m sn^{-1})	10. 4 ± 0.48	1.03 ± 0.38	.31
A peak velocity (m sn^{-1})	0.77 ± 0.19	0.75 ± 0.15	.46
E/A ratio	0.85 ± 0.22	0.87 ± 0.28	.85
IVRT (msn)	95.5 ± 20.0	94.9 ± 16.7	.31
PAP (mm Hg^{-1})	26.4 ± 5.8	28.0 ± 4.7	.59

A peak, late diastolic filling velocity; E peak, early diastolic filling velocity; IVRT, isovolumic relaxation time; LVEDD; left ventricle end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter; PAP, pulmonary artery pressure.
Values are median (interquartile range) or n (%).

Finally, ROC analysis was performed in cardiotoxicity and non-cardiotoxicity groups to detect the cutoff value of PLR for predicting cardiotoxicity. The cutoff value of PLR on admission to predict cardiotoxicity in all study population was 96, with a sensitivity of 69% and 68% and a specificity of 65% and 66%, respectively (area under curve = .675 and .700, *P* <.001 and <.001, respectively; Figure 3).

DISCUSSION

Many chemotherapeutics agents like anthracyclines have been associated with severe early and late cardiovascular side effects that started mainly in the early stage of therapy within a wide range of symptoms from nonspecific symptoms to cardiogenic shock. Clinicians' subsequent experience with anthracyclines has demonstrated considerable cardiotoxicity even at low doses, making them frightened to use them at therapeutic level. Consequently, patients were left with incomplete therapy and added new cardiovascular problems. Diagnosis of acute and late cardiotoxicity from cancer therapeutics has become increasingly important, and several studies were done to evaluate the risk, as cancer evolved into a chronic disease with new drugs and surgery techniques that require a life-long lasting therapy and need a long-term follow-up for ongoing cardiovascular toxicity. As more patients with cancer are treated, achieve remission, and enter survivorship, there is a need to monitor those at risk and to design best therapy for them.

Figure 1. PLR values of the study groups.

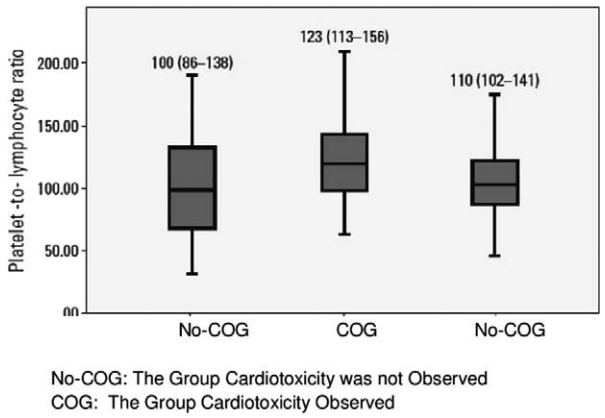
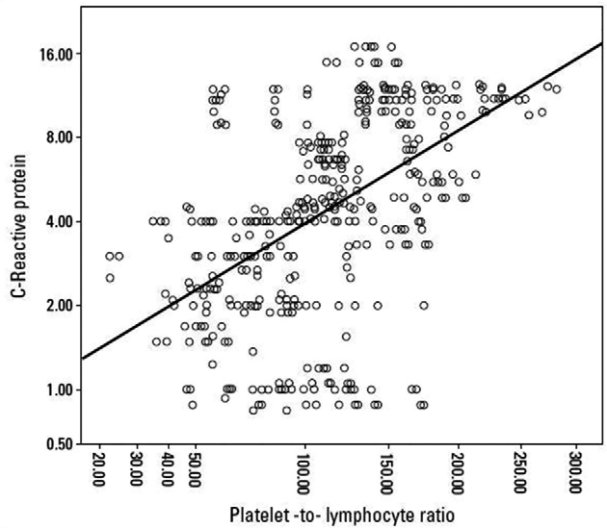


Figure 2. Correlation of PLR and hs-CRP values.



In the United States, cancer survivors are estimated to be by nearly 11 million: it will be 26.1 million in 2040, and only 18% of patients will be between the ages of 50 and 64 years and 8% will be younger than age 50 years.[17] Thus, the older population became the largest proportion of survivors requiring more imaging and treatment approaches for diagnosis and follow-up.

The incidence of toxicity reported in the larger trials is 4.1-35.4%.[18–24] There are insufficient data about predicting the cardiotoxicity in these patients. Although many studies were done to define the risky group, any clear evidence was not present at the moment.[25,26] Newly completed study results showed a correlation between cardiac and inflamamtory markers as troponins (TnI), myeloperoxidase and hs-CRP, and cardiotoxicity, but study investigators claimed that their study results needed more confirmative studies.[27]

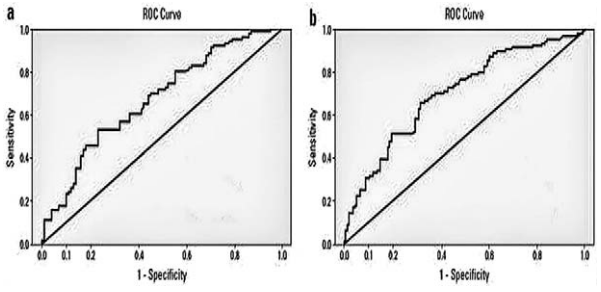
Although the exact mechanism of cardiac toxicity is not yet fully understood, autopsy studies of patients' cardiotoxicity showed myocarditis with the infiltration of predominantly platelets, macrophages, and lymphocytes, and the chemokines causing the cell death. These inflammatory molecules are overexpressed, which might contribute to cardiac injury.[28] Patients with multiple diseases hemograms demonstrated increased neutrophil, monocyte, and platelet counts. Several studies reported a strong association between inflammation and cancer and various other chronic diseases and correlate positively with other markers of systemic inflammation, particularly with NLR and PLR.[29,30] They served as a laboratory marker for predicting various neoplastic, prothrombotic, and metabolic diseases in clinical practice.[31] In fact, PLR gives information about both aggregation and inflammatory pathways that can be superior to the platelet or lymphocyte counts alone for the prediction of cardiotoxicity since both inflammation and endothelial damage play a role in the pathogenesis of the disease. Some small studies also have shown an association between high PLR and NLR levels and heart failure.[32]

Table 4. Comparison Long-Term Cardiac Biomarkers in Group C and Group D

Characteristics	Group C (n = 29)	Group D (n = 36)	*P*
Troponin I (ng mL^{-1})	0.5 (0.0-0.1)	0.3 (0.0-0.1)	.15
CK-MB (ng mL^{-1})	1.57 (0.53-6.0)	1.61 (0.5-7.1)	.43
hs-CRP (mg L^{-1})	3.24 (0.5-29.7)	4.12 (0.27-41.3)	.001
pro-BNP (pg mL^{-1})	64.8 (33-550)	116 (69-880)	.001

hs-CRP, high-sensitive CRP; CK-MB, creatine kinase MB; pro-BNP, pro-brain natriüretic peptide.

Figure 3. ROC analysis of PLR for predicting cardiotoxicity in patients with (a) no change in LVEF values and (b) in patients with decreased LVEF values.



We hypothesized that PLR could be associated with chemotherapy-induced cardiotoxicity. There are no prior data testing pretreatment PLR and detection of cardiotoxicity. Our findings suggested that a PLR of >96 was significantly correlated with chemotherapy-induced cardiotoxicity. Besides its close relation with chemotherapy-induced cardiotoxicity, PLR also had a positive correlation with serum CRP and BNP level in our study, which supported its role in systemic inflammation. From a clinical point of view, PLR may be used as a predictor of chemotherapy-induced cardiotoxicity as a new inflammatory marker in daily clinical practice.

Our study had some limitations; first it is a retrospective study; therefore, we could analyze the available parameters in data for cardiotoxicity and also could not analyze the follow-up data adequately. Second, only a small number of our patients had the cardiac enzymes and inflammatory markers other than CRP, such as IL-6, TNF-a, and MMP, which were not analyzed and, therefore, not compared with PLR. Third, we had analyzed one blood sample, and repeated analysis was not done. This study is not the first to use echocardiography to assess cardiac functions, but we did not employ speckle tracking techniques like strain parameters to evaluate the cardiotoxicity and RV function, and this is another limitation. Finally, our study group was a relatively small group, that is why our subgroup analysis was inadequate.

Besides, chemotherapy-induced cardiac side effects are more dramatic than other side effects; doctors avoid from chemotherapy and do not want their patient to compel with therapy-induced another disease at an expense of mortality.[33,34]

CONCLUSION

The need to diagnose cardiotoxicity rapidly and efficiently is of great concern to involved clinicians and must be aware of these adverse events due to their high fatality rate. A high level of clinical suspicion and early diagnosis indicators are required due to the rapid progress and fulminant course of the disease. The assessment of clinical features in combination with laboratory examinations, ECG, TTE, CMR, and EMB, contributes to the diagnosis of cardiotoxicity.

Our study has shown the relationship between pretreatment PLR level and the development of cardiotoxicity, demonstrating PLR is a powerful and independent predictor of cardiotoxicity in breast cancer patients. Patients were at greater risk of toxicity in the higher PLR vs lower PLR group (30.3% vs 1.9%, $P < .001$).

Finally, our results suggest that more sensitive methods needed to detect LVEF decrease, and a multimarker approach may increase the sensitivity of cardiotoxicity risk prediction in patients treated with chemotherapeutic agents.

Ethics Committee Approval: This study was approved by the Ankara Numune Education and Research Hospital Ethics Committee on March 5, 2017 (study number 2017E- 18).

Informed Consent: Consent was obtained from the patients in accordance with the Declaration of Helsinki for participation.

Peer-review: Externally peer-reviewed.

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

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Original Article

Importance of the Diastolic Flow Reversal Parameters on Quantitation of Aortic Regurgitation

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ABSTRACT

Objective: Aortic regurgitation (AR) is one of the common cardiac valve diseases in the world. Grading the severity of chronic AR is quite critical. Despite the several clinical and echocardiographic data used, AR quantitation still remains challenging today. Findings obtained from the previous studies suggest that not only the duration of the retrograde flow but also the speed of the retrograde flow and diastolic velocity time integral (dVTI) may be associated with the AR grade. In our study, we aim to investigate the relationship and importance of the diastolic flow reversal parameters in the aorta with the grading of aortic regurgitation.

Method: The study is designed as a single-center observational study for the evaluation of dVTI and end-diastolic flow velocity (EDFV) parameters in AR grading. A total of 93 patients were included in our study after exclusion criteria. Patients were divided according to the aortic regurgitation degree into three groups as mild (n = 33), moderate (n = 21), or severe (n = 39). Echocardiographic acquisitions were done. Pulse wave velocity measurements were recorded in the descending aorta by positioning ultrasound rays parallel to the flow in the aorta and EDFV and dVTI parameters were determined.

Result: According to echocardiographic measurements; between the groups; dVTI in the mild, moderate and severe AR groups were (8.5 ± 2.4, 12.8 ± 5.8, 17.4 ± 6.2 cm, respectively, $P < .001$), and EDFV in the mild, moderate, and severe AR groups were (0.11 ± 0.11, 0.10 ± 0.11, and 0.24 ± 0.13 m/s, respectively, $P < .001$), statistically significant different.

Conclusion: In the light of the data obtained in our study, echocardiographic evaluation of the diastolic flow reversal profile in the descending aorta in patients with chronic AR and dVTI and EDFV measurements can contribute to AR grading.

Keywords: Aortic Valve Insufficiency, Heart Valve Diseases, Diagnostic Imaging, aortic valve diseases

INTRODUCTION

Aortic regurgitation (AR) is one of the common cardiac valve diseases in the world. Although there are many factors in AR etiology, valve degeneration and annuloaortic ectasia are the most common causes. Rheumatic heart disease protects its importance as etiological reason in developing countries.[1,2]

Echocardiography is the key method for the diagnosis of AR. Echocardiography may suggest opinions on several issues such as etiological factor, valve and aortic structure, bicuspid/tricuspid valve discrimination, grade of insufficiency, and ventricular dimensions.

Grading the severity of chronic AR is quite critical as it gives ideas about prognosis and determines the follow-up periods of the patients and more importantly, the timing for surgery required to be performed prior to the development of left ventricular (LV) dysfunction. Despite the several clinical and echocardiographic data used, AR quantitation still remains challenging today.

Several parameters (effective regurgitant orifice area, regurgitant volume, Jet/left ventricular outflow tract ratio, vena contracta, holodiastolic flow reversal, LV dilatation, and AR pressure half time [PHT]) obtained through two-dimensional (2D) echocardiography are used in quantitation.

Retrograde diastolic flow in the aorta is observed in most of the patients with chronic AR. The duration, peak speed, end-diastolic flow velocity (EDFV), and diastolic velocity time integral (dVTI) measurements of the flow reversal observed in the aorta have been addressed in certain studies and have been

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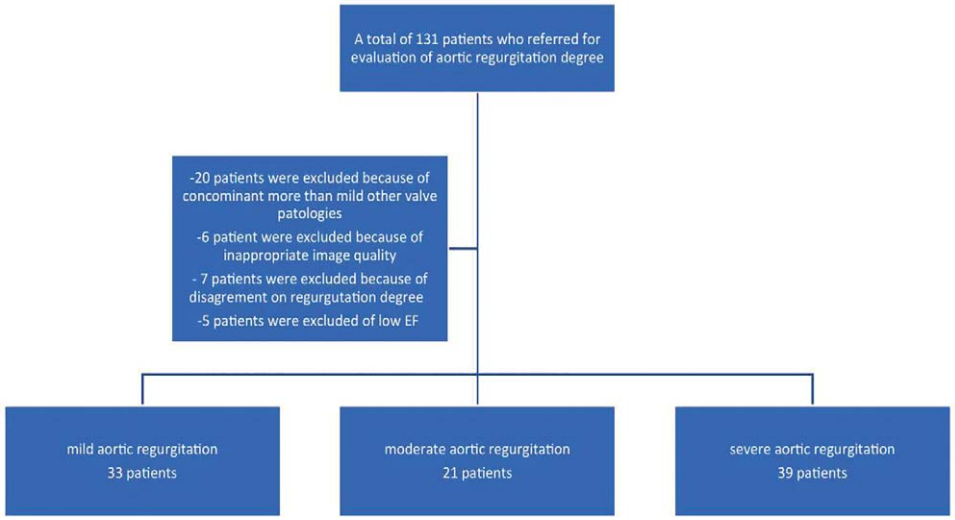
Figure 1. Flow diagram of study patients.



suggested that they can be a guide for aortic insufficiency grading.[3–5]

"Holodiastolic flow reversal" which is defined as retrograde flow seen in the aorta throughout the whole diastole is one of the important parameters used in the advanced assessment of AR. Findings obtained from the previous studies suggest that not only the duration of the retrograde flow but also the speed of the retrograde flow, and dVTI may be associated with the AR grade. In our study, we aim to investigate the relationship and importance of the diastolic flow reversal parameters in the aorta with the grading of aortic regurgitation.

METHODOLOGY

Study Protocol

The study is designed as a single-center observational study for the evaluation of dVTI and EDFV parameters in AR grading and the local ethics committee approval (22.09.2020/3) was obtained. All AR patients who apply to the echocardiography laboratory of our hospital within 6 months and meet the exclusion and inclusion criteria were included in the study sequentially. All patients were informed about the study and their consents were obtained. A total of 131 patients were evaluated in our study. Of these, 20 patients were excluded from the study due to accompanying additional valve pathology, 6 patients were excluded due to inadequate image quality, 5 patients were excluded since their EF value was detected under 50%, and 7 patients were excluded due to the conflict of the experts evaluating on insufficiency grade. In addition, 93 patients were included in our study after exclusion criteria (Figure 1). Patients were divided according to the aortic regurgitation degree into three groups as mild (n = 33), moderate (n = 21), or severe (n = 39). Patients with acute AR or decompensated valvular failure, other concomitant valvular disease of more than mild in severity, chronic pulmonary obstructive disease, previous cardiac or valve surgery, reduced left ventricular ejection fraction (LVEF; $\leq$50%), known ischemic heart disease, atrial fibrillation, and inadequate echocardiographic data for 2D-speckle tracking echocardiography analysis were excluded. The study population chart was shown in Figure 1.

Main Points

- Aortic regurgitation (AR) is one of the common cardiac valve diseases in the world and grading the severity of chronic AR is quite critical.
- Despite the several clinical and echocardiographic data used, AR quantitation still remains challenging today.
- Main findings of our study are diastolic flow reversal end-diastolic flow velocity in the aorta is higher and different in severe AR compared to mild and moderate AR and diastolic velocity time integral increases linearly with the AR grade and is different between AR patient groups.
- In the light of the data obtained in our study, diastolic flow reversal profile in the aorta can be a guide in addition to the current parameters in AR grading.

Physical Examination and Echocardiography

A complete physical examination was performed by obtaining clinical history and anamnesis from all the subjects. Demographical and clinical particulars are given in Table 1.

Transthoracic echocardiographic images were obtained using an ultrasound system, Vivid-7 (General Electric Vingmed), from the patients in the left lateral decubitus position, and these images were digitally kept for offline examination (EchoPAC version 110.0.0, GE-Vingmed). Echocardiographic acquisitions (colored, standard 2D, pulsed, and continuous-wave Doppler) were done. Standard M-mode images at a parasternal long-axis view were used to obtain the LV dimensions. Then, LV end-diastolic and end-systolic volumes were calculated using biplane Simpson's method from the apical views (two- and four-chamber).

Table 1. Demographic Features of Mild/Moderate and Severe AR Patients

	Mild (n = 33)	Moderate (n = 21)	Severe (n = 39)	*P*
Age (years)	54.9 ± 15.3	47.6 ± 18.6	40.5 ± 18.2	.006
Gender (male n, %)	12 (36.3)	12 (54.5)	25 (64.1)	.062
DM (n, %)	6 (18.1)	4 (18.1)	6 (15.3)	.939
HT (n,%)	7 (21)	9 (40.9)	8 (20.5)	.167
Smoking (n, %)	12 (36)	8 (40)	15 (37)	.326
DL (n, %)	3 (9.1)	5 (22)	6 (15.3)	.378

Abbreviations: DM: diabetes mellitus; HT: hypertension; DL: dyslipidemia.

Table 2. Echocardiographic and Diastolic Flow Reversal Features of Mild/Moderate and Severe AR Patients

	Mild (n = 33)	Moderate (n = 21)	Severe (n = 39)	*P*
Aort diastolic diameter (cm)	3.02 ± 0.57	3.25 ± 0.55	3.26 ± 0.68	.212
EDD (cm)	4,74 ± 0.43	4.86 ± 0.41	5.71 ± 0.63	<.001
ESD (cm)	3.09 ± 0.45	3.12 ± 0.37	3.7 ± 0.43	<.001
Septum	1.04 ± 0.15	1.14 ± 0.19	1.20 ± 0.25	.013
Posterior wall	1.06 ± 0.16	1.13 ± 0.22	1.25 ± 0.25	.002
EF (%)	63.2 ± 6.68	64.5 ± 6.96	62.9 ± 7.16	.691
E (cm/s)	0.5 ± 0.1	0.6 ± 0.2	0.5 ± 0.1	.89
A (cm/s)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	.51
TAPSE (cm)	2.29 ± 0.4	2.48 ± 0.46	2.42 ± 0.6	.362
AR VC (cm)	0.32 ± 0.9	0.48 ± 0.12	0.63 ± 0.13	<.001
Jet/LVOT	0.29 ± 0.8	0.39 ± 0.11	0.49 ± 0.10	<.001
AR PHT (ms)	480.0 ± 96.2	435.4 ± 89.06	293.7 ± 97.89	<.001
dVTI (cm)	8.5 ± 2.4	12.8 ± 5.8	17.4 ± 6.2	<.001
EDFV (m/s)	0.11 ± 0.11	0.10 ± 0.11	0.24 ± 0.13	<.001

EDD, end-diastolic diameter; ESD, end systolic diameter; TAPSE, tricuspid annular plane systolic excursion; EF, ejection fraction; AR, aortic regurgitation; PHT, pressure half time; VC, vena contracta; EDFV, end-diastolic flow velocity; dVTI, diastolic VTI; LVOT, left ventricular outflow tract.

Following the aforementioned measurements, LVEF was calculated and the results were expressed with percentage.

All measurements and evaluations performed in the study were carried out considering the guidelines of the European Society of Echocardiography. Detailed examination of the aortic root, AV, and proximal ascending aorta was performed taking into account the standard guidelines. To evaluate the AR severity, comprehensive, color, continuous, and pulsed-wave Doppler recordings were carried out considering the recommendations that included the measurement of regurgitant jet width, vena contracta width, pressure half-time, and diastolic flow reversal in the descending aorta.[6,7]

The transducer was placed in the suprasternal notch to measure the diastolic flow reversal parameters. Pulse wave velocity measurements were recorded in the descending aorta by positioning ultrasound rays parallel to the flow in the aorta. The existence of holodiastolic flow reversal, duration of diastolic flow reversal, and speed of peak and end-diastolic flow and dVTI were calculated. EDFV was determined at the peak R wave on a simultaneously recorded electrocardiogram and the EDFV

measurements were performed on three consecutive RR intervals. Echocardiographic and diastolic flow reversal parameters are given in Table 2.

AR severity was fixed on by two expert cardiologists who were working in an echocardiography laboratory with more than 5 years of experience. They used conventional echocardiographic evaluation methods for deciding severity degree if both of them are in the same decision on severity degree these patients concluded in the study.

Statistical Analysis

All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) Version 22.0. (IBM SPSS Corp.; Armonk, NY, USA).

Descriptive statistics for numerical variables are expressed as mean ± standard deviation (SD), while categorical data are reported as numerical values and percentages. The chi-square test and Fisher's exact chi-square test were used to compare categorical variables between the groups. One-way analysis of variance test was used to compare means between groups. The statistical significance was set at $P < .05$, and the confidence interval at 95%.

RESULTS

According to the AR degree, the patients were divided into three groups: mild, moderate, and severe AR. The basal variables among these groups are presented in Table 1. No statistically significant difference was noticed on parameters among the groups.

Echocardiographic and diastolic flow reversal parameters are defined in Table 2. According to these parameters, end-diastolic diameter (EDD) was detected to be 4.74 ± 0.43 cm in the mild AR group, 4.86 ± 0.41 cm in the moderate AR group and 5.71 ± 0.63 cm in the severe AR group ($P < .001$). End-systolic diameter (ESD) was detected to be 3.09 ± 0.45 cm in the mild AR group 3.12 ± 0.37 cm in the moderate AR group and 3.7 ± 0.43 cm in the severe AR group ($P < .001$). AR vena contracta (VC) was detected to be 0.3 ± 0.9 cm in the mild AR group, 0.48 ± 0.12 cm in the moderate AR group and 0.63 ± 0.13 cm ($P < .001$) in the severe AR group. AR PHT was detected to be 480.0 ± 96.2 ms in the mild AR group, 435.4 ± 89.06 ms in the moderate AR group and 293.7 ± 97.89 ms in the severe AR group with a P value <.001.

Diastolic VTI (dVTI) was detected to be 8.5 ± 2.4 cm in the mild AR group 12.8 ± 5.8 cm in the moderate AR group and 17.4 ± 6.2 cm in the severe AR group ($P < .001$). EDFV was detected to be 0.11 ± 0.11 m/s in the mild AR group, 0.10 ± 0.11 m/s in the moderate AR group and 0.24 ± 0.13 m/s in the severe AR group ($P < .001$).

DISCUSSION

Main findings of our study are as follows:

1. Diastolic flow reversal EDFV in the aorta is higher and significantly different in severe AR compared to mild and moderate AR,
2. dVTI increases linearly with the AR grade and is significantly different between the mild/moderate and severe AR patient groups,
3. Diastolic flow reversal profile in the aorta can be a guide in addition to the current parameters in AR grading.

AR grading with echocardiography is quite complex. The flow reversal in the descending aorta (in a way to reflect the amount of blood that flows back inside from the aortic valve) is directly proportional to the AR grade and remains important in AR grading as a result of the studies performed for many years. Echocardiographic parameters such as flow reversal which continues throughout the diastole, high end-diastolic flow speed, and high diastolic/systolic flow ratio were suggested as guides in AR rating.[8] Diastolic flow reversal seen in chronic AR can be observed markedly and as holodiastolic in patients with moderate/severe AR.[9]

It was determined in the previous studies that flow reversal in ascending aorta was less reliable compared to the examination of flow reversal in the descendant aorta due to the irregular flow pattern.[8] It was highlighted that early diastolic flow reversal may be affected by the aortic compliance, therefore, the flow reversal in late diastole was more reliable in AR grading.[4] Therefore, the importance of the measurements of the descending aorta increased, and EDFV was studied intensively.

In the study conducted by Tribouilloy et al.[3] published in 1991; EDFV assessed with pulse wave doppler (PWD) was suggested as a routine noninvasive parameter that may be beneficial for AR grading. It was concluded that the EDFV being above 18 cm/s may predict the moderate and severe AR. Again in another study, EDFV measured in the descending aorta was found correlated with regurgitant reaction detected in MRI.[8]

In the study conducted by Kalaycı et al.,[5] dVTI detected in the descending aorta with PWD may predict severe AR with high specificity and susceptibility. dTVI cut-off value was determined as 13.5 cm for severe AR in this study. In another study, it was concluded that EDFV and dVTI were effective in AR grading. In the same study, cut-off values for severe AR were suggested as dVTI >13 and for EDFV as >13 cm/s.[9]

The gold standard methods for AR grading are MRI and cardiac catheterization.[5] It is often not possible to assess all patients with interventional procedures such as catheterization or hard-to-reach methods such as MRI. The guidelines are suggesting the concomitant use of quantitative, semiquantitative, and quantitative echocardiographic parameters to evaluate the AR severity.[6,7] The most accurate results can be obtained with quantitative methods, but these methods are both time-consuming and have inter-observer variability.[5] Most of these methods have specific limitations and may be inadequate for AR grading alone. Nonplanar/noncircular regurgitant orifice and a thickened, calcified valve may limit the use of proximal isovelocity surface area method.[10] Increased AR grade is

associated with increased LV remodeling and prolonged PHT; and PHT may be an indicator for LV filling pressure, rather than AR grade.[11] Therefore, all parameters that can be obtained with a noninvasive method such as echocardiography and contribute to AR grading are important. This situation increases the importance of parameters such as EDFV and dVTI.

The diagnostic importance of diastolic flow reversal in AR grading is also indicated in the guidelines. Recent European guideline (>20 cm/s for severe AR) recommends EDFV as a parameter to be used in grading, while American Society of Echocardiography[6] emphasizes the existence of holodiastolic flow reversal as a criterion for severe AR in its suggestions.[7]

Examining the flow reversal profile in AR may have limitations in some situations. When AR is mild, flow speed may be low or flow reversal may not be observed. Regular flow that may be seen in the aorta in congenital diseases such as patent ductus arteriosus, coarctation of aorta, or clinical situations such as aortopulmonary fistula, aortic dissection can disturb the flow reversal profile. And again in the cases of acute AR, the benefit of the evaluation of flow reversal is limited due to the rapid equalization of aortic and ventricular pressures.[3]

The results we obtained in our study show the importance of EDFV and dVTI parameters in AR grading in parallel with the previous studies. Therefore, routine evaluation of diastolic flow reversal with echocardiography, which is an easily accessible noninvasive method, may be a reasonable approach in AR grading.

The limitations of our study are that it is single-center, the number of patient population is limited, we are unable to validate the AR grade with gold standard methods and AR degree was calculated by semi-quantitative methods. Multicenter extensive studies that will be validated with a large patient population and gold standard methods will show the role of EDFV and dVTI parameters in AR grading more clearly.

CONCLUSION

In the light of the data obtained in our study, echocardiographic evaluation of the diastolic flow reversal parameters like EDFV and dVTI measured in the descending aorta can contribute to AR grading. Handling these semiquantitative parameters with other grading criteria as a whole may strengthen the prediction in AR grading.

Ethics Committee Approval: This study was approved by Ethics committee of Kartal Koşuyolu Heart Training and Research Hospital (Approval No: 22.09.2020/3).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Original Article

Bibliometric Analysis of Turkey's Research Activity in the *Anatomy and Morphology* Category from the Web of Science Database

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ABSTRACT

Objective: The measurement of international publication activities is one of the essential indicators used to evaluate the scientific development level of countries. Although many studies are using the bibliometric method in the literature, it is seen that there are very few bibliometric studies in the field of anatomy. This study aimed to analyze the articles bibliometrically which conducted by researchers at institutions from Turkey and indexed in Science Citation Index Expanded (SCI-E) of the Web of Science database in the category of *Anatomy and Morphology*.

Materials and Methods: According to 2019 data, journals in the *Anatomy and Morphology* category and indexed in the SCI-E were determined. Publications from Turkey that were published in these journals was determined. The full-texts of these articles were examined, and study types were defined. Also, VOSviewer software was used to create a collaboration and word co-occurrence network.

Results: It was determined that there were 48,002 publications in 21 journals. It was found that 1,461 publications (3.04%) have at least one author from Turkey. The total number of citations was 11,728 for these publications. The average number of citations was 8.02 ± 11.95. The radiological studies have increased statistically more than both experimental animal and cadaveric studies by years. In addition, it has been determined that the total number of articles, especially the radiological studies, has increased significantly over the years.

Conclusion: The increase in the number of scientific studies in the field of anatomy is important in terms of the contribution of Turkey to literature in this area.

Keywords: Anatomy, bibliometric analysis, Web of Science

INTRODUCTION

Anatomy, one of the oldest known medical sciences, is a discipline that forms the basis of medical education and is an integral part of the medical curriculum.[1] It is thought that the first studies in the field of anatomy date back to the 19th century B.C. These studies started with animal dissections.[2] Undoubtedly, cadavers have been the essential teaching method in anatomy education in this long process. As a matter of fact, many scientists who have made significant contributions to anatomy owe these contributions to cadaveric studies.[3] On the other hand, with the development of medical imaging methods over time, radiological and clinical studies also have been added to cadaver dissection studies, which are still valuable and relevant.[4]

Because countless scientists contributed to the development of anatomy over this long period, the highly detailed knowledge of anatomy in today's medical literature has emerged.[1,5] For this reason, every study in the field of anatomy is exceptionally essential in terms of its contribution to the field.

Bibliometry (*βιβλίο: Book, μέτρηση: Measurement*) is a Greek origin word.[6] It is a kind of research approach used to measure and analyze the productivity of the literature in a particular area or journal. Today, many disciplines use bibliometric analysis to examine the impact of their field.[7] The bibliometric analysis includes features such as the article type, content of article, number of citations to the article, number of authors, the affiliation of authors, index, and category of the journals.[7–9] Although many studies are using the bibliometric method in the literature, it is seen that there are very few bibliometric studies in the field of anatomy.[5,10,11]

The Web of Science (WoS) database is one of the widely used databases in bibliometric research. The most valid measure of the quality of scientific publications and the productivity of researchers at the international level are the number of articles

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Table 1. List of Journals in the *Anatomy and Morphology* Category of the WoS Database Indexed in SCI-E

Journal Name	Abbreviated Journal Name	ISSN	Publication Period in the WoS Database
Surgical and Radiologic Anatomy	Surg Radiol Anat	0930-1038	1986-present
International Journal of Morphology	Int J Morphol	0717-9502	2008-present
Clinical Anatomy	Clin Anat	0897-3806	1997-present
Folia Morphologica	Folia Morphol	0015-5659	2009-present
Microscopy Research and Technique	Microsc Res Tech	1059-910X	1992-present
Anatomia Histologia Embryologia	Anat Histol Embryol	0340-2096	1992-present
Annals of Anatomy-Anatomischer Anzeiger	Ann Anat	0940-9602	1992-present
Journal of Anatomy	J Anat	0021-8782	1980-present
Applied Immunohistochemistry and Molecular Morphology	Appl Immunohisto M M	1541-2016	1994-present
Anatomical Science International	Anat Sci Int	1447-6959	2006-present
Journal of The Anatomical Society of India	J Anat Soc India	0003-2778	2008-present
Tissue and Cell	Tissue Cell	0040-8166	1980-present
Anatomical Record-Advances in Integrative Anatomy and Evolutionary Biology	Anat Rec	1932-8486	2007-present
Acta Zoologica	Acta Zool	0001-7272	1980-present
Cells Tissues Organs	Cells Tissues Organs	1422-6405	1999-present
Journal of Morphology	J Morphol	0362-2525	1980-present
Brain Structure and Function	Brain Struct Funct	1863-2653	2007-present
Developmental Dynamics	Dev Dyn	1058-8388	1992-present
Zoomorphology	Zoomorphology	0720-213X	1980-present
Frontiers in Neuroanatomy	Front Neuroanat	1662-5129	2007-present
Advances in Anatomy Embryology and Cell Biology	Adv Anat Embryol Cell Biol	0301-5556	1982-present

published in journals in the WoS database and the number of citations of these articles. All these criteria can be interpreted as a quality indicator and used to evaluate institutions, academicians, and even countries.[12] On the other hand, the measurement of international publication activities is one of the essential indicators used to evaluate the scientific development level of countries. In the WoS database, there are articles indexed in the Science Citation Index Expanded (SCI-E) since 1980. In 2019, journals indexed in SCI-E were classified into 178 different categories. One of these categories is *Anatomy and Morphology*.[13] To the best of our knowledge, in the literature, there is no bibliometric study that evaluated the *Anatomy and Morphology* category. We think that this study is the first study to examine the *Anatomy and Morphology* category in the WoS database studies on a country basis bibliometric.

Main Points

- It has been found that the total number of articles in the field of *Anatomy and Morphology*, especially radiological studies, has increased significantly over the years.
- With this study to examine the articles originated from Turkey in the anatomy field and determination of research trends of authors is thought to be guiding the work to be done in this area.

This study aimed to assess the bibliometric characteristics of related articles in the *Anatomy and Morphology* category, which indexed in SCI-E of the WoS database by researchers from Turkish institutions.

METHODS

According to 2019 data, in the WoS database, journals in the *Anatomy and Morphology* category and indexed in the SCI-E

were determined using Clarivate Analytics' Journal Citation Reports database. The names, abbreviated names, publication periods, and ISSN numbers of these journals were recorded (Table 1). The WoS database was searched for each journal with ISSN numbers by using the advanced search. Also, it has been taken into consideration that there may be changes in ISSN over the years, so another search also was done with the journal names. Articles published from January 1, 2020, onwards, it was excluded as any capture from that period forward would include incomplete bibliometric data for that year. In the WoS options, all categories such as Conference Proceedings Citation Index-Science, Arts and Humanities Citation Index, Social Sciences Citation Index, and Book Citation Index-Science were excluded, except for SCI-E. Afterward, meeting abstract, proceedings paper, early access, reprint, book series titles, and conference titles were excluded. Finally, in the Countries/Regions option, Turkey was chosen, and articles were determined. For each publication, all information relevant to the analysis was exported to Microsoft Excel and a bibliography manager (EndNote Desktop). Concretely this was: Author(s), Title, Source, Addresses, Times Cited, and Keywords. Since the document type in WoS is not detailed enough to evaluate the output of different types of papers, each article was separately examined while evaluating the document types. Therefore, the full texts of the articles were examined, and study types were defined as per the National Library of Medicine's MeSH database[14] and the evaluated journals. Also, VOSviewer software (version 1.6.15) was used to create a collaboration and word co-occurrence network.[15]

Statistical Analysis

Descriptive statistics are given as mean ± standard deviation for numerical variables and number and percentage values for categorical variables. The relations between numeric variables were tested by using the Pearson correlation coefficient, and study designs were compared with years using Tamhane Post Hoc Tests. SPSS (IBM SPSS Corp.; Armonk, NY, USA) for Windows version 22.0 package software was used for statistical analysis, and $P < .05$ was considered statistically significant.

RESULTS

The journals listed in the *Anatomy and Morphology* category of the WoS database and all the publications, publications remaining after exclusion criteria, and publications from Turkey that were published in these journals, are shown in Table 2. It was determined that there were 48,002 publications in these 21 journals. It was found that 1,461 publications (3.04%) which have at least one author from Turkey and published in 20 different journals (Figure 1). In one of the journals (*Adv Anat Embryol Cell Biol*), there is no publication from Turkey. When examined with the VOSviewer software, it was determined that there was a total of 25,979 different words in the titles and abstracts of 1,461 publications (Figure 2). The colors used in Figure 2 indicate words within the same topic cluster and distinguishing three colored clusters. In spite of the WoS database started indexing SCI-E journals since 1980, it was seen that most of these journals started to be indexed in the following years. Although we examine the 40 years between 1980 and 2019, our results obtained belong to the articles published in 1983-2019. However, in the first year (1983), only one document was published, and this is the same for 1986, 1989, and 1990. Besides, it was determined that there was no publication in 1984, 1985, 1987, and 1988. The distribution of all publications by years is shown in Figure 3. The articles were found to be published most in 2019 (n = 138, 9.45%). Furthermore, it was determined that financial support was received from various institutions for 232 out of 1,461 publications (15.88%). These supports were mostly given by TUBITAK (in 25 publications).

Table 2. The Total Number of Articles in 21 Journals and the Number of Articles That Afliate to Turkey*

Journal	Publication Numbers of the Journals: Total	From Turkey (%)
Surg Radiol Anat	3,556	431 (12.12%)
Int J Morphol	2,714	181 (6.67%)
Clin Anat	3,099	160 (5.16%)
Anat Histol Embryol	2,160	148 (6.85%)
Folia Morphol	841	149 (17.72%)
Microsc Res Tech	4,589	102 (2.22%)
Ann Anat	2,125	71 (3.34%)
J Anat	4,943	34 (0.69%)
Appl Immunohisto M M	1,900	35 (1.84%)
Anat Sci Int	604	28 (4.64%)
J Anat Soc India	500	28 (5.60%)
Tissue Cell	2,677	27 (1.01%)
Anat Rec	2,526	25 (0.99%)
Acta Zool	1,296	12 (0.93%)
Cells Tissues Organs	1,224	11 (0.90%)
J Morphol	3,998	5 (0.13%)
Brain Struct Funct	1,838	5 (0.27%)
Dev Dyn	5,088	4 (0.08%)
Zoomorphology	1,152	4 (0.35%)
Front Neuroanat	1,067	1 (0.09%)
Adv Anat Embryol Cell Biol	105	0 (0.00%)
Total	**48,002**	**1,461 (3.04%)**

*The data belong to 21 journals in the Anatomy and Morphology category.

While the maximum number of publications (n = 431/1,461, 29.50%) from Turkey were published in *Surg Radiol Anat*, the journal with the highest rate of publications from Turkey was

Figure 1. Distribution of publications from Turkey by the journals.

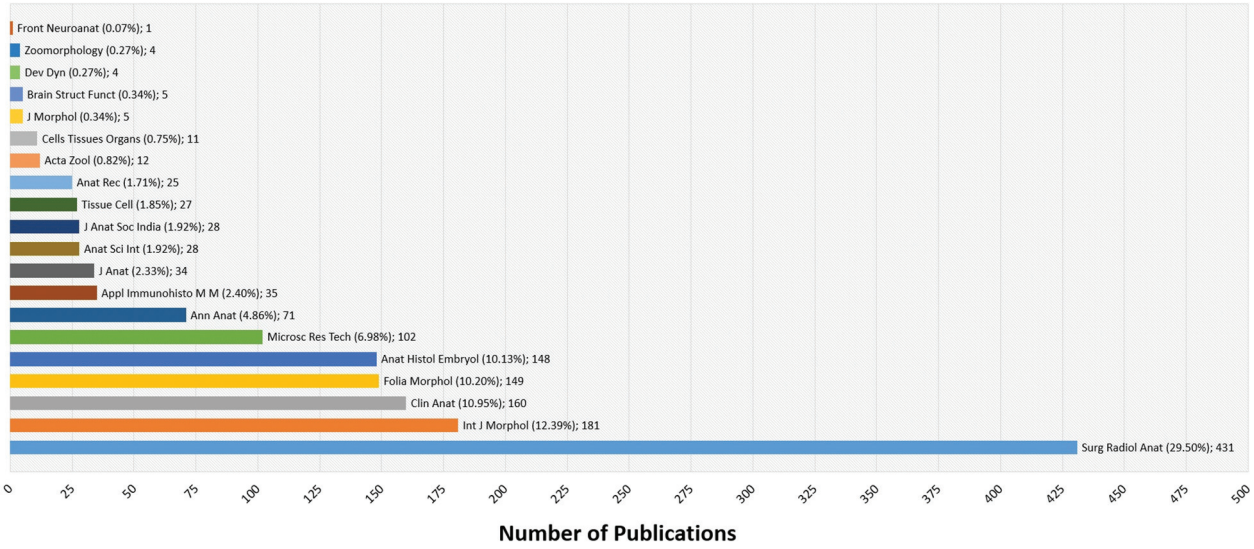


Figure 2. Word co-occurrence network built using words present in titles and abstracts of publications.

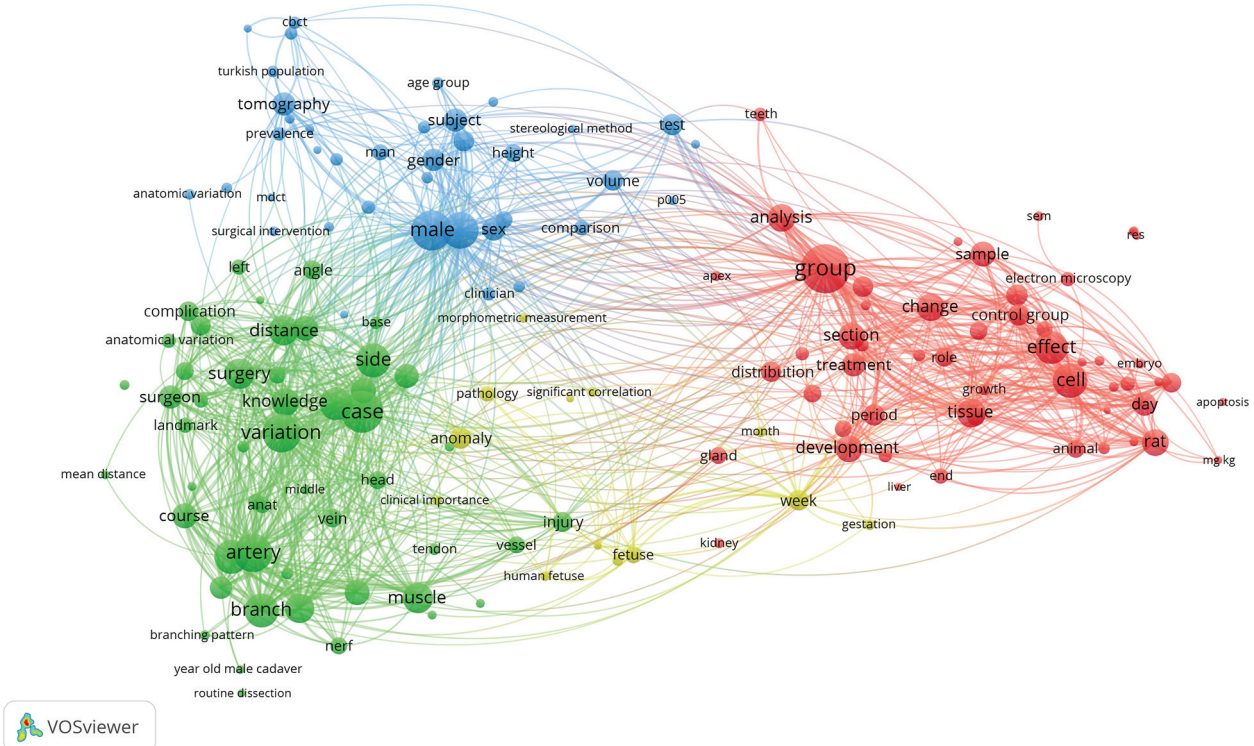
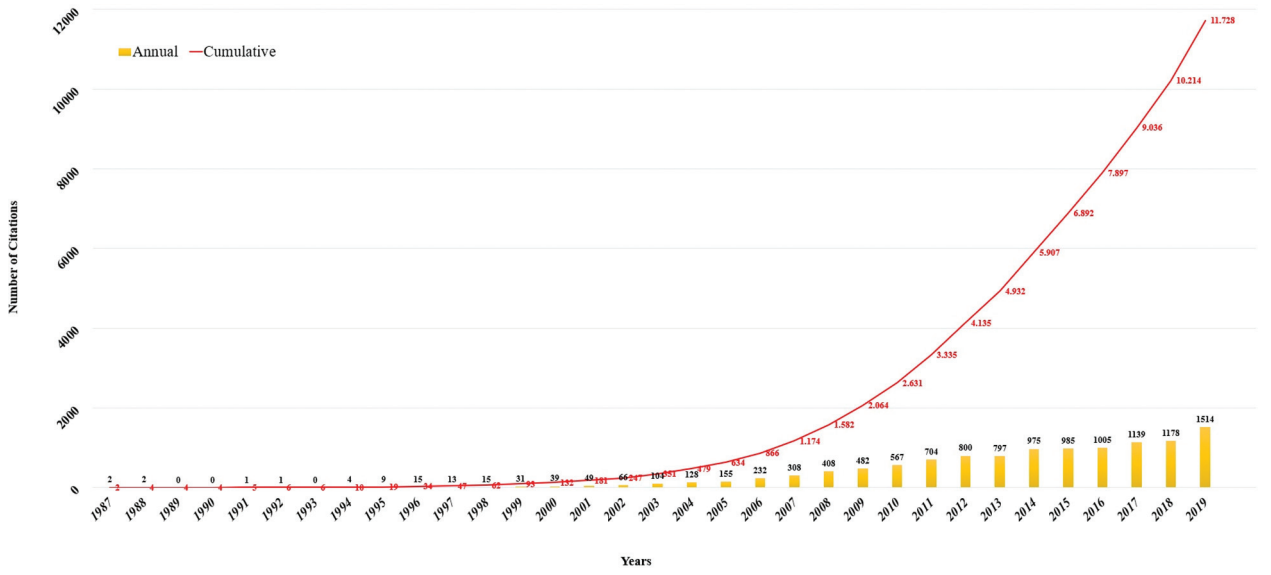


Figure 3. Distribution of published articles by the years.



Folia Morph (n = 149/841, 17.72%) when the journals were evaluated separately.

When the institutions according to the affiliations of authors were examined, it was determined that there are nearly 200 institutions. The 25 institutions with the highest number of publications are shown in Table 3. In addition, Figure 4 presents these publications' collaboration map of universities in Turkey.

While all author(s) were from Turkey in 1,275 out of 1,461 publications (87.27%), the authors from Turkey were collaborating with the researchers from 46 different countries in 186 out of 1,461 publications (12.73%). The USA was leading these countries with 69 publications. The collaboration map of the publications between Turkey and other countries is shown in Figure 5.

The total number of citations was 11,728 for all publications. The average number of citations was 8.02 ± 11.95 (min: 0, max: 127). At least one citation was made to 1,179 out of 1,461 publications (80.70%). When the number of citations was examined by years (Figure 6), it was seen that most citations were made in 2019. The H-index of 1,461 publications was 41. The 25 most cited publications are shown in Table 4.[16–40] It was seen that 11 of these 25 publications (44%); in other words, the vast majority of them were published in the *Surg Radiol Anat*.

The study types and the average number of citations according to the study types are given in Table 5. It was determined that 1,233 of them (84.39%) were original articles, and 184 of them (12.59%) were case reports. It was found that the most cited publications type was review. On the other hand, subtypes of the original articles and the case reports are detected and given in Table 6. In addition, the three study types with the highest number of publications were compared by years, a statistically significant difference was found (Table 7). Accordingly, the radiological studies have increased statistically more than both experimental animal and cadaveric studies by years (Tamhane post hoc test: $P = .001$ and $P = .001$). Furthermore, experimental animal studies have also increased statistically more than cadaveric studies by years (Tamhane post hoc test: $P = .001$). While cadaver studies have decreased in recent years, experimental animal studies and especially radiological studies have increased (Figure 7). It was determined that there was a very strong positive correlation between the number of publications and the years ($P = .001$, $r = .939$). Although it was found that there were very strong positive correlations between experimental animal studies and years ($P = .001$, $r = .838$) and radiological studies and years ($P = .001$, $r = .906$), there was no correlation between cadaveric studies and years ($P = .199$).

DISCUSSION

Bibliometric studies allow us to measure the productivity and effectiveness of a field in the literature.[7] The number of publications of any institutions or countries in the WoS database and the number of citations of these publications can be interpreted as a quality indicator.[12] Although there are numerous articles that evaluated the bibliometry for different specialties and subspecialties, we were unable to find a study about bibliometric analysis of the *Anatomy and Morphology* category in the WoS database in the literature.

On the other hand, Tellioglu et al.[41] reported that most of the publications of Turkish Anatomists were published in *Surg Radiol Anat* between 2000 and 2014, with a rate of 27%. Similarly, Gürses et al.[42] examined the publication rates of oral and poster presentations in 2007 and 2008 national anatomy congresses in Turkey and determined that the most preferred

Table 3. The 25 Institutions With the Highest Number of Publications

Institutions	N (%)
Ankara University	126 (8.62%)
Hacettepe University	107 (7.32%)
Dicle University	101 (6.91%)
Ege University	79 (5.41%)
Gülhane Military Medical Academy	73 (5%)
Ondokuz Mayıs University	63 (4.31%)
Istanbul University	60 (4.11%)
Gazi University	58 (3.97%)
Selcuk University	56 (3.83%)
Erciyes University	55 (3.76%)
Akdeniz University	46 (3.15%)
Suleyman Demirel University	43 (2.94%)
Mersin University	41 (2.81%)
Afyon Kocatepe University	40 (2.74%)
Adnan Menderes University	39 (2.67%)
Dokuz Eylul University	39 (2.67%)
Kirikkale University	39 (2.67%)
Cumhuriyet University	38 (2.6%)
Uludag University	36 (2.46%)
Atatürk University	32 (2.19%)
Cukurova University	30 (2.05%)
Gaziantep University	27 (1.85%)
Baskent University	25 (1.71%)
Marmara University	25 (1.71%)
Kafkas University	21 (1.44%)

journal is *Surg Radiol Anat*. In this study, it was seen that the most preferred journal was *Surg Radiol Anat*, similar to these two studies.[41,42]

In the study conducted by Petekkaya,[10] it was reported that the articles in the anatomy field showed a significant increase, especially between 1997 and 2010. In the present study, it was determined that there was a great positive relationship between the years and the number of publications annually. Many reasons, such as an increase in the number of academicians, the number of medical faculties, and changes in the academic promotion criteria in Turkey in the anatomy field, maybe the reasons for this situation.

Although it is considered as the most reliable database, it is known that document types are not sufficient in WoS database.[43] As a matter of fact, when the journals in the *Anatomy and Morphology* category are examined in the WoS database, it is determined that there is no study design as a case report. On the other hand, it is seen that some studies published as an original article in journals in the *Anatomy and Morphology* category, they are scanned as reviews in the WoS database.[44,45] The criteria of the WoS database in this regard are as follows; any article containing more than 100 references and articles whose titles contain the word "review" or "overview" are coded as a review.[46] For this reason, the full texts of 1,461 publications were examined in order to obtain the more precise information and to classify the publications in detail. These publications were classified according to both study types, which were defined by the National Library of Medicine's MeSH database[14] and categories in the journals evaluated.

It is known that the reviews had higher average numbers of citations than original articles,[46] as determined in this study. Notwithstanding, it is noteworthy that there are very few numbers of reviews in the field of anatomy (1.03%). Kramer et al.[47] reported this rate as 13.2% in the bibliometric analysis of traumatic dental injuries in the primary dentition. Hafeez et al.[48] stated this rate as 6.8% in the bibliometric analysis of six major psychiatry journals. On the other hand, the rate of the case reports was found as 33.6% in the study of Kramer et al.[47] and as 4.8% in the study of Hafez et al.[48] In this study, the rate of case reports was found to be 12.59%. Differences in these rates suggest that the distribution of study designs varies for different areas.

Petekkaya[10] reported that the majority of the top 100 most cited articles in the anatomy field consisted of experimental studies. In this study, contrary to Petekkaya,[10] it was found that most of the studies were radiological anatomy studies. Undoubtedly, there are many reasons for this situation. The probable reason for this situation is the increase in radiological anatomy studies, especially in recent years. In addition, in recent years, the importance and place of cadavers in the field of medicine have become a subject of discussion.[4] The number of cadaver studies has not increased, maybe due to the number of people donating their bodies being very low in many countries, including Turkey, while the development of technology has led to an increase in radiologic studies. Although cadaver studies are examined by years, it is observed that there is no correlation. However, it is seen that the highest number of studies was between 2004 and 2010 and gradually decreased in the following years. Despite the increase in radiologic and experimental animal studies, we think that this decline in cadaver studies is alarming.

On the other hand, in Turkey, the establishment of the universities that have the highest number of publications in *Anatomy and Morphology* category generally is known to be older than other universities. In addition, it has been observed that these universities have more publication requirements for academic assignment criteria.[49] The first two universities, Ankara University and Hacettepe University, with the highest number of publications of this field are the most prominent examples of this situation.

Figure 4. Collaboration map of universities in Turkey.

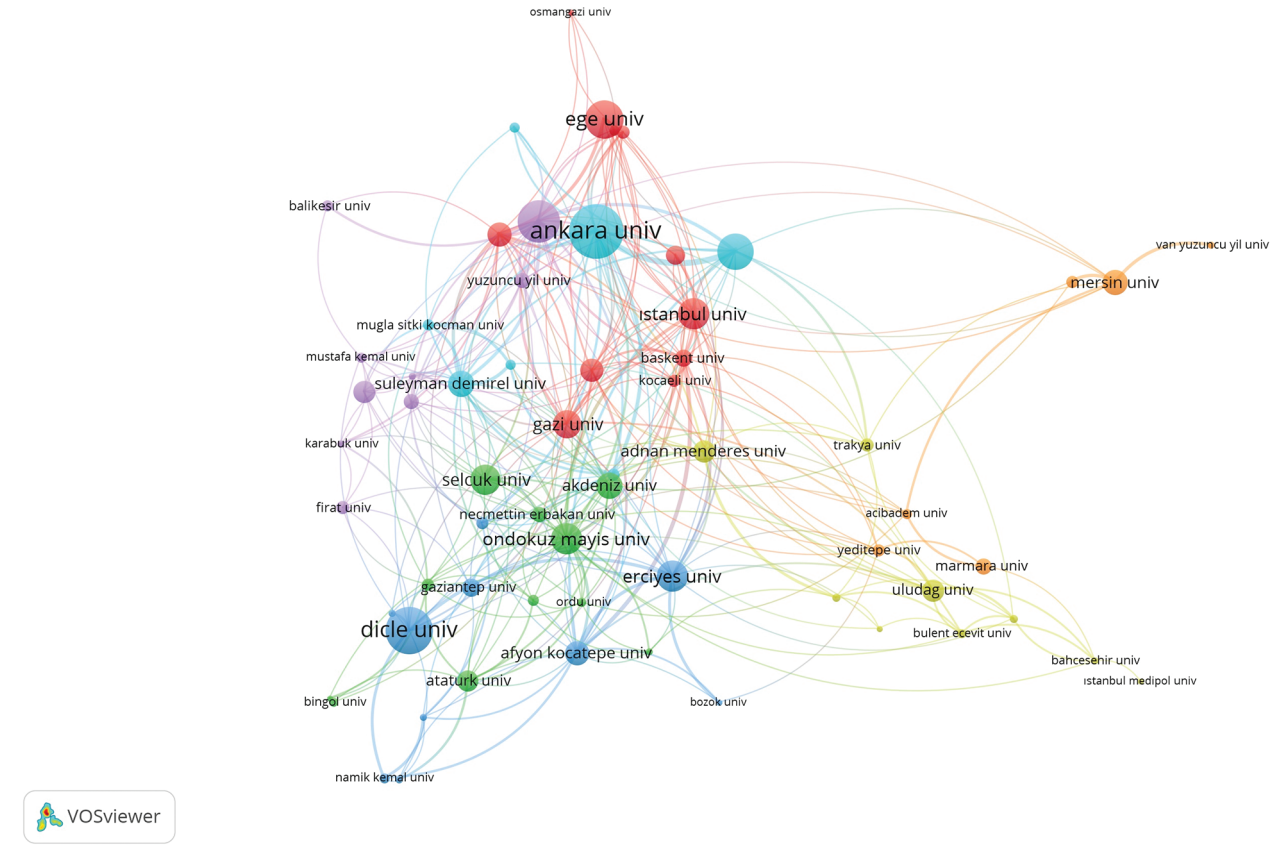


Figure 5. Collaboration map in the publications with Turkey and other countries.

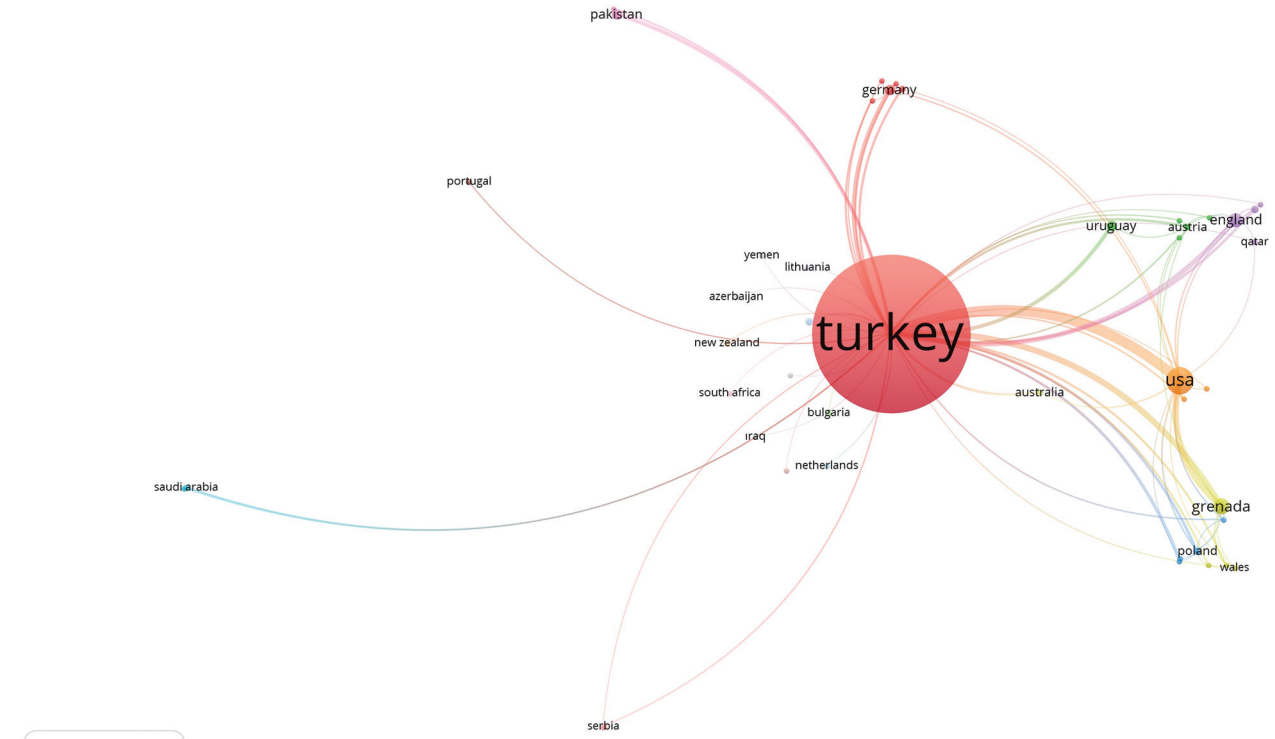


Figure 6. Distribution of citations by years.

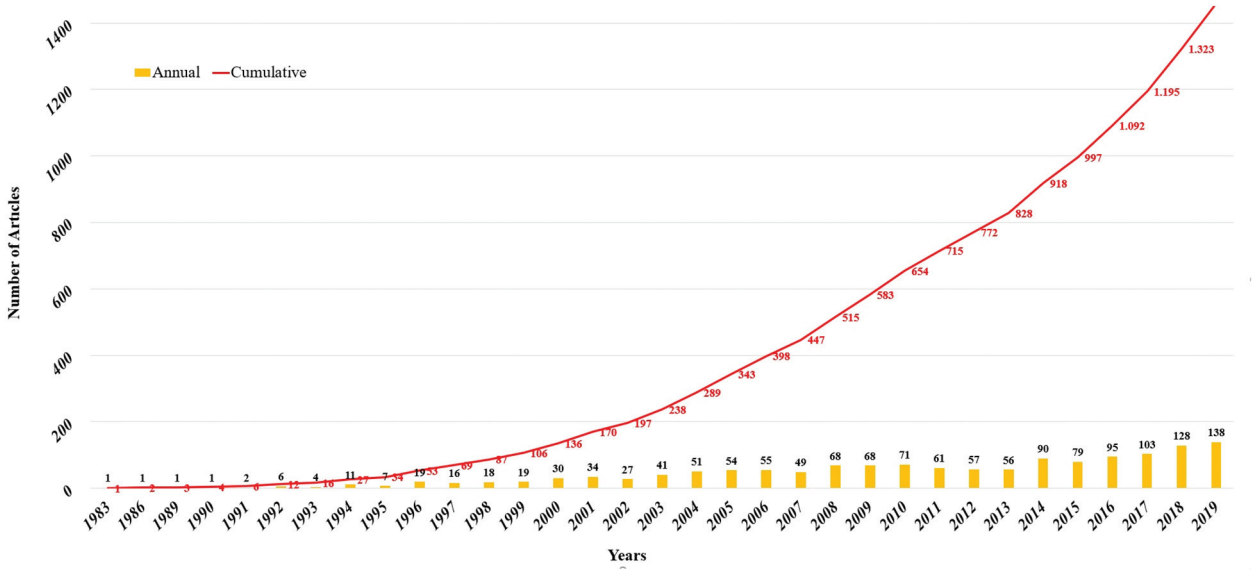


Table 4. Top 25 Cited Publications in the *Anatomy and Morphology* Category*

	Author(s)	Title	Journal	Year	NC	PY
1	Kargi et al.[25]	The diagnostic value of TTF-1, CK 5/6, and p63 immunostaining in classication of lung carcinomas	Appl Immuno-histo M M	2007	127	9.77
2	Pinar and Govsa[32]	Anatomy of the supercial temporal artery and its branches: Its importance for surgery	Surg Radiol Anat	2006	111	7.93
3	Vilhelmsen et al.[39]	Host location and oviposition in a basal group of parasitic wasps: The subgenual organ, ovipositor apparatus and associated structures in the Orussidae (Hymenoptera, Insecta)	Zoomorphology	2001	92	4.84
4	Unal et al.[38]	Risky anatomic variations of sphenoid sinus for surgery	Surg Radiol Anat	2006	87	6.21
5	Sanli et al.[34]	Stature estimation based on hand length and foot length	Clin Anat	2005	85	5.67
6	Ercan et al.[21]	Facial asymmetry in young healthy subjects evaluated by statistical shape analysis	J Anat	2008	78	6.50
7	Demir et al.[19]	Classication of human placental stem villi: Review of structural and functional aspects	Microsc Res Tech	1997	77	3.35
8	Pinar et al.[31]	Anatomic study of the blood supply of perioral region	Clin Anat	2005	70	4.67
9	Saylam et al.[35]	Reduced hippocampal volume in drug-free depressed patients	Surg Radiol Anat	2006	69	4.93
10	Durgun et al.[20]	Evaluation by angiography of the lateral dominance of the drainage of the dural venous sinuses	Surg Radiol Anat	1993	64	2.37

Table 4. Top 25 Cited Publications in the *Anatomy and Morphology* Category* (Continued)

	Author(s)	Title	Journal	Year	NC	PY
11	Tekdemir et al.[37]	A clinico-anatomic study of the auricular branch of the vagus nerve and Arnold's ear-cough reex	Surg Radiol Anat	1998	62	2.82
12	Karakas et al.[24]	Morphometric measurements from various reference points in the orbit of male Caucasians	Surg Radiol Anat	2003	62	3.65
13	Kalender et al.[23]	Evaluation of the mental foramen and accessory mental foramen in Turkish patients using cone-beam computed tomography images reconstructed from a volumetric rendering program)	Clin Anat	2012	61	7.63
14	Altunkaynak et al.[16]	The effects of high-fat diet on the renal structure and morphometric parametric of kidneys in rats	J Anat	2008	60	5.00
15	Coskun et al.[18]	Incidence of accessory ossicles and sesamoid bones in the feet: A radiographic study of the Turkish subjects	Surg Radiol Anat	2009	60	5.45
16	Huijing et al.[22]	Effects of knee joint angle on global and local strains within human triceps surae muscle: MRI analysis indicating in vivo myofascial force transmission between synergistic muscles	Surg Radiol Anat	2011	55	6.11
17	Kiray et al.[27]	Surgical anatomy of the cervical sympathetic trunk	Clin Anat	2005	55	3.67
18	Ozturk et al.[30]	Measurement of the distance and angle between the aorta and superior mesenteric artery: Normal values in different BMI categories	Surg Radiol Anat	2007	54	4.15
19	Orhan et al.[28]	Evaluation of bid mandibular canals with cone-beam computed tomography in a Turkish adult population: A retrospective study	Surg Radiol Anat	2011	52	5.78
20	Cavdar et al.[17]	The pathways connecting the hippocampal formation, the thalamic reuniens nucleus and the thalamic reticular nucleus in the rat	J Anat	2008	51	4.25
21	Kilic et al.[26]	The position of the mandibular canal and histologic feature of the inferior alveolar nerve	Clin Anat	2010	51	5.10
22	Zumre et al.[40]	Investigation of the bifurcation level of the common carotid artery and variations of the branches of the external carotid artery in human fetuses	Ann Anat	2005	50	3.33
23	Ozdogmus et al.[29]	Connections between the facial, vestibular and cochlear nerve bundles within the internal auditory canal	J Anat	2004	50	3.13
24	Taskaya-Yilmaz et al.[36]	A possible etiology of the internal derangement of the temporomandibular joint based on the MRI observations of the lateral pterygoid muscle	Surg Radiol Anat	2005	48	3.20
25	Safak et al.[33]	The thickness of the ligamentum avum in relation to age and gender	Clin Anat	2010	48	4.80

*Citations before January 1, 2020 were examined, NC, Number of Citations, PY, Average Citations Per Year.

Table 5. Study Types and Citation Averages by the Study Types

Study Type	n (%)	Average Number of Citations (Mean ± SD)
Original Article	1,233 (84.39%)	7.44 ± 11.38
Case Report(s)	184 (12.59%)	6.66 ± 7.09
Letter to the Editor	24 (1.64%)	0.67 ± 1.49
Review	15 (1.03%)	16 ± 20.91
Clinical Vignette	3 (0.21%)	15 ± 4.58
Viewpoint*	1 (0.07%)	38
Short Report*	1 (0.07%)	12
Total	1,461	8.02 ± 11.95

n, the total number of articles; SD, standard deviation.
*It was determined that there is only one article in viewpoint and short report article type.

Table 6. Distribution of Original Articles and Case Reports by Study Design

Study Design	Original Articles, n (%)	Case Reports, n (%)	Both of These Types, n (%)
Radiological Study	278 (22.55%)	58 (31.52%)	336 (23.71%)
Experimental Animal Study	316 (25.63%)	2 (1.09%)	318 (22.44%)
Cadaveric Study	173 (14.03%)	109 (59.24%)	282 (19.90%)
Histological Study	189 (15.33%)		189 (13.34%)
Experimental Study	81 (6.57%)		81 (5.72%)
Fetus Study	72 (5.84%)	2 (1.09%)	74 (5.22%)
Dry Bone Study	44 (3.57%)	2 (1.09%)	46 (3.25%)
Autopsy Study	6 (0.49%)	3 (1.63%)	9 (0.64%)
Clinical Study		8 (4.35%)	8 (0.56%)
Dry Bone and Cadaveric Study	7 (0.57%)		7 (0.49%)
History of Anatomy	6 (0.49%)		6 (0.42%)
Cadaveric and Radiologic Study	5 (0.41%)		5 (0.35%)
Teaching Anatomy	5 (0.41%)		5 (0.35%)
Dry Bone and Radiologic Study	4 (0.32%)		4 (0.28%)
Dry Bone and Radiologic and Cadaveric Study	2 (0.16%)		2 (0.14%)
Cadaver and in vivo	2 (0.16%)		2 (0.14%)
Fetus and Cadaveric	1 (0.08%)		1 (0.07%)
Fetus and Radiologic	1 (0.08%)		1 (0.07%)

Table 6. Distribution of Original Articles and Case Reports by Study Design (Continued)

Study Design	Original Articles, n (%)	Case Reports, n (%)	Both of These Types, n (%)
Other Studies*	41 (3.33%)		41 (2.89%)
Total	**1,233 (100%)**	**184 (100%)**	**1,417 (100%)**

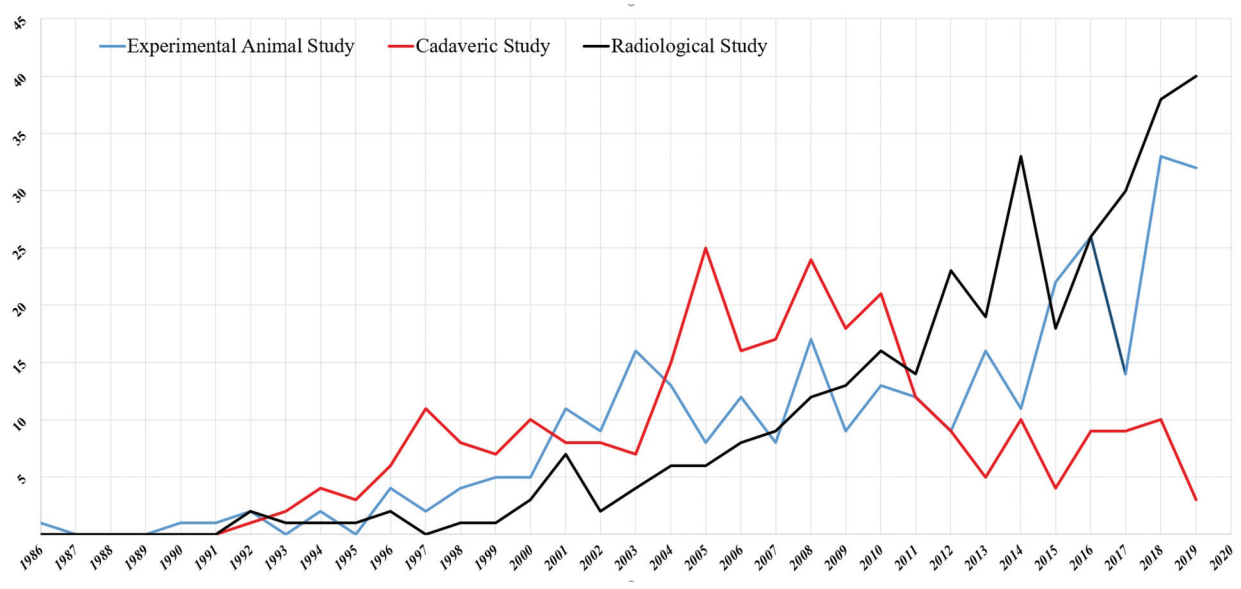
n, the total number of articles; SD, standard deviation.
*Other studies include studies in which new methods and approaches are introduced.

Table 7. Multiple Comparison of the Study Designs by Tamhane Post Hoc Tests

			95% Confidence Interval		
Study Design (I)	Study Design (J)	Mean Difference (I-J)	Lower Bound	Upper Bound	*P*
Experimental Animal Study	Cadaveric Study	3.73	2.43	5.02	.001*
	Radiological Study	−2.29	−3.49	−1.09	.001*
Cadaveric Study	Experimental Animal Study	−3.73	−5.02	−2.43	.001*
	Radiological Study	−6.02	−7.17	−4.87	.001*
Radiological Study	Experimental Animal Study	2.29	1.09	3.49	.001*
	Cadaveric Study	6.02	4.87	7.17	.001*

*Significant difference ($P < .05$).

Figure 7. Distribution of the radiological, experimental animal and cadaveric studies by years.



Limitations of This Study

Although the articles in the WoS database published before 2019 were scanned, the journals that were not active in 2019 could not be included in the study due to the inaccessibility of current data about these journals. Another limitation of this study is that the scanned 21 journals in the *Anatomy and Morphology* category in the Web of Science database published not only anatomical studies but also studies from the other fields. In fact, there were publications in the field of pathology and zoology in the first 25 articles with the most citations. The reason for this is that the types of articles accepted by some of these journals were from different scientific fields. Despite this limitation, we believe that the findings obtained in this study will be very useful in the field of anatomy.

CONCLUSIONS

A large amount of the articles conducted by researchers at institutions from Turkey and indexed in SCI-E of the WoS database in the category of *Anatomy and Morphology* were published in *Surg Radiol Anat*. In addition, it has been determined that the total number of articles, especially the radiological studies, has increased significantly over the years. The increase in the number of scientific studies in the field of anatomy is important in terms of the contribution of Turkey to literature in this area. With this study to examine the articles originated from Turkey in the anatomy field and determination of research trends of authors is thought to be guiding the work to be done in this area.

Ethics Committee Approval: Ethics committee approval is not required for this bibliometric study.

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - I.B., S.S.A., P.K, M.O., F.G.; Supervision - I.B., S.S.A., P.K, M.O., F.G.; Resource - I.B., S.S.A., P.K, M.O., F.G.; Materials - I.B., S.S.A., P.K, M.O., F.G.; Data Collection and/or Processing - I.B., S.S.A., P.K, M.O., F.G.; Analysis and/or Interpretation - I.B., S.S.A., P.K, M.O., F.G.; Literature Search - I.B., S.S.A., P.K, M.O., F.G.; Writing - I.B., S.S.A., P.K, M.O., F.G.; Critical Reviews - I.B., S.S.A., P.K, M.O., F.G.

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

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Original Article

Propolis Attenuates Nitrosative Stress in the Brain Tissue of Rats Exposed to Total Head Irradiation

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ABSTRACT

Objective: This study aimed to research the radioprotective aspect of propolis on the brain tissue of rats exposed to ionizing radiation and its ability in reducing nitrosative stress resulting from ionizing radiation.

Methods: In this study, 32 rats were used. They were randomly divided into four equal groups: two control groups, one irradiation only group, and the last group is both IR exposed and propolis administered. A single dose of 5 Gy was given to the other two groups except the control groups. Biochemical parameters were measured by spectrophotometry to determine whether protective effects of propolis were present.

Results: In this study, it was determined that nitric oxide, peroxynitrite values, and nitric oxide synthase activity were significantly higher in the radiotherapy only group in comparison to both propolis and irradiation-treated groups.

Conclusion: These findings suggest that the use of propolis has a protective effect against the adverse effects of nitrosative stress caused by ionizing radiation. However, to be assured of these beneficiary effects of propolis should be supported by further pharmacological and toxicological research.

Keywords: Irradiation, propolis, nitric oxide, nitric oxide synthase, peroxynitrite

INTRODUCTION

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are constantly produced in living organisms and are rendered harmless.[1–3] Reduced antioxidative capacity and increase in free radical (FR) production cause significant damage to the components of the cell by causing oxidative/nitrosative stress.[4–7]

Cancer, which was accepted as the second cause of death in 2015, caused the death of 8.8 million people in the world and is an expensive and important health problem. Although many strategies have been found to treat cancer such as surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, great care has been taken to investigate additional strategies to combat cancer using natural plants and their bioactive components.[8]

Radiotherapy is one of the indispensable treatment methods in cancer treatment, and approximately two-third of the cancer patients are receiving radiotherapy. While the total dose required for effective local control with radiotherapy is exited, damage occurs in normal tissues in the field of irradiation. The resulting damage is also closely related to the sensitivity to radiation. It is known that ionizing radiation forms FRs.[4,9,10]

Radiation effects can be grouped into two types: direct and indirect effects. The direct effect occurs with ionization in DNA, whereas the indirect effect occurs with water ionization in the organism. Since about two-thirds of the human body weight is water, most of the radiation damage is caused by FR, which is caused by the effect of radiation on water.[11] The aim of the radiotherapy is to preserve as much as of the normal tissue possible and to give maximum ionizing radiation to the tumor tissue. Because radiation is toxic to both tumor tissues and healthy tissues, normal tissue damage can also increase as the radiation dose increases as a result of the near healthy tissues exposure to radiation. Unfortunately, most of the radioprotectors used today have significant toxic side effects that limit their role in medical treatment.[12] Therefore, the search for effective and nontoxic compounds with radioprotective ability has led to increased interest in antioxidants such as thymoquinone and propolis.[13]

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Table 1. Parameters Measured in Brain Tissue of Rats

	Nitric Oxide (μmol g^{-1} Weight)	Nitric Oxide Synthase (U mg^{-1} Protein)	Peroxynitrite (μmol g^{-1} Weight)
Sham control group	4.58 ± 0.3[b]	3.48 ± 0.7[b]	74.41 ± 23.7[b]
The control of IR + propolis	5.52 ± 1.9[a]	3.28 ± 0.9[b]	62.96 ± 23.2[b]
IR group	7.21 ± 0.8	5.12 ± 1.0	189.34 ± 60.4
IR + propolis group	5.65 ± 1.2[a]	2.99 ± 0.5[b]	63.06 ± 20.9[b]

IR, Irradiated.
[a]$P < .01$.
[b]$P < .0001$ vs IR group.

Propolis has immunomodulatory, antitumoral, cancer-preventative, antimetastatic, anti-inflammatory, cytotoxic, and antioxidant properties. Our main focus here is the antioxidant activity and radioprotective effects of propolis.[13,14]

To our knowledge, we did not find an experimental study investigating the effect of propolis on nitrosative stress parameters in the brain tissues of rats given ionizing radiation. Therefore, in this study, we aimed to investigate the possible effects of propolis from total cranial irradiation on nitrosative stress.

METHODS

Study Protocol and Rats and Experimental Groups

This research was conducted at the Departments of Medical Biochemistry and Radiation Oncology after obtaining ethical approval from Animal Ethics Committee of Gaziantep University (ethical committee number: 2017/2). Thirty-six Sprague–Dawley rats (200 ± 20 g) fed with standard laboratory chow and water were used. Experimental animals were quarantined for at least 1 week. Later, they were randomly divided into four groups, including eight rats in each group. Information on groups is as follows:

Sham control group: no propolis but sham irradiation.

The control group of irradiation (IR) plus propolis group: saline only (1 mL) through an orogastric tube, no IR, no propolis.

The IR group received 5 gray (Gy) gamma irradiation and 1 mL saline as a single dose. IR plus propolis group received both 5 Gy of gamma irradiation as a single dose to total cranium and propolis (80 mg kg^{-1} day^{-1}) starting 1 hour before irradiation and continuing for 10 days through an orogastric tube. Supplementation period was 10 days.

Main Points

- Ionizing radiation produces free radicals.
- Excessive free radicals create nitrosative stress.
- Nitrosative stress plays an important role in the pathogenesis of many diseases.
- Propolis prevented nitrosative stress caused by ionizing radiation.

All rats that received 80 mg kg^{-1} ketamine hydrochloride (Pfizer Pharmaceuticals, Istanbul, Turkey) were anesthetized. Then, the rats in the IR and IR plus propolis groups were given a single dose of ionizing radiation with the aid of a Cobalt-60 teleotherapy unit (Picker, C9, Maryland, NY, USA).

Biochemical Analysis

Determination of nitric oxide synthase activity, nitric oxide, and peroxynitrite levels

All rats were anesthetized with ketamine hydrochloride 50 mg kg^{-1} i.p. on Day 11. Approximately equal amounts of tissue were obtained from the frontal lobes of each rat brain. The homogenization of tissues was carried out in a Teflon glass homogenizer. The supernatant obtained after homogenization was taken into eppendorf tubes and kept at −80°C until biochemical analyzes.

Nitric oxide synthase (NOS) was studied according to the method described by Durak et al.[15] NOS activity was determined by the diazotization of sulfanilic acid by NO at acid pH and subsequent coupling to *N*-(1-napthyl) ethylenediamine. To 0.1 mL of sample, 0.2 mL of 0.2 M arginine was added, and the mixture was incubated at 37°C for 1 hour, after which 0.2 mL of 10 mM HCl, 100 mM sulfanilic acid, and 60 mM N-(1-napthyl) ethylenediamine were added. Absorbance at 540 nm was measured after 30 minutes. Sodium nitroprusside standard solution (25 mM) was used as standard. Results were expressed as U mg^{-1} protein. Nitric oxide ($NO^{\bullet}$) levels were measured as previously described,[16] which express as μmol g^{-1} weight. Peroxynitrite ($ONOO^{-}$) determination was performed according to the method proposed by Vanuffelen et al.[17] and modified by Al-Nimer et al.,[18] which expresses as μmol g^{-1} wet weight. The protein content was determined as described.[19]

Statistical Analysis

The data obtained from the study were analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). The Kolmogorov–Smirnov test

Figure 1. Mean ± SD of nitric oxide ($NO^{\bullet}$) assigned in the brain tissue of rats. IR: irradiated.

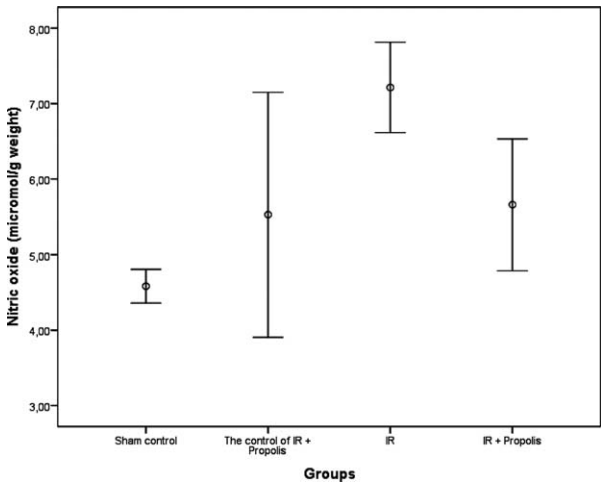


Figure 2. Mean ± SD of nitric oxide synthase (NOS) assigned in the brain tissue of rats. IR: irradiated.

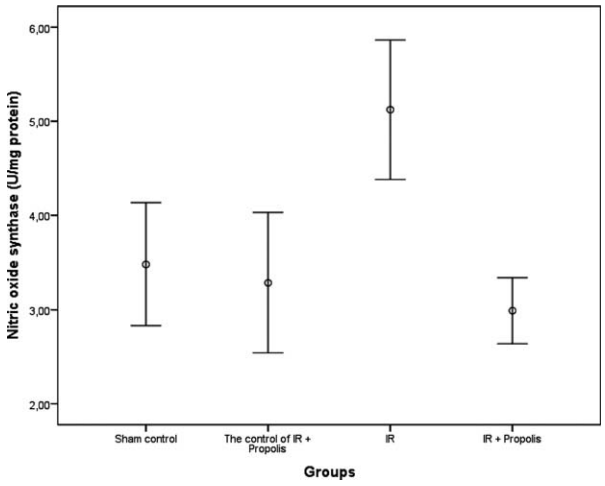
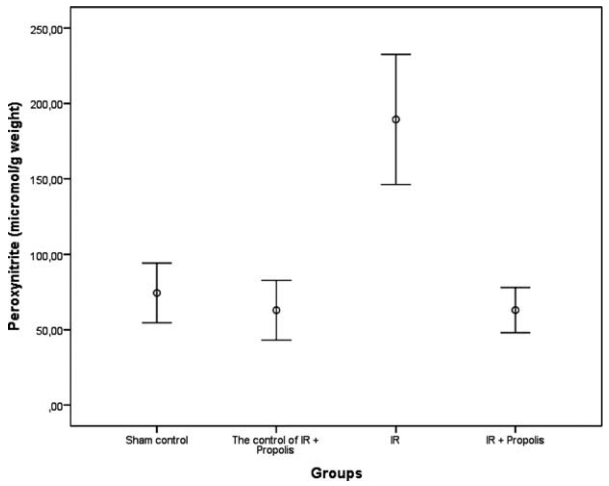


Figure 3. Mean ± SD of peroxynitrite ($ONOO^{-}$) assigned in the brain tissue of rats. IR: irradiated.



was used to test whether the data are parametrical or not. ANOVA and LSD multiple comparison tests were used to compare three independent groups of variables with normal distribution. Mean ± standard deviation was given as descriptive statistics. $P \leq .05$ was considered statistically significant.

RESULTS

Results are shown in Table 1 and Figures 1-3. In statistical analysis, the difference between the groups in terms of $ONOO^{-}$ ($P < .0001$) and $NO^{\bullet}$ ($P < .0001$) values, and NOS activity ($P < .01$) was found to be statistically significant. $ONOO^{-}$, $NO^{\bullet}$ values, and NOS activities were significantly higher in rats in the irradiation-only group than sham control group, irradiation plus propolis, and control group of group given propolis.

DISCUSSION

The physiological processes of all aerobic organisms generate FRs necessary for the maintenance of normal life activities. There are many endogenous FR scavenging pathways in living things, and the balance between FRs and antioxidant systems is crucial to maintain the health of the organism. However, excessive accumulation of FRs damages normal cells and tissues, damages human tissues, and organs and cells and plays a role in the pathogenesis of many diseases.[3,9,20]

Although there are some possible mechanisms by which oxidative/nitrosative stress plays a regulatory role in tumor growth and progression, some important questions remain unanswered. Whether oxidative/nitrosative stress is caused by the increased oxidant production of the tumor, or the deficiency of the antioxidant defense system is not completely explained. Although significant changes in cellular redox homeostasis during tumor growth have been documented in experimental models, such changes have not been demonstrated in humans. Most of the difficulties encountered in these studies are related to the complexity of the biochemical pathways that regulate the cellular redox balance.[21,22]

The purpose of radiation therapy is to carefully give ionized radiation doses to a defined tumor volume to protect the cells and tissues around the tumor with minimal damage, destroy tumor cells, provide the patient with a high quality of life, and prolong survival. The purpose of radiation therapy is to carefully give ionized radiation doses to a defined tumor volume to protect tissues around the tumor with minimal damage, destroy tumor cells, provide the patient with a high quality of life, and prolong survival.[9,11,23]

In some studies, investigating the parameters affected by ionizing radiation as a result of oxidation, it has been reported that ionizing radiation increases the levels of NO in cells and tissues,

leading to an increase in RNS and consequently cause oxidative and nitrosative stress.[9,23] Even though antioxidant properties of propolis are proven in a large number of studies, to our knowledge, this is the first investigation that studied the effects of propolis on radiation-induced nitrosative stress in brain tissue. In the present study, we found that NO• and ONOO− levels and NOS activity in the rats given propolis were significantly lower compared to the rats received irradiation-only group. The results obtained in the study support the research hypothesis that the systemic administration of propolis would reduce the nitrosative damage in irradiated brain tissue.

The brain's antioxidant defense system is vulnerable to brain FR damage, as its ability to cleanse FRs is weaker compared to other tissues. Therefore, a decrease in the antioxidant defense system of brain tissue can cause ROS/RNS deposition during IR.[23–25]

In the present study, we found a significant increase in $NO^{\bullet}$ and $ONOO^{-}$ levels and NOS activity in irradiated rats when compared to other groups, which is similar to that reported by previous studies.[9,23,26] The results support the research hypothesis that the systemic administration of propolis would reduce the nitrosative damage in irradiated brain tissue in the experimental rat model. Our findings support the antioxidant properties of propolis in radiation-induced brain tissue damage.

Although biochemical analyzes suggest that propolis has a radioprotective effect against nitrosative damage in the brain tissue of irradiated rats, the absence of histopathological evaluation supporting this study was one of the limitations of the study.

CONCLUSION

Our findings demonstrated increased nitrosative stress in brain tissue of irradiated rats. This is the first study that investigates the effects of propolis on the nitrosative stress in the brain tissue of the irradiated rats. Oxidative/nitrosative stress is mainly a result of increased ROS and RNS productions and may be one of the main causes of cardiovascular, inflammatory, neurodegenerative, and autoimmune diseases, as well as important in cancer. The current results have shown that propolis clearly prevents from nitrosative stress in radiation-induced brain tissue damage by inhibiting FR generation or scavenging ROS/RNS. The use of propolis as an antioxidant against serious side effects in patients with head and neck cancer exposed to ionizing radiation may be beneficial in obtaining a more beneficial treatment. However, further research is needed to support these results.

Ethics Committee Approval: Ethical committee approval was received from the Gaziantep University (2017/2).

Informed Consent: N/A.

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Author Contributions: Concept - S.T., N.A., E.D.; Design - S.T., E.D.; Supervision - S.T.; Materials - S.T., N.A., E.D.; Data Collection and/or Processing - S.T., N.A., E.D.; Analysis and/or Interpretation - S.T.; Literature Search - S.T., N.A.; Writing Manuscript - S.T., K.C.; Critical Review - S.T., K.C.

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

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Original Article

Ischemia–Reperfusion Injury of Sciatic Nerve in Rats and Protective Role of Benidipine Hydrochloride

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ABSTRACT

Objective: Benidipine is an antihypertansive agent which elicits vasodilatation of arteries by blocking Ca2+. The aim of this study is to investigate the neuroprotective effects of benidipine on rat sciatic nerves exposed to ischemia and reperfusion (I/R).

Method: 30 male Wistar Albino rats were used in this study. The rats were divided into three groups(n=10 per group). I/R procedure was administered to the IR group, 10 μg/kg/day, i.v. benidipine was given for 2 hours (h) to the BIR group before I/R procedure. And a sham group (SG) was created. Next, histopathological and biochemical investigations were performed on sciatic nerve tissues. Superoxide dismutase (SOD), Malondialdehyde (MDA) and glutathione (GSH) were analyzed as oxidative stress markers; interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) were analyzed as inflammatory stress markers in biochemical tests.

Results: Axonal swelling, myelin loss and disorganisation were seen in the IR group. Schwann cells showed hypertrophy, hyperplasia, blood vessels were seen as congested. But these results were under normal values and almost similiar between BIR and SG groups. In the BIR group ischemic fibere degeneration score was significiantly lower than IR group. And MDA, TNF-α, IL-1β values higher, GSH and SOD values were lower in the IR group, but in the BIR group all these values were kept within normal limits.

Conclusion: This study showed that benidipine reduced oxidative stress and inflammation in rat sciatic nerve after I/R injury.

Keywords: ischemia-reperfusion, sciatic nerve, benidipine hydrochloride

INTRODUCTION

Prolonged hypoperfusion of the peripheral nerves usually causes irreversible neuronal damage and neurologic worsening during the first 24–48 hours (h).[1,2] Some studies have mentioned that reperfusion should be achieved within 4.5 h to get rid of irreversible damage.[3,4] Therefore, blood supply to the tissues should be restored as early as possible. Unfortunately, tissue damage may be aggravated after reperfusion.[5,6] This undesirable situation makes it difficult to treat peripheral nerve ischemia. And the pathophysiological mechanism of tissue damage due to ischemia-reperfusion (I/R) injury has not been not fully elucidated. Especially, mediators secreted from endothelial cells have been reported to be effective in I/R injury.[7–10] In this present study, we used benidipine hydrochloride to reduce the damage of I/R injury in the peripheral nerves. Many previous studies mentioned that benidipine reduced the formation of lipid peroxidation and showed antioxidant activity in cells exposed to I/R damage.[11,12] Therefore, our hypothesis is that benidipine may have a protective effect in I/R damaged peripheral nerve tissues. So biochemical and histopathological effects of benidipine hydrochloride on sciatic nerve cells damaged by I/R were investigated.

METHODS

Animals

Before conducting the experiments, permission was obtained from the Animal Care and Use Committee of the Ataturk

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University, Erzurum, Turkey (11/198/25.10.2018). Thirty Wistar Albino rats (280-298 g) were kept in polypropylene cages with a 12/12 h light/dark cycle and controlled temperature (22 ± 2°C) for 1 week prior to the experiments.

Animal Groups

Three different groups (n = 10 per group) were formed.

IR group: Only I/R procedure was administered to the animals of this group.

BIR group: Benidipine hydrochloride, 10 μg/kg, iv for 2 h, was administered to the animals of this group before I/R procedure.

SG group: Sham operation was performed on this group.

Experimental Procedure

An appropriate laboratory environment was prepared for the experiments of all the animal groups. Body temperature of all of the animals was regulated at 37°C. BIR group was pretreated with benidipine hydrochloride (Deva-Turkey) (10 μg/kg/day, i.v. for 2 h). Then all of the animals were anesthetized with 25 mg/kg of thiopental sodium (Ulagay-Turkey). They were fixed to the operating table in supine position. After shaving the anterior abdominal wall of the animals, operation region was sterilized with povidone-iodine solution. Laparotomy was performed. Then, a Yasargil aneurysm clip was used to clamp the abdominal aorta. Blood flow was measured with laser-Doppler flowmetry (PF5010; Perimed Co.Ltd., Sweden). The abdominal region was closed with a sterile surgical thread and all animals were taken into separate single cages for resting. The abdominal cavity was opened from the same skin incision and the clips were removed after 3 hours. After checking the reperfusion with laser-Doppler flowmetry, the abdominal region was closed with a sterile surgical thread. After 24 hours of reperfusion time, animals were sacrificed by thiopental sodium. Animals in the SG underwent only abdominal dissection with the same methods. Left sciatic nerves of the animals were carefully removed (Figure 1). Half of the samples were taken for histopathological examination and the other half was stored in a freezer at −80°C for biochemical evaluation.

Histopathological Examination

The tissue samples were fixed in a 10% formaldehyde solution, washed under tap water, treated with alcohol, and then embedded in paraffin. Four to 5 μm sections were cut from the paraffin blocks, hematoxylin–eosin (H/E) and modified Gomori trichrome staining was administered. Ischemic fiber degeneration (IFD) values were graded according to the method specified by Mitsui et al.[13] According to their method the sections were graded as follows: grade 0: ≤2%, grade 1: 3–25%, grade 2: 26–50%, grade 3: 51–75%, and grade 4: >75%.

Figure 1. Appearance of the left sciatic nerve in a rat.

Biochemical Examination

Determination of superoxide dismutase (SOD) was performed according to the method specified by Sun et al.[14] Malondialdehyde (MDA) measurements were made according to the method specified by Ohkawa et al.[15] The absorbance of supernatant was determined at 530 nm. Total thiobarbituric acid-reactive materials were expressed as MDA. Determination of glutathione (GSH) measurements were made according to the method specified by Sedlak and Lindsay.[16] Determination of interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) levels were performed in the same way as in the previous studies by using rat-specific sandwich enzyme-linked immunosorbent assay Rat Interleukin 1β ELISA Kit (Cat no: YHB0616Ra, Shanghai LZ) and Rat Tumor Necrosis Factor α ELISA kits (Cat no: YHB1098Ra, Shanghai LZ).[16] Analyses were performed in accordance with the manufacturers' instructions.

Statistical Analysis

The results were presented with continuous variables as mean ± standard deviation. The normality of distribution was confirmed with Shapiro–Wilk test. One-way analysis of variance was used for the comparison of three groups. As a post hoc test Tukey's HSD or Games-Howell test was used according to the homogeneity of variances. In graphical representations, the

Main Points

- Prolonged hypoperfusion of the peripheral nerves causes irreversible neuronal damage.
- I/R injury of peripheral nerves usually leads to the release of oxidative stress and acute inflammatory changes in the tissues.
- Benidipine hydrochloride showed histopathologically verified neuroprotective effects against cellular damage after I/R injury.

Figure 2. Hematoxylin (H/E) staining of the sciatic nerve tissues. (A) Hematoxylin–eosin staining of the sciatic nerve tissue obtained from the SG. Axons with normal shape and morphology and normal shape Schwann cells and blood vessels are seen. (B) H/E staining of the sciatic nerve tissue obtained from the IR group. Swollen and degenerated myelinated axon and dilated and congested blood vessel are seen. (C) H/E staining of the sciatic nerve tissue obtained from the BIR group. Decreased congestion in blood vessels and no pericellular edema are seen. ▶: myelinated axon; ▷ Schwann cell nucleus (normal shape); ⋆: blood vessel.

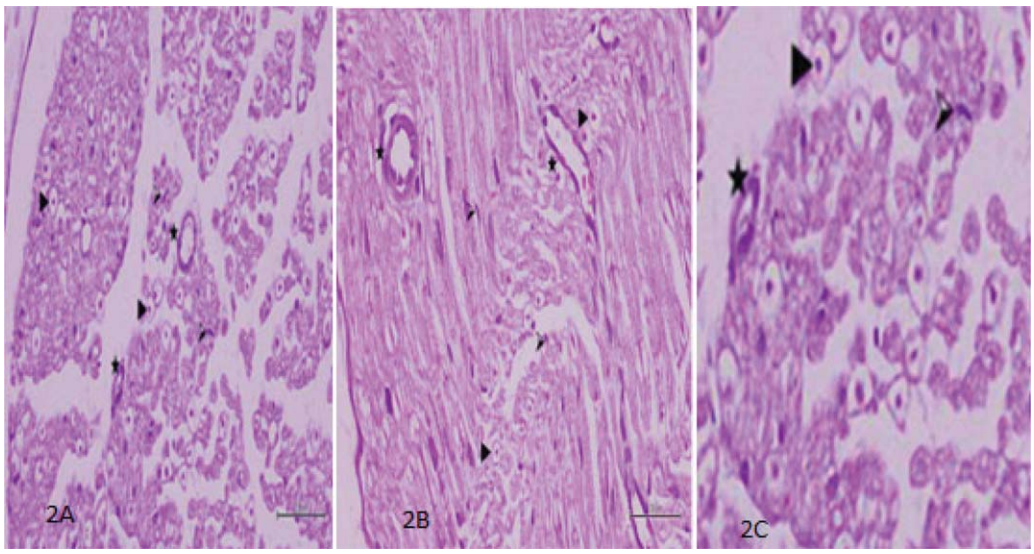
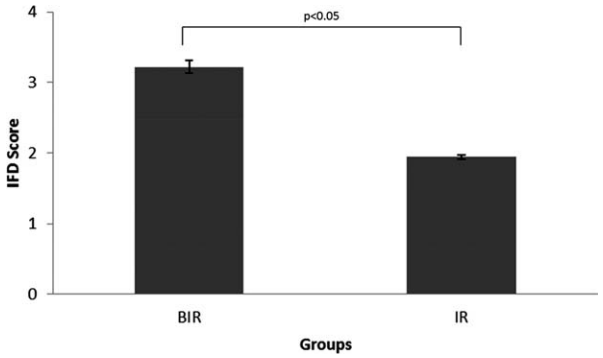


Figure 3. IFD (Ischemic fiber degeneration) scores of sciatic nerves. All data were presented as mean ± SD.



mean levels and standard errors were shown. The statistical level of significance for all tests was considered to be 0.05. Statistical Package for the Social Sciences (SPSS) Version 22.0. (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Histopathological Findings

In the SG group, the nerve structures were generally normal, axons were located centrally and surrounded by normal myelin sheaths. Also, blood vessels were in normal shape and number. Moreover in the SG group, Schwann cells showed neither hypertrophy nor hyperplasia (Figure 2A). On the other hand, there was severe fiber degeneration, axonal swelling, and shrinkage in the IR group. The myelin loss and disorganization were found to be more in this group compared to the SG. Furthermore, Schwann cells showed hypertrophy, and hyperplasia and blood vessels were found as congested (Figure 2B). In addition, histopathological results were almost similar between BIR and SG groups. Myelinated nerve fibers were partially swollen but generally normal in sight and axons located centrally. Schwann cells were found to be normal in shape and morphology. Degeneration of myelin sheaths were decreased and blood vessels were mostly normal in the BIR group (Figure 2C).

And in the IR group, the mean IFD score was 3.22 ± 0.09, and in the BIR group, it was 1.94 ± 0.02. There was a significant difference between the IR and BIR groups about the IFD scores ($P < .05$) (Figure 3).

Biochemical Findings

SOD levels

Figure 4 shows the SOD levels in all of the groups. The mean SOD levels were found statistically lower in the IR group than SG and BIR group ($P < .05$ and $P < .05$, respectively), and there was no significant difference between SG and BIR groups ($P = .602$).

MDA levels

Figure 5 shows the MDA levels in all of the groups. Significantly ($P < .001$) higher levels of MDA were found in the IR group compared to SG and BIR groups.

Figure 4. The levels of SOD on rat sciatic nerves.

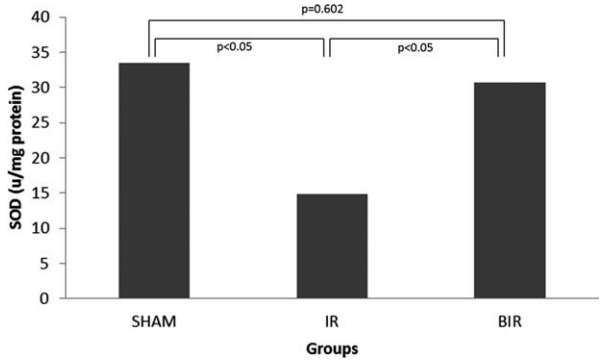


Figure 5. The levels of MDA on rat sciatic nerves.

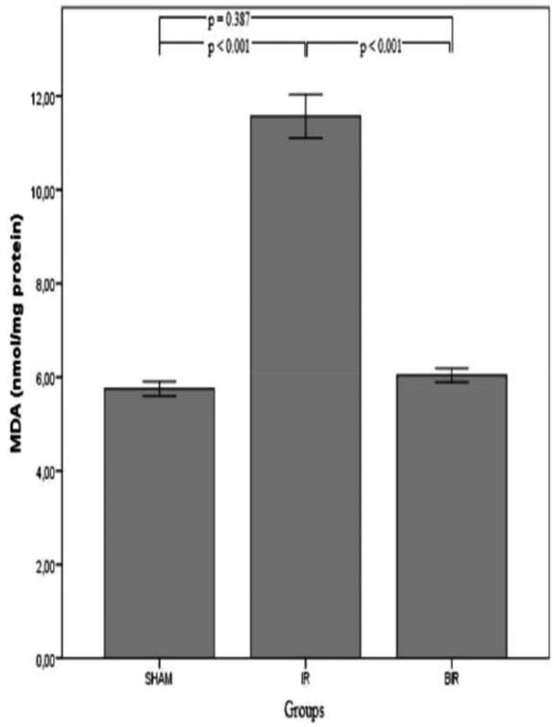


Figure 6. The levels of total GSH on rat sciatic nerves.

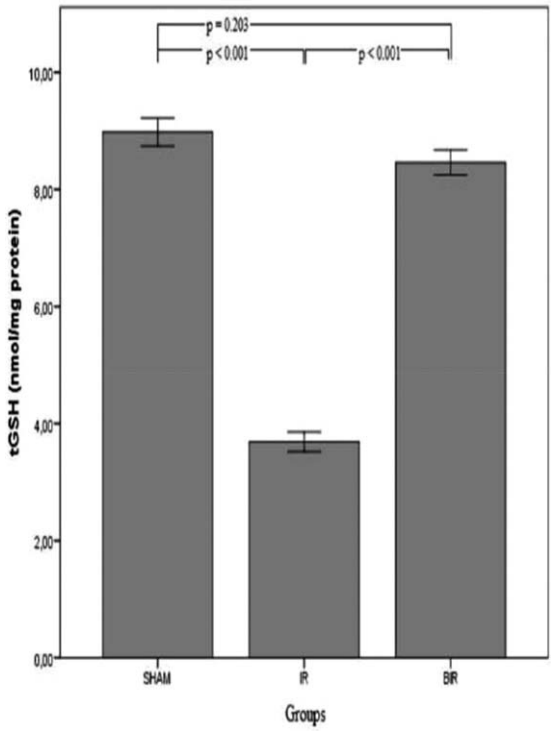
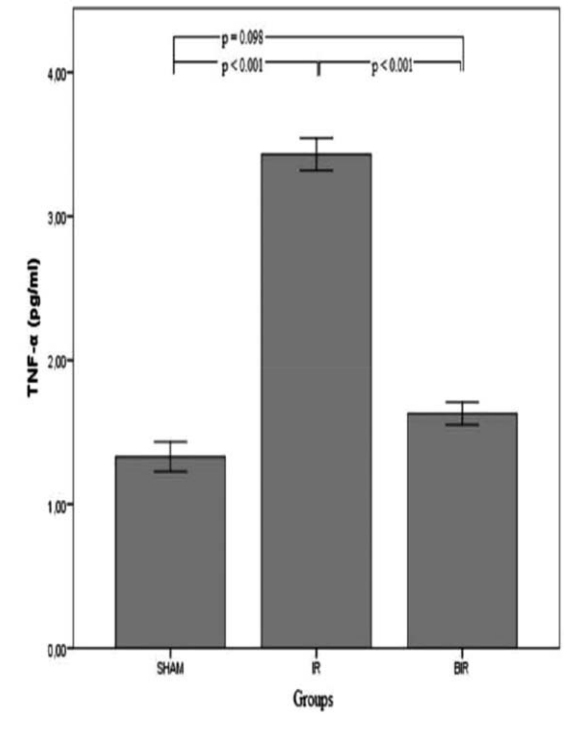


Figure 7. The levels of TNF-α levels on rat sciatic nerves.



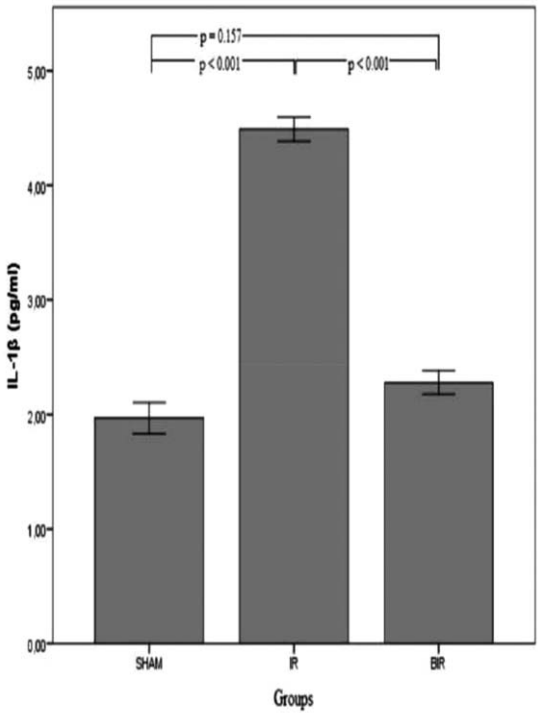
Total GSH levels

Figure 6 shows the GSH levels in all of the groups. There was a significant ($P < .001$) decrease in the levels of GSH in the IR group compared to SG and BIR groups. Pretreatment with benidipine was found to have statistically higher ($P < .001$) GSH levels in the BIR group compared to IR group.

TNF-α and IL-1β Levels

Figures 7 and 8 show the TNF-α and IL-1β levels in all of the groups. Mean TNF-α and IL-1β levels in the IR group were found to be statistically higher than that of BIR group ($P < .001$

Figure 8. The levels of IL-1β levels on rat sciatic nerves.



and $P < .001$, respectively). There were significant decreases in TNF-α and IL-1β levels in the BIR group. Furthermore, there was no significant difference between sham and BIR groups ($P = .098$, $P = .157$).

DISCUSSION

We investigated the tissue-protective effects of benidipine hydrochloride on sciatic nerve I/R injury in rats. Benidipine hydrochloride (10 μg/kg) was administered orally to the BIR group for 2 h. This dose was selected based on the previous studies, which demonstrated that administration of benidipine hydrochloride at this dose markedly reduced calcium overload in the tissues.[17,18] And benidipine showed histopathologically verified neuroprotective effects against cellular damage such as reduction of cellular swelling, hypertrophy/hyperplasia of Schwann cells, and the occurrence of myelin degeneration after I/R injury. Namely, we found significantly lower IFD levels with pretreatment of bendipine hydrochloride. Although various mechanisms have been proposed for the pathophysiology of tissue damage after I/R, the mechanism of this cascade has not been clearly known.[19,20] Many studies state that I/R injury usually leads to the release of oxidative stress and acute inflammatory changes.[2,8,21] Presumably, oxidative stress caused by I/R injury is a result of overproduction of reactive oxygen species (ROS) and excessive ROS production causes tissue damage.[22,23] Bendipine hydrochloride showed a decrease in the levels of, MDA, TNF-α, and IL-1β and an increase in GSH and SOD levels indicating a significant reduction in oxidative stress, inflammation, and an increase in antioxidant marker. According to the previous studies among calcium channel blockers, it was found that benidipine had antioxidative specifications.[11,24] Yasunari et al.[25] indicated that benidipine hydrochloride exhibited protective effect for the tissue at an approximately 100-fold lower concentration than amlodipine and nifedipine. Various methods of measuring the amount of oxidative stress in the tissues have been available in the literature.[26–28] As a sample; measurement of MDA levels has been known as one of the methods to determine the level of oxidative stress and the degree of lipid peroxidation in tissues.[29–33] It was noted by Matsubara et al.[10] that benidipine decreased lipid peroxidation and MDA levels in tissues exposed to I/R injury. And Hassan et al.[9] reported that membrane injury due to lipid peroxidation was ameliorated by the pretreatment of benidipine in myocardial cells. According to the results of our study; benidipine decreased the MDA levels and thus inhibited the formation of lipid peroxidation in sciatic nerve tissues being exposed to I/R.

Also, significantly higher GSH levels were found in the sciatic nerve tissues in the BIR group. The decrease in the antioxidative status also supports the development of oxidative stress and an increase in cellular damage.[34] Therefore, maintaining GSH, an antioxidant enzyme, in normal limits is crucial for the variety of life processes.[35] Because one of the major functions of GSH is detoxification of xenobiotics and/or their metabolites by producing oxidized glutathione in the form of glutathione disulfide. Unlubilgin et al.[16] revealed that benidipine hydrochloride prevented ovaries from the increase in oxidants and proinflammatory cytokines and they found that benidipine prevented the decrease in GSH in the tissues after I/R injury. In the light of all these findings, benidipine hydrochloride may reduce the consumption of GSH by inhibiting the increase in ROS by Ca + 2 channel blockade in tissues exposed to I/R.

It was found in our study that there were statistically significant higher levels of TNF-α and IL-1β in the IR group than BIR group. In other words, benidipine prevented the formation of acute inflammation and inflammatory injury of sciatic nerve cells exposed to I/R. As known, there has been a strong evidence that TNF-α and IL-1β are central regulators of inflammation and their antagonists have proven to be efficacious in treating inflammatory diseases.[36–39] And Yuan et al.[40] showed in their study that myocardial TNF-α and IL-1β expression were significantly less in rats treated with low-dose benidipine hydrochloride compared with untreated rats. Also, it was stated in the previous studies that the tissue protection of benidipine hydrochloride may be caused by suppression of inflammatory cytokines such as TNF-α and IL-1β.[40,41]

In addition, SOD, which is one of the markers of defense against tissue damage caused by ROS, catalyzes the dismutation of superoxide anion to hydrogen peroxide and prevents the formation of the hydroxyl radicals.[42] So SODs have been reported to alleviate inflammatory, respiratory, metabolic, cardiovascular diseases, and central nervous system disorders in the literature.[43] As a sample Ohno et al.[44] mentioned the cardiovascular protective effect of benidipine in their study and they stated that this agent increased SOD levels in the tissues. And this mechanism had been reported to be achieved by Ca + 2 channel blockade in addition to its antihypertensive efficacy.

CONCLUSIONS

Lack of neurophysiological evaluation by electromyography was the limitation of our study. On the contrary, we are at the opinion that benidipine hydrochloride may become an alternative or a supplementary agent in the treatment of axonal I/R injury.

Ethics Committee Approval: This study was approved by Ethics committee of Animal Care and Use Committee of the Ataturk University, Erzurum, Turkey (Approval No: 11/198/25.10.2018).

Informed Consent: N/A

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Original Article

Effect of Sugammadex on Coagulation Parameters in Cesarean Section Patients a Prospective Controlled Observational Study

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ABSTRACT

Objective: To evaluate, for the first time in the literature, the effect of sugammadex in elective C/S patients in terms of hemostatic parameters and postoperative bleeding.

Methods: Seventy-six patients enrolled for this observational prospective controlled study. Patients were divided into two groups according to anesthetic reversal agent: sugammadex (group I) vs neostigmin (group II). Intraoperative and postoperative amount of bleeding were recorded. At the end of the surgery, after administration of reversal agent, and at postoperative 30th minute, 1st, and 2nd hours, activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) values were recorded. Postoperative Hct, Hgb, and Plt values at 6th and 24th hours of reversal agent administration were also recorded.

Results: Alterations in aPTT, PT, and INR values were similar between the groups ($P = .986, .549, .05$, respectively).

Conclusion: Sugammadex at 2 mg kg^{-1} in cesarean section patients has a similar effect on coagulation parameters compared to neostigmin. Further studies are needed particularly in patients under thromboprophylaxis.

Keywords: Cesarean section, coagulation, sugammadex, aPTT, neostigmin, postpartum bleeding

INTRODUCTION

Maintenance of pregnancy and fetal well-being depends on several changes in hemostatic system. However, these changes in pregnancy may also cause an increase in maternal hematological complications during pregnancy, delivery, and postpartum period.[1-4] Hemostasis comprises very complex mechanisms with several alterations in both coagulation and fibrinolytic systems. In normal pregnancy concentration of coagulation factors, V, VII, IX, XII, fibrinogen, and von Willebrand factors show a significant increase.[5-8]

On the other hand, factor XI level, which is the one of the key factors for thrombin formation, decreases in pregnancy. Levels of coagulation inhibitors also show alterations during pregnancy. Protein C and antithrombin remain at the same levels, while protein C inhibitors and free and total protein S increase during pregnancy. Fibrinolytic system function is also inhibited during pregnancy and returns its normal activity just after the delivery.[5] As a result of all of these alterations, pregnancy becomes a hypercoagulable state. This hypercoagulable state is one of the preventive mechanism for postpartum hemorrhage after the delivery. Because we know that postpartum hemorrhage is still an important maternal mortality and morbidity reason in both vaginal and cesarean section (C/S) delivery, proper functioning of this system is very important.

Due to increasing trend of cesarean delivery in whole world, anesthetic management of C/S is more in sight of the researchers. Although regional anesthesia is more recommended by the guidelines for C/S, general anesthesia is still widely used around the world. Intubation of pregnant women is one of major challenges because of the higher incidence of difficult intubation compared to normal population.[9] Recently, a newly introduced sugammadex has being used for the reversal of nondepolarizing neuromuscular blocking agents (rocuronium and vecuronium) in C/S patients. Sugammadex shows its effect by encapsulation of vecuronium and rocuronium.[10-13] Compared to other acetylcholinesterase inhibitors (neostigmine, etc.), sugammadex has better recovery and less residual blocking effect.[14] Also, several studies have been showed its applicability in C/S patients.[15-19] On the other hand, studies have been reported the alterations in hemostatic parameters as an

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effect of sugammadex.[20-22] These studies especially underlined the prolongation in activated partial thromboplastin time (aPTT) and prothrombin time (PT). However, its clinical consequences, in the context of postoperative bleeding, in different surgical patients are still unknown.

In this study, we aimed to evaluate, for the first time in the literature, the effect of sugammadex in the elective CS patients in terms of hemostatic parameters and postoperative bleeding.

METHODS

This observational prospective study was conducted at a university hospital. After obtaining Ethical Committee approval was obtained in 2019 from Niğde Ömer Halisdemir University Medical Faculty Ethics Committee, informed consents were taken from all participants. A total of 76 patients scheduled for elective C/S were included in this study. All the patients were in the ASA I-II (American Society of Anesthesiologists). Patients with pre-eclampsia, intrauterin growth retardation (IUGR), pregestational or gestational diabetes mellitus, multiple gestation, macrosomic fetus, known hematologic disorders, abnormal blood tests result in platelet (Plt) count, activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR), and patients receiving anticoagulant/antiaggregant drugs were excluded from the study cohort. General anesthesia indications were maternal refusal of, or inability to cooperate with, neuraxial anesthesia.

Patients were divided into two groups: sugammadex (group I, n = 39) and neostigmine (group II, n = 37). Assignment of patients into groups was done by two anesthesiologists (D.D. and F.K.) preoperatively according to ASA guideline. All C/S operations were performed by same physician (E.D.).

In the operating room, all patients were monitorized for heart rate, pulse oximeter, end-tidal carbon dioxide level, noninvasive arterial pressure, and neuromuscular block monitoring (train of four (TOF) Watch SX monitor; Organon, Dublin, Ireland). Following the administration of 2-2.5 mg kg^{-1} propofol and 0.6 mg kg^{-1} rocuronium, intubation was performed. Maintenance of anesthetic status of patients was achieved with sevoflurane 2%, 2 L oxygen + 2 L dry air with 0.8 mL kg^{-1} tidal volume. To keep end-tidal volume CO_2 level at 30-35 mmHg, frequency of respiration was adjusted as 12 min^{-1}. Paracetamol (Parol flacon 10 mg mL^{-1}, Mefar Chemistry, İstanbul, Turkey) infusion 1 g/100 mL was applied to all patients after the removal of placenta. The modified Misgav-Ladach technique was used as C/S method in all patients. After the cord clamping, all patients received 20 U oxytocin infusion with 1,000 mL saline solution. Intraoperative blood loss was calculated by measurements of blood-soaked pads and amount of blood in aspiration tube. At the end of the surgery, group I patients were applied 2 mg kg^{-1} sugammadex (Bridion® 200 mg/2 mL, N.V. Organon Kloosterstraa 6, Holland), and group II patients were applied 0.05 mg kg^{-1} neostigmine and 0.02 mg kg^{-1} atropine. When TOF $\geq$ 0.9, patients were extubated and transferred to postoperative recovery room. After the operation, in the postoperative obstetric unit, blood samples were taken for coagulation parameters at 30th minute, 1st, and 2nd hours of following the administration of sugammadex or neostigmine. Whole blood counts samples were also taken from all patients at postoperative 6th and 24th hours. Pad weights were measured to evaluate the blood loss at first 24 hours.

Main Points

- Sugammadex prolongs activated partial thromboplastin and prothrombin time, but the association between prolongation and effect on postoperative bleeding remains unknown in cesarean section patients.
- Sugammadex was evaluated, for the first time, in cesarean section patients, in terms of alterations in coagulation parameters and postoperative bleeding.
- In this study, we found that sugammadex is safe to use in cesarean section, because it did not cause an increase in activated partial thromboplastin and prothrombin time.

Statistical Analysis

The data were analyzed using IBM SPSS Corp.; Armonk, NY, USA. The alterations in aPTT, PT, INR, Hgb, Htc, and Plt values according to group and time were examined with generalized linear models (Wald Chi-square test). Demographic characteristics, intraoperative bleeding, and pad weight comparisons of groups were evaluated with independent t-test. The Mann–-Whitney U test was used to examine gravida, parity, and number of CS between the groups. *P* value of <.05 was considered statistically significant. Power analysis was performed using the G-power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany). Post hoc power analysis demonstrated that we achieved a power of 0.83 with a 5% level of significance and a 0.60 effect size to use one-tailed two independent mains t-test.

Hemostatic Tests

Preoperative and postoperative aPTT and PT blood samples were taken into citrate-included tubes and centrifuged at 2,000 × *g* for 10 minutes at 4° C, and plasma samples were analyzed by original reagent on ERBA analyzer.

RESULTS

A total of 76 patients who met the criteria were included. Comparison of groups demographic data and amount of bleeding is shown in Table 1. There were no differences between the groups in terms of age, BMI, gravida, parity, and amount of intraoperative bleeding and duration of surgery. At the first 24 hours of postoperative period, mean pad weights of groups were significantly higher in group I (*P* = .037). aPTT, PT, and INR values were evaluated in terms of time, group, and group–time interaction effect. The group and time interaction had no significant effect on the aPTT and PT mean values (*P* = .986 and .549, respectively) (Table 2). Main effect of time on aPTT and PT was statistically significant within the groups themselves (*P* = .022 and <.001, respectively) (Table 2). But, upper or lower limit of aPTT, PT, and INR values did not exceed at any time of sugammadex administration (Table 3). Main effect of group and time on INR mean values showed no significant differences (*P* > .05). Also, the effect of group and time interaction on INR mean values was similar between the groups (*P* > .05) (Table 2). While the main effect of groups on Hgb and Htc values was not significant, the main effect of time on Hgb, Htc, and Plt values

Table 1. Comparison of Demographic and Operative Data between the Groups

	Sugammadex (n = 39)	Neostigmin (n = 37)	Total (n = 76)	*P*
Age (year)	27.9 ± 5.3	29.4 ± 5.2	28.6 ± 5.3	.217*
Height (cm)	163.6 ± 4.1	163.2 ± 6.1	163.4 ± 5.1	.757
Weight (kg)	77.5 ± 6.8	73.6 ± 10.5	75.6 ± 8.9	.062
BMI	28.9 ± 2.5	27.6 ± 3.5	28.3 ± 3.1	.056
Gravity, n	3 (1–6)	2 (1–5)	2 (1–6)	.199**
Parity, n	2 (0–5)	1 (0–4)	1 (0–5)	.251**
Number of C/S, n	2 (1–4)	2 (1–3)	2 (1–4)	.836**
Amount of intraoperative bleeding (mL)	513.6 ± 191.5	547.7 ± 203.7	530.2 ± 196.9	.454*
Ped weight (mg)	433.5 ± 150.7	365.9 ± 124.6	400.6 ± 141.8	**.037***

*Independent samples t test (mean ± SD).
**Mann–Whitney U test [median (min – max)].
Note: Statistically significant values are indicated in bold.

Table 2. Comparison of aPTT, PT, and INR Values between the Groups in Terms of Group and Time

	APTT*	PTZ*	INR*
Group	0.263	0.997	0.190
Time	**0.022**	**<0.001**	0.333
Group × time	0.986	0.549	0.396

*Generalized linear models *P* value.
Note: Statistically significant values are indicated in bold.

was significantly different between the groups ($P < .001$, <.001, and .020, respectively) (Table 4). The effect of group and time interaction on Hgb, Htc, and Plt was also similar between the groups ($P > .05$) (Table 4). Descriptive statistics and multiple comparison results of hemoglobin, Hct, and Plt values by group and time were shown in Table 5.

DISCUSSION

In this study, we found that coagulation parameters showed no significant differences after the administration of sugammadex at a dose of 2 mg kg^{-1} when compared to neostigmine. Also, postoperative hemoglobin, hematocrit, and platelet values were similar between the groups.

Literature about sugammadex is relatively new. The effect of sugammadex on coagulation parameters was documented with in vitro studies, which showed a limited and transient increase in both aPTT and PT values via the inhibition of factor Xa activity.[23] This effect was first observed at 10 minute after the administration and resolved within 60 minutes. For the last 10 years, several studies have been showed this effect with in vivo research. In 2013 and 2014, De Kam et al.[21,22] showed a transient and limited increase in aPTT and PT related to sugammadex use. However, this increment was not associated with more postoperative bleeding. Studies were randomized and double-blinded, sugammadex was administered at doses of 4 mg kg^{-1} or 16 mg kg^{-1} to patients, and also each patient was taking aspirin alone or enoxaparin and unfractioned heparin. In another study, Rahe-Meyer et al.[20] found similar results in patients with increased risk of bleeding because of concomitant use of thromboprophylaxis agent. They revealed a transient (<1 hour) and limited (<%8) rise in aPTT and PT. Also, their results were not accompanied by an arise in postoperative bleeding. In current study, we did not observe any increase in aPTT and PT. In the assessment of postoperative bleeding, hemoglobin, hematocrit, and platelet levels showed similar alteration between the groups. However, mean pad weights were significantly higher in sugammdex group. In 2015, Taş et al.[24] investigated the effect of sugammadex on coagulation parameters and postoperative bleeding in patients who had septoplasty surgery. They found no difference in terms of coagulation parameters, while the amount of postoperative bleeding was higher in sugammadex group. Their results were similar to ours, but they measured amount of postoperative bleeding by nasal tip dressing, which is more objective to accurately detect the amount of bleeding than our method. Also, the effect of sugammadex on Hgb and Htc values was similar compared to neostigmine administration in our study, which is more objective criteria to evaluate the amount of postoperative bleeding. One prospective observational study published in 2015 investigated the patients who underwent open abdominal cancer surgery.[25] In their study, cohort divided into three groups: neostigmine, sugammadex 2 mg kg^{-1}, and sugammadex 4 mg kg^{-1}. At the end of the study, they did not observe

Table 3. Descriptive Statistics and Multiple Comparison Results of APTT(sn), PTZ(sn), and INR Values by Group and Time

Group	Time	APTT	PTZ	INR
Sugammadex	Preoperative	26.5 ± 2.4	11.1 ± 0.8	0.969 ± 0.066
	Postoperative 30th minute	25.8 ± 2.2	11.4 ± 0.8	0.992 ± 0.071
	Postoperative 1st hour	25.4 ± 2.4	11.5 ± 1.1	1.006 ± 0.089
	Postoperative 2nd hour	25.7 ± 2.6	11.6 ± 1.0	1.004 ± 0.084
	Total	25.8 ± 2.4	11.4 ± 0.9	0.993 ± 0.078
Neostigmin	Preoperative	26.2 ± 2.2	10.9 ± 0.5	0.951 ± 0.042
	Postoperative 30th minute	25.6 ± 2.1	11.6 ± 0.8	1.265 ± 1.579
	Postoperative 1st hour	25.1 ± 2.2	11.6 ± 0.5	0.955 ± 0.225
	Postoperative 2nd hour	25.3 ± 2.6	11.6 ± 0.6	1.251 ± 1.472
	Total	25.5 ± 2.3	11.4 ± 0.7	1.105 ± 1.085
Total	Preoperative	26.3 ± 2.3[a]	11.0 ± 0.7[a]	0.960 ± 0.056
	Postoperative 30th minute	25.7 ± 2.2ab	11.5 ± 0.8b	1.125 ± 1.104
	Postoperative 1st hour	25.2 ± 2.3[b]	11.5 ± 0.8[b]	0.981 ± 0.170
	Postoperative 2nd hour	25.5 ± 2.6[b]	11.6 ± 0.8[b]	1.124 ± 1.029
	Total	25.7 ± 2.4	11.4 ± 0.8	1.048 ± 0.760

There is no difference between times with the same letter (a, b) in each parameter.

Table 4. Comparison of Hgb, Htc, and Plt Values by Group and Time

	Hemoglobin*	HTC*	PLT*
Group	0.714	0.575	**0.005**
Time	**<0.001**	**<0.001**	**0.020**
Group × time	0.963	0.754	0.922

*Generalized linear models *P* value.
Note: Statistically significant values are indicated in bold.

any significant difference between the groups in terms of coagulation parameters and postoperative hemoglobin concentrations. Relative weakness of this study is that they had small number of patients in neostigmine group (n = 11), which were 37 in our study.

To our knowledge, this is the first study in the literature that evaluated the effect of sugammadex in C/S patients in the context of coagulation parameters and postoperative bleeding. However, the effect of sugammadex on coagulation parameters only has been seen so far with doses of 4 mg kg^{-1} and 16 mg kg^{-1}.[26] Mean prolongations of aPTT and PT were both by 22%.[26] Our study was conducted with doses of 2 mg kg^{-1}, which is advised by ASA for C/S patients.

In conclusion, our prospective observational study demonstrated that sugammadex is not related to a significant increase in aPTT and PT or decrease in postoperative hemoglobin, hematocrit, and platelet levels. This study is the first one that investigated coagulation parameters and postoperative bleeding among C/S patients. But, further studies are needed to investigate the relation between the sugammadex and postcesarean patients particularly with patients who use thromboprophylaxis during the pregnancy.

Table 5. Descriptive Statistics and Multiple Comparison Results of Hgb (g dL^{-1}), Htc (%), and Plt Values by Group and Time

Group	Time	Hgb	Htc	Plt
Sugammadex	Preoperative	12.2 ± 1.4	37.2 ± 3.2	236,948.7 ± 67,050.2
	Postoperative 6 hours	10.9 ± 1.4	33.4 ± 3.8	214,256.4 ± 66,148.4
	Postoperative 24 hours	10.5 ± 1.3	32.6 ± 3.5	222,128.2 ± 59,198.2
	Total	11.2 ± 1.5	34.4 ± 4.0	224,444.4 ± 64,369.3
Neostigmin	Preoperative	12.4 ± 1.4	37.3 ± 3.4	219,405.4 ± 56,810.8
	Postoperative 6 hours	11.0 ± 1.5	33.2 ± 3.9	191,162.2 ± 50,417.4
	Postoperative 24 hours	10.6 ± 1.5	31.8 ± 3.7	197,324.3 ± 50,666.7
	Total	11.3 ± 1.7	34.1 ± 4.4	202,630.6 ± 53,634.6
Total	Preoperative	12.3 ± 1.4*	37.3 ± 3.3*	228,407.9 ± 62,489.5*
	Postoperative 6 hours	10.9 ± 1.4b	33.3 ± 3.8**	203,013.6 ± 59,767.2**
	Postoperative 24 hours	10.6 ± 1.4**	32.2 ± 3.6**	210,052.6 ± 56,245.4**
	Total	11.3 ± 1.6	34.3 ± 4.2	213,824.6 ± 60,255.4

There is no difference between times with the same letter *,**in each parameter.

Ethics Committee Approval: Ethical committee approval was received from the Niğde Ömer Halisdemir University (2019/34).

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

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Original Article

A Bibliometric Analysis of Turkish Research Activity in the Rheumatology Category of the Web of Science Database

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ABSTRACT

Objective: The aim of this study was to investigate a bibliometric analysis of publications produced by researchers from Turkey and cataloged in Web of Science's (WoS) Science Citation Index-Expanded (SCI-E) under the rheumatology category.

Methods: The WoS database's 2019 data was scanned for journals in the rheumatology category and indexed in the SCI-E. Articles identified as having been published before January 1, 2020 in the advanced search section of the WoS database were examined using their journal ISSN numbers. Meeting summaries, proceedings, early access studies, book series, and conference titles were excluded. All bibliometric data were evaluated for each publication.

Results: Thirty-one journals scanned in the rheumatology category were investigated. It was determined that a total of 84,761 articles were published over 40 years (1980-2019), and that 3,179 (3.75%) of these articles were written solely by Turkish authors. It was observed that these 3,179 articles were cited 43,494 times, and that the average number of citations was 13.68 ± 23.52. The total h-index value was 76. The most cited article received 444 citations and the article with the highest annual average number of citations had a value of 20.17 citations/year. It was found that of the top 20 most cited articles, seven articles were about Behçet's disease, and four concerned familial Mediterranean fever.

Conclusion: This study will contribute to the literature by reflecting upon the amount of research that has been carried out and shedding light on future work that could be considered in the field of rheumatology in Turkey.

Keywords: Bibliometric analysis, rheumatology, Turkey

INTRODUCTION

Rheumatology is a branch of medicine that deals with the treatment (preventive, active, and rehabilitation) of musculoskeletal diseases, including autoimmune and autoinflammatory conditions.[1] Rheumatic disorders are some of the most common health problems in the world, and they can lead to disability in both children and adults.[2] Although a large number of studies have been conducted on common rheumatic diseases, such as rheumatoid arthritis and spondylarthritis, research on the prevalence of all rheumatic diseases in the general population is limited, with figures ranging from 9.8% to 25%.[3–5] Rheumatology as a study dates back to ancient times, while its development as a specialty began in the 20th century. Thanks to the administration of medication such as steroids, methotrexate, and anti-TNF, crucial developments have occurred in the field of rheumatology, particularly over the last five decades.[6,7]

Rheumatology is an extensive field of research with a long standing in scientific publications. The demand for rheumatology has increased due to the widespread presence of these diseases in the community and the recent discovery of new drugs.[7] The number of publications in the field of rheumatology has therefore been increasing almost every year, on a par with other fields.[8,9]

A bibliometric study is one method that can be used to numerically analyze the publications produced by people or institutions in a particular area, period, or region, to investigate associations between these publications, and to draw conclusions from these findings.[10] In bibliometric studies, a large number of features, such as publication type, topic, number of citations, number of authors, the affiliations of these authors, and journal index and category, may be examined.[11] Moreover, a bibliometric analysis can provide insight into the growing tendencies and characteristics of research output by analyzing keywords and subject categories. Additionally, an investigation into bibliometric properties may reveal differences in research orientation and capacities.[12] Bibliometric analyses are now

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being performed in many scientific fields in order to investigate the impact of research.[13]

Web of Science (WoS) is recognized as the world's most reliable publisher-independent global citation database.[14] WoS features a wide range of indexes, including Science Citation Index Expanded (SCI-E). According to the data for 2019, the SCI-E index includes 178 different scientific disciplines across approximately 9,200 journals.[14] Each journal and book covered by WoS' core collection is assigned to at least one subject category, one of which is rheumatology.[15]

The scope of a country's international publications is an essential indicator of its level of scientific advancement.[16] Bibliometric analysis is a popular method that has been used to assess this in recent years.[17] Nonetheless, to the best of our knowledge, no comprehensive bibliometric study on Turkish research in the field of rheumatology has previously been carried out.

The present study aims to conduct a bibliometric analysis of Turkish research in the WoS' SCI-E index, under the rheumatology category, in order to provide a holistic view of these publications and a new perspective for directions in which future research could go.

MATERIALS AND METHODS

In line with Journal Citation Reports' data for 2019, 32 journals were found in the SCI-E index under the rheumatology category. *Rev Bras Reumatol* (ISSN: 0482-5004) was renamed as *Adv Rheumatol* (ISSN: 2523-3106) in 2018. Articles published in both versions of the journal were therefore combined for the purpose of this study. This means that the total number of journals examined was 31 (Table 1). All relevant articles published in these journals were determined by conducting a WoS advanced search with the journals' ISSN numbers. Among these publications, the following were excluded: Articles published after 31 December 2019, meeting abstracts, proceedings papers, early access articles, reprints, book series titles, and conference titles.

This study was conducted in order to investigate articles under the WoS' rheumatology category written by authors with Turkish-based affiliations. Multicenter publications involving the participation of more than one country could have affected the statistical values, thus all countries except Turkey were excluded from the countries/regions search. The names of these articles, the journals to which they belonged, the authors, the year of publication, the authors' affiliations, and the numbers of citations were recorded in line with the WoS' data. To ascertain the number of citations, data before January 1, 2020 was evaluated in the same way as the publication data. The details for each publication were recorded under the following column headings: Author(s), title, year, journal name, author(s)' affiliations, and document type. For each publication, all information relevant to the analysis was exported to Microsoft Excel, Plain Text, and a reference management tool (EndNote Desktop). The extracted data include author(s), title, source, addresses, times cited, and keywords. VOSviewer software (Version 1.6.15, Center for Science and Technology Studies, Leiden University, Netherlands) was used to create a collaboration and word co-occurrence network and to evaluate citation densities.[18]

Main Points

- With this study, providing information about the Turkey-based articles in the field of *Rheumatology* and it is aimed at helping researchers in future studies.
- It is thought that this article could help direct future studies.
- In this study, it has been determined that Turkey-based articles in the field of Rheumatology have increased over the years.

RESULTS

Over a period of 40 years (1980-2019), 84,761 publications were published in the 31 journals scanned in the rheumatology category. The number of publications with an author with a Turkish-based affiliation was 3,717 (4.39%), while the number of publications written by authors all with a Turkish-based affiliation was 3,179 (3.75%). The articles' distribution by year is illustrated in Figure 1. Of the publications, 3,179 were cited a total of 43,494 times before January 1, 2020. The mean number of citations per publication was 13.68 ± 23.52. It was observed that 2,692 of the articles had been cited, while 487 articles have never been cited. The *h-index* for all the articles was found to be 76. The most cited article had 444 citations,[19] and the article with the highest annual average number of citations had 20.17 citations.[20]

The top 20 most cited articles on rheumatology written by authors all with Turkish-based affiliations are presented in Table 2.[19–38] The top 20 articles with the most citations per year are presented in Table 3.[19,20,22–24,27,28,31,32,35,38–47] The totals of 11 articles are included in both tables.[19,20,22–24,27,28,31,32,35,38] Seven of the top 20 most cited articles were on Behçet's disease[19,23,24,28,30,33,34] and four were on familial Mediterranean fever.[26,29,35,38]

Turkey is ranked 13 when it comes to the number of articles published in the field of rheumatology (3.23%). As a comparison, the rankings of other countries are ordered as follows: USA (23.22%), UK (11.99%), Germany (8.66%), France (6.77%), Italy (6.58%), Canada (6.39%), Netherlands (6.29%), Japan (5.93%), Spain (3.97%), China (3.71%), Sweden (3.31%), and Australia (3.29%).

It was observed that the three institutions with the highest number of publications were Hacettepe University with 383, Istanbul University with 364, and Ankara University with 180. A collaboration map for the top 25 most productive institutions is shown in Figure 2. It was seen that 4,188 different keywords were used in all the articles. The 50 most frequent keywords are presented in Figure 3.

In terms of number of citations, the most cited institution was Istanbul University, with 5,568 citations, followed by Hacettepe University, with 5,326 citations, and Ankara University, with 2,924 citations. In addition, the cooperation map of the top 25 most cited institutions is shown in Figure 4.

Table 1. Journals in the Rheumatology Category in the Web of Science Database in 2019

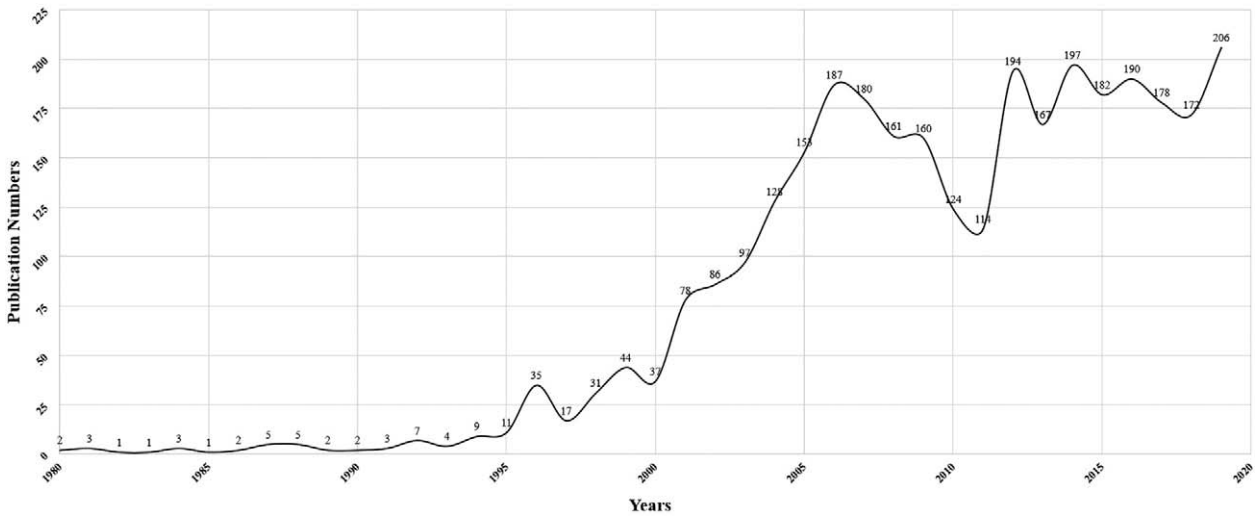
	Journal Title	Journal Title Abbreviation	ISSN	IF	NP	
					Contributions of All country	Contributions of Turkey
1	Acta Reumatologica Portuguesa	Acta Reumatol Port	0303-464X	1.183	836	80
2	Advances in Rheumatology *	Adv Rheumatol	2523-3106	0.854	106	3
3	Aktuelle Rheumatologie	Aktuel Rheumatol	0341-051X	0.316	2.082	9
4	Annals of The Rheumatic Diseases	Ann Rheum Dis	0003-4967	16.102	12.596	69
5	Archives of Rheumatology	Arch Rheumatol	2148-5046	0.731	421	258
6	Arthritis Care & Research	Arthrit Care Res	2151-464X	4.056	2.759	6
7	Arthritis Research & Therapy	Arthritis Res Ther	1478-6354	4.103	4.560	11
8	Arthritis & Rheumatology	Arthritis Rheumatol	2326-5191	9.586	2.322	9
9	Best Practice & Research in Clinical Rheumatology	Best Pract Res Cl Rh	1521-6942	2.727	1.371	11
10	BMC Musculoskeletal Disorders	BMC Musculoskel Dis	1471-2474	1.879	4.932	15
11	Clinical and Experimental Rheumatology	Clin Exp Rheumatol	0392-856X	3.319	7.940	294
12	Clinical Rheumatology	Clin Rheumatol	0770-3198	2.394	7.136	601
13	Current Opinion in Rheumatology	Curr Opin Rheumatol	1040-8711	4.006	1.930	14
14	Current Rheumatology Reports	Curr Rheumatol Rep	1523-3774	3.873	726	6
15	International Journal of Rheumatic Diseases	Int J Rheum Dis	1756-1841	1.980	2.039	157
16	JCR-Journal of Clinical Rheumatology	JCR-J Clin Rheumatol	1076-1608	2.360	2.567	88
17	Joint Bone Spine	Joint Bone Spine	1297-319X	3.741	3.138	111
18	Journal of Rheumatology	J Rheumatol	0315-162X	3.350	18.599	136
19	Lupus	Lupus	0961-2033	2.251	4.987	58
20	Modern Rheumatology	Mod Rheumatol	1439-7595	2.113	1.886	73
21	Nature Reviews Rheumatology	Nat Rev Rheumatol	1759-4790	16.625	1.371	5
22	Osteoarthritis and Cartilage	Osteoarthr Cartilage	1063-4584	4.793	4.009	1
23	Pediatric Rheumatology	Pediatr Rheumatol	1546-0096	2.595	617	4
24	Revista Brasileira De Reumatologia†	Rev Bras Reumatol	0482-5004	1.810		1

Table 1. Journals in the Rheumatology Category in the Web of Science Database in 2019 (Continued)

	Journal Title	Journal Title Abbreviation	ISSN	IF	NP	
					Contributions of All country	Contributions of Turkey
25	Rheumatic Disease Clinics of North America	Rheum Dis Clin N Am	0889-857X	3.244	1.783	-
26	Rheumatology	Rheumatology	1462-0324	5.606	8.261	97
27	Rheumatology and Therapy	Rheumatol Ther	2198-6576	3.615	156	
28	Rheumatology International	Rheumatol Int	0172-8172	1.984	5.756	939
29	Scandinavian Journal of Rheumatology	Scand J Rheumatol	0300-9742	3.025	3.928	68
30	Seminars in Arthritis and Rheumatism	Semin Arthritis Rheu	0049-0172	4.751	2.444	10
31	Therapeutic Advances in Musculoskeletal Disease	Ther Adv Musculoskel	1759-720X	5.043	131	6
32	Zeitschrift Fur Rheumatologie	Z Rheumatol	0340-1855	1.166	3.777	35

Abbreviations: IF: impact factor; NP: number of publications.
The name of the journal called Rev Bras Reumatol.
*In 2018; in the evaluations, both were combined and analyzed.
†Changed to Adv Rheumatol.

Figure 1. Illustration of the distribution of articles by year.



Twenty-nine of the rheumatology journals included articles with a Turkish affiliation. It was observed that the most articles with a Turkish affiliation were published in *Rheumatol Int* journal (939 articles). *Clin Rheumatol* was second with 601 articles, and *Clin Exp Rheumatol* was third with 294 articles. The number of Turkish articles published in these journals is shown in Table 1.

It was seen that the top three journals also ranked in the same order when it came to the citation analysis of the articles

Table 2. The 20 Most Cited Articles in Rheumatology from Turkey Between 1980 and 2019

	Title	Journal	Year	TC	PC
1	Vascular Involvement in Behçet's Disease[19]	J Rheumatol	1992	444	15.86
2	Inuence of Age of Onset and Patient's Sex on the Prevalence and Severity of Manifestations of Behçet's Syndrome[30]	Ann Rheum Dis	1984	285	7.92
3	Behçet's Disease: Infectious Etiology, New Autoantigens, and HLA-B51[23]	Ann Rheum Dis	2001	243	12.79
4	Mean platelet volume (MPV) as an inammatory marker in ankylosing spondylitis and rheumatoid arthritis[20]	Joint Bone Spine	2008	242	20.17
5	Behcet's disease: An update on the pathogenesis[24]	Clin Exp Rheumatol	2001	236	12.42
6	Familial Mediterranean Fever[35]	Rheumatol Int	2006	221	15.79
7	Diagnostic values of clinical diagnostic tests in subacromial impingement syndrome[22]	Ann Rheum Dis	2000	193	9.65
8	The Validity and Reliability of the Turkish Version of the Fibromyalgia Impact Questionnaire[36]	Rheumatol Int	2000	192	9.60
9	Short-term trial of etanercept in Behcet's disease: A double-blind, placebo-controlled study[28]	J Rheumatol	2005	188	12.53
10	A new set of criteria for the diagnosis of familial Mediterranean fever in childhood[38]	Rheumatology	2009	174	15.82
11	Signicance of catechol-O-methyltransferase Gene Polymorphism in Fibromyalgia Syndrome[25]	Rheumatol Int	2003	164	9.65
12	Lipid peroxidation, some extracellular antioxidants, and antioxidant enzymes in serum of patients with rheumatoid arthritis[37]	Rheumatol Int	2002	161	8.94
13	The Prevalence of Behçet's Syndrome in a Rural Area in Northern Turkey[33]	J Rheumatol	1988	157	4.91
14	Vasculitis in Familial Mediterranean Fever[29]	J Rheumatol	1997	152	6.61
15	Acceptability, reliability, validity, and responsiveness of the Turkish version of WOMAC osteoarthritis index[32]	Osteoarthritis Cartilage	2005	150	10
16	Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome[31]	Rheumatol Int	2005	149	9.93
17	Kikuchi-Fujimoto Disease: Analysis of 244 cases[27]	Clin Rheumatol	2007	148	11.38
18	A Turkish version of the bath ankylosing spondylitis disease activity index: Reliability and validity[21]	Rheumatol Int	2005	137	9.13
19	Acute phase response in familial Mediterranean fever[26]	Ann Rheum Dis	2002	135	7.50
20	The arthritis of Behcet's disease: A prospective study[34]	Ann Rheum Dis	1983	134	3.62

Abbreviations: TC: sum of times cited; PY: average citations per year.

Table 3. The 20 Most Average Citations Per Year in Rheumatology from Turkey Between 1980 and 2019

	Title	Journal	Year	TC	PY
1	Mean platelet volume (MPV) as an inammatory marker in ankylosing spondylitis and rheumatoid arthritis[20]	Joint Bone Spine	2008	242	20.17
2	Vascular Involvement in Behçet's Disease[19]	J Rheumatol	1992	444	15.86
3	A clinical guide to autoinammatory diseases: Familial Mediterranean fever and next-of-kin[43]	Nat Rev Rheumatol	2014	104	17.33
4	A new set of criteria for the diagnosis of familial Mediterranean fever in childhood[38]	Rheumatology	2009	174	15.82
5	Familial Mediterranean Fever[35]	Rheumatol Int	2006	221	15.79
6	Behçet's Disease: Infectious Etiology, New Autoantigens, and HLA-B51[23]	Ann Rheum Dis	2001	243	12.79
7	Management of Takayasu arteritis: A systematic review[42]	Rheumatology	2014	76	12.67
8	Short-term trial of etanercept in Behcet's disease: A double-blind, placebo-controlled study[28]	J Rheumatol	2005	188	12.53
9	Behcet's disease: An update on the pathogenesis[24]	Clin Exp Rheumatol	2001	236	12.42
10	Two new inammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio[47]	Int J Rheum Dis	2015	62	12.40
11	Kinesio taping compared to physical therapy modalities for the treatment of shoulder impingement syndrome[41]	Clin Rheumatol	2011	111	12.33
12	Behcet's disease: How to diagnose and treat vascular involvement[44]	Best Pract Res Clin Rheumatol	2016	46	11.50
13	Kikuchi-Fujimoto Disease: Analysis of 244 cases[27]	Clin Rheumatol	2007	148	11.38
14	The effect of dry needling in the treatment of myofascial pain syndrome: A randomized double-blinded placebo-controlled trial[46]	Clin Rheumatol	2013	76	10.86
15	Familial Mediterranean fever in childhood: A single-center experience[39]	Rheumatol Int	2018	21	10.50
16	Vascular involvement in Behcet's syndrome: A retrospective analysis of associations and the time course[45]	Rheumatology	2014	62	10.33
17	Acceptability, reliability, validity, and responsiveness of the Turkish version of WOMAC osteoarthritis index[32]	Osteoarthritis Cartilage	2005	150	10.00
18	Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome[31]	Rheumatol Int	2005	149	9.93
19	Takayasu's arteritis in Turkey—clinical and angiographic features of 248 patients[40]	Clin Exp Rheumatol	2009	109	9.91
20	Diagnostic values of clinical diagnostic tests in subacromial impingement syndrome[22]	Ann Rheum Dis	2000	193	9.65

Abbreviations: TC: sum of times cited; PY: average citations per year.

Figure 2. Collaboration map of the 25 institutions with the highest number of publications.

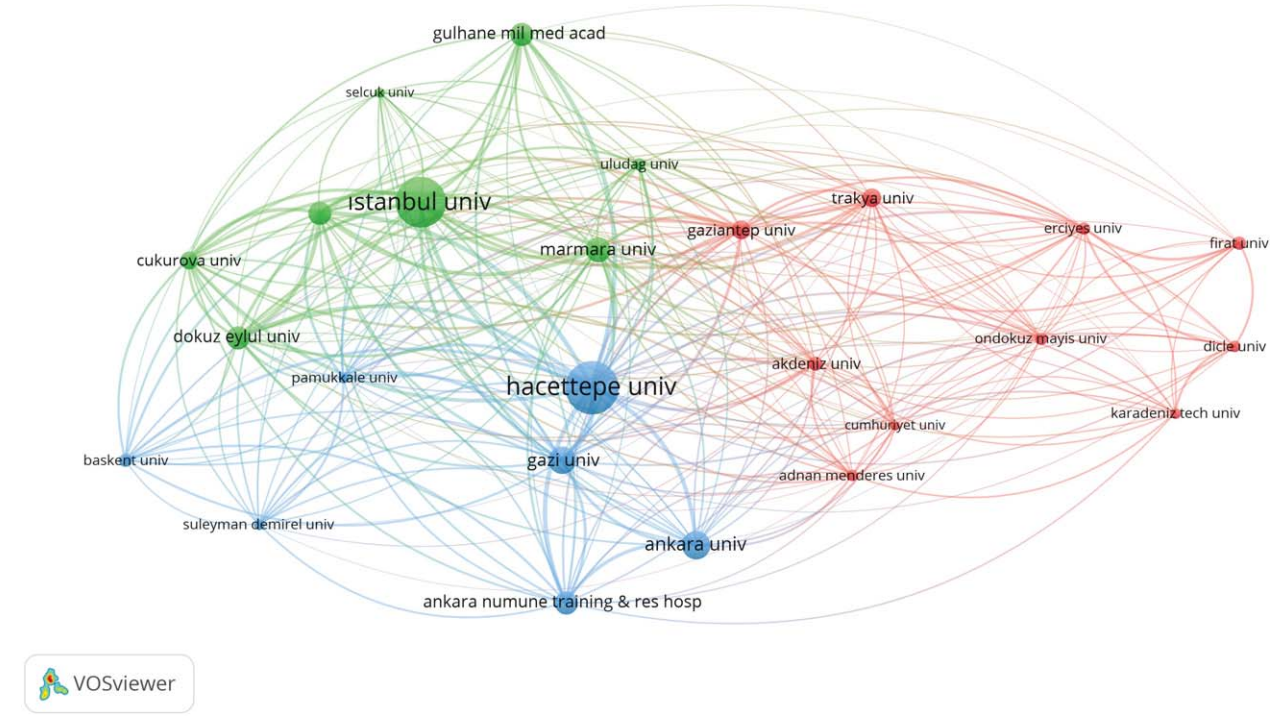


Figure 3. Collaboration map of the 50 most frequently used keywords.

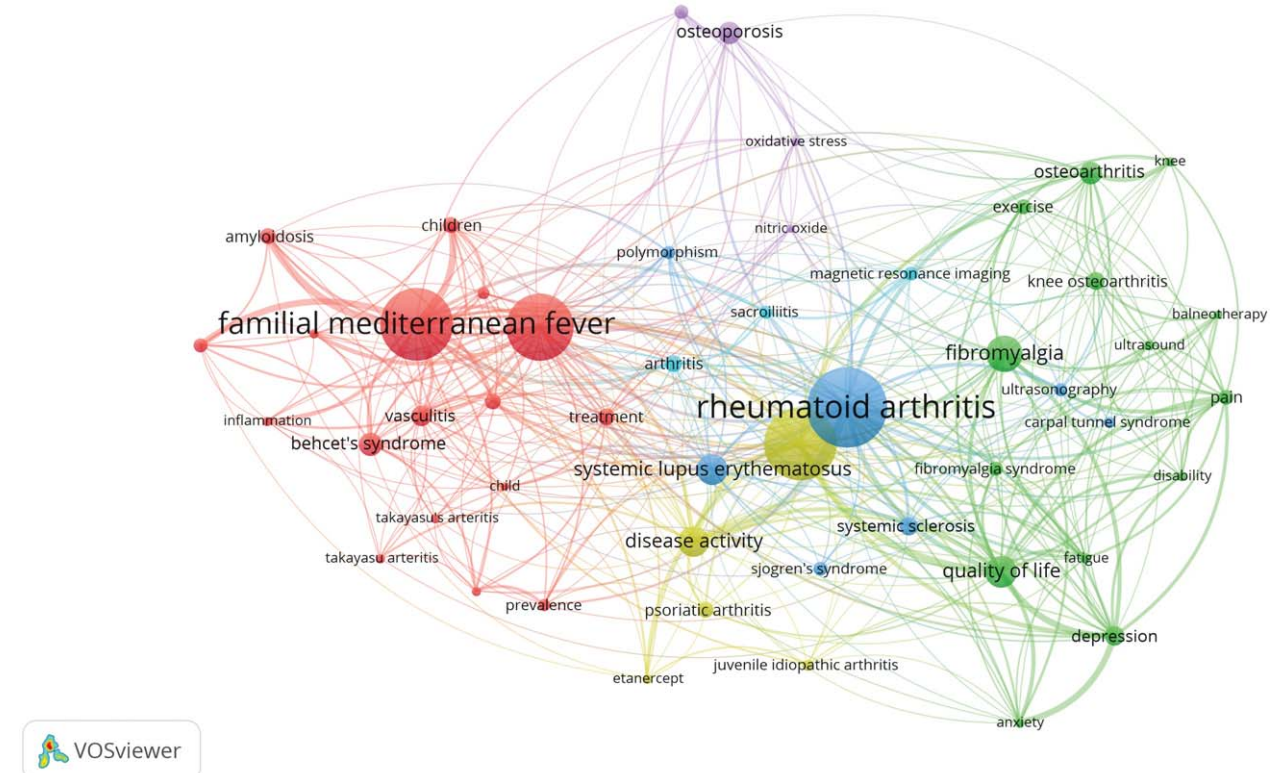


Figure 4. Collaboration map of the top 25 most cited institutions.

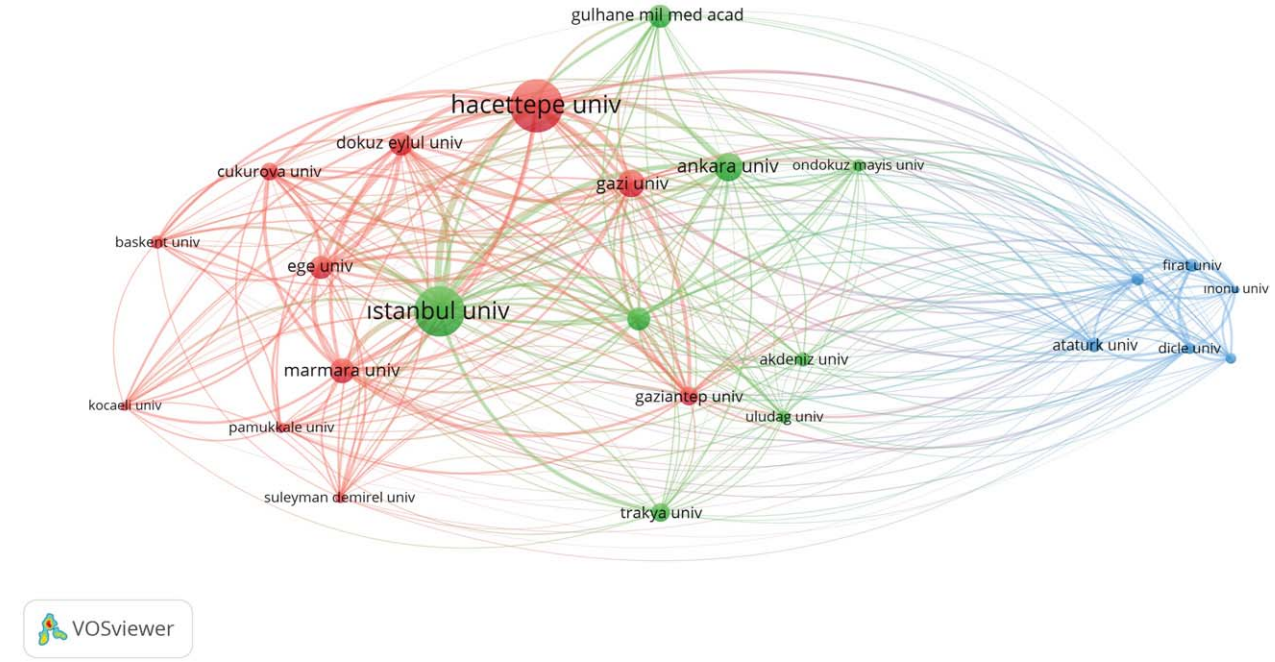


Figure 5. Cooperation map of the top 15 most cited journals.

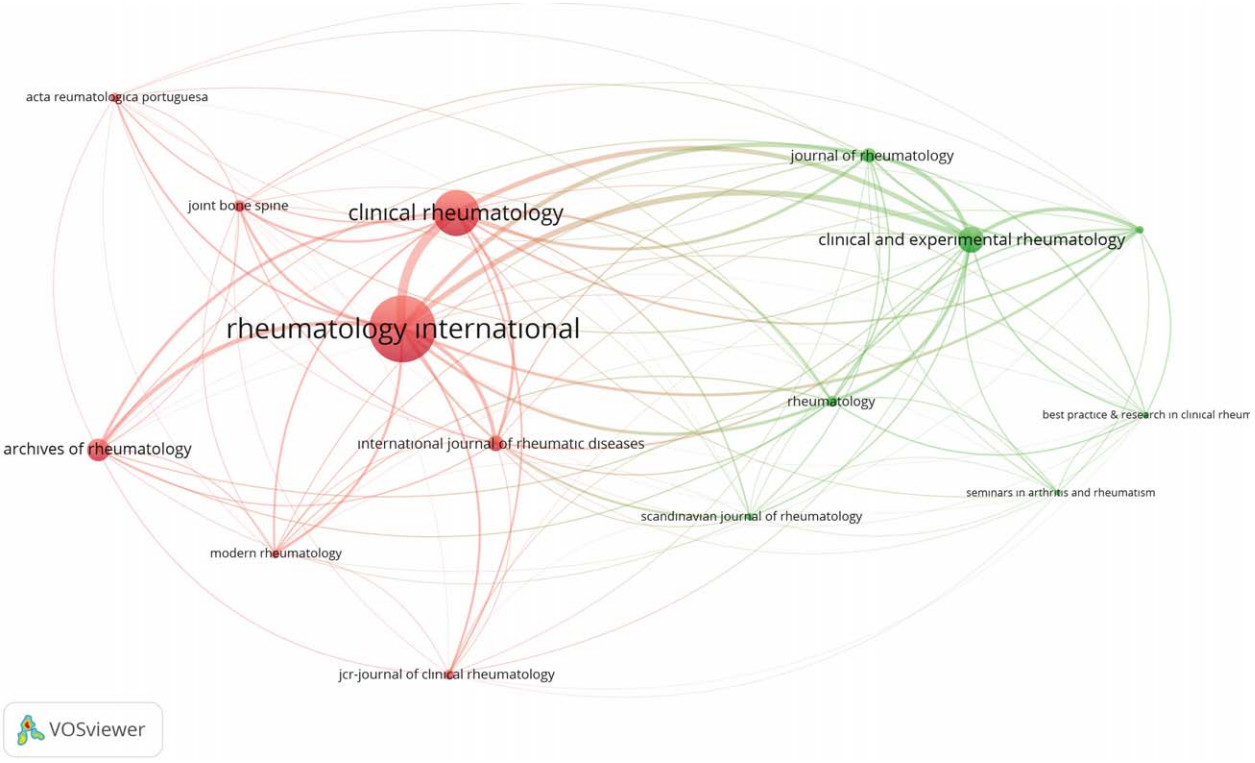
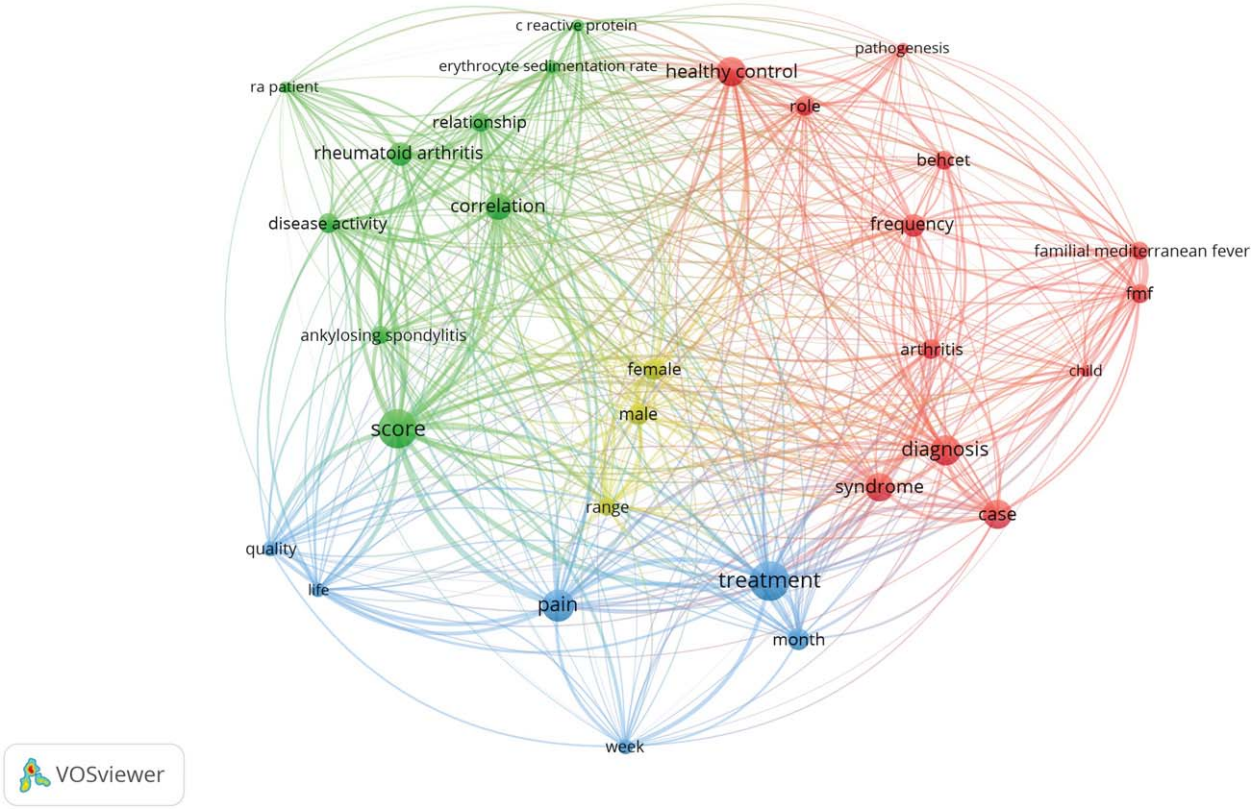


Figure 6. Word co-occurrence network of the 30 most frequently used words.



printed within them. There were 13,819 citations of the articles published in *Rheumatol Int*, 10,263 citations of the articles published in *Clin Rheumatol*, and 4,544 citations of the articles published in *Clin Exp Rheumatol*. The cooperation map of the top 15 most cited journals is given in Figure 5.

Using VOSviewer software, it was possible to see that 33,245 different words are present in the titles and abstracts of these articles. The top three most frequently used words were "treatment" appearing 681 times, "score" appearing 678 times, and "pain" 540 appearing times. The crossover network for the 30 words with the highest usage rate is given in Figure 6. Words shown in the same color in Figure 6 have been analyzed according to their frequency of use together.

DISCUSSION

Science has progressed from ancient times to the present with the contribution of countless scientists.[48] Especially in the last few centuries, scientific articles play a significant role in introducing new medical knowledge and ensuring it is applied by physicians and researchers.[17] A bibliometric analysis is one of the methods that can be used to determine the number and quality of publications in a particular country.[10,49] In the literature, it was observed that bibliometric analyses had been conducted for many countries in the field of rheumatology, among them Malaysia,[50] Bulgaria,[51] China,[52–54] and countries in the Arab League.[55] Bibliometric studies have been carried out for Turkey in a great number of medical fields, such as anesthesia,[16] emergency medicine,[56] anatomy,[57] pathology,[58] endocrine surgery,[59] dermatology,[60] orthopedy,[49] psychiatry[61] and otorhinolaryngology.[62] However, a detailed review of the literature revealed that no bibliometric studies had been conducted for Turkey in the field of rheumatology. It is therefore thought that the present article is the first comprehensive bibliometric analysis of Turkish articles in the field of rheumatology. Although there are databases other than the WoS database, such as PubMed, Google Scholar, and Scopus, the WoS database is generally known to be the most trusted, especially in bibliometric studies. This is because the WoS database is more objective.[63,64] For this reason, the WoS database was preferred in this study.

One of the biggest advantages of this study is that it evaluated a long period of 40 years. On the other hand, although this long-term evaluation is an important advantage of this study, the comparison with numerical values such as the number of citations and articles in other studies does not yield meaningful results due to the different time examined. Even so, if a comparison is made, Zhang et al.[54] reported that there were 2,898 publications from China in the SCI-E between 2007 and 2017. Similarly, Cheng and Zhang[52] stated that there were 788

publications from China between 2000 and 2009. This situation clearly demonstrates that the number of publications in the field of rheumatology from China is more than the Turkey. Developed countries are more productive in the number of publications to which they contribute and their distribution of these. Many studies have reported that a country's economic wealth is associated with its academic publication productivity.[63,65] In addition, the western country especially the USA and European countries have dominant influenced on the production of scientific publications in rheumatology as in many branches.[51] On the other hand, Bayoumy et al.[55] reported the number of rheumatology publications as 944 between 1976-2014 in Arab countries in the Web of Science Core Collection database. This shows that the number of publications originating from Turkey more than Arab countries. Moreover, it has been reported that there has been a continued increase in all publications on rheumatology in many countries.[54,55] Zhang et al.[54] are of the opinion that the consistent rise in the number of rheumatologists, improved economic situations, increases in research and development funds, incentive reward schemes, and career requirements are possible causes for this increase. One of the main reasons why the increase has slowed in Turkey may be due to a shortage of rheumatologists similar to in Ukraine.[51]

In this study, the number of publications written in the field of rheumatology in Turkey is shown to have increased remarkably up until 2006. However, a standstill is seen after this year. In contrast, Zhao et al.[17] stated that the number of articles published annually on ankylosing spondylarthritis has rapidly grown worldwide over the past 10 years. Georgiev and Stoilov[51] reported that the vast majority of rheumatology publications from Bulgaria are rheumatoid arthritis, systemic lupus erythematosus, osteoporosis, and osteoarthritis. In this study, it is seen that the two most common diseases among the most frequently cited 20 articles and among the most frequently used word groups are Behçet's disease and familial Mediterranean fever. Behçet's disease is more common in countries along the ancient Silk Road is seen all over the world and the highest prevalence was reported in Turkey.[66] Behçet's disease clinical findings are highly influenced by ethnic origin and environmental factors. Systemic involvement has been reported variable in different countries and regions.[67] Familial Mediterranean fever is an autoinflammatory and autosomal recessive disease. It affects primarily Jews, Arabs, Turks, and Armenians.[68,69] In this study, it was seen that many of the reviewed publications focus on Behçet's disease and familial Mediterranean fever. The reason for this may be associated with a more frequent incidence of both diseases in Turkey. It is also observed that those institutions with the highest number of publications are the more established ones. The larger bodies of academic staff at these institutions and the stricter criteria for academic appointment within them may contribute to this.

The fact that the journals with the highest number of articles and citations are ranked similarly suggests that the publications are distributed in a balanced way. The top three journals for both are *Rheumatol Int*, *Clin Rheumatol*, and *Clin Exp Rheumatol*. Authors wishing to publish an article in the field of rheumatology may therefore want to consider these journals first.

Limitations

The authors are aware that articles on rheumatology are not only published in journals classified under the rheumatology category, but also in journals focusing on many different disciplines. The most significant limitation of this study is the fact that only journals in the rheumatology category were assessed, since it would be enormously challenging to examine all journals in the other categories for articles on rheumatology. Another limitation is the fact that the article type could not be evaluated in this study, as the articles scanned in WoS did not have sufficient article type categories.

CONCLUSIONS

This study investigated articles in the field of rheumatology written by authors with a Turkish-based affiliation and identified research trends. For this reason, it is thought that this article could help direct future studies. In the field of rheumatology, to increase in the years the number of publications originating from Turkey hopeful results. Even so, we believe that rheumatology science in Turkey still have a long way to go to take its deserved place. Furthermore, we hope that this article will be a useful guide for academics investigating Turkish publications in the field of rheumatology. We are also of the opinion that scientists should be encouraged to increase the number of publications produced in the field of rheumatology.

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Original Article

Evaluation of Corrected QT Intervals of 74 COVID-19 Patients Treated with Hydroxychloroquine in Combination with or without Azithromycin and/or Favipiravir

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ABSTRACT

Objective: We aimed to evaluate the degree of QTc prolongation and associated factors in patients with COVID-19 in association with their usage of hydroxychloroquine (HCQ) with or without the combination of azithromycin (AZ) and/or favipiravir (FAV).

Methods: This single-center, retrospective study was conducted in a tertiary care university hospital. We retrospectively examined the pre- and post-treatment electrocardiogram (ECG) records of 74 patients.

Results: The median age was 44 (interquartile range [IQR] 27), and 34 (45.5%) of them were women. All these 74 patients were treated with HCQ. Sixty-three of them (83.2%) were treated with AZ, and eight patients (10.8%) also were treated with plus favipiravir. All ECGs were in sinus rhythm, and arrhythmia was not developed in any patients. The median (IQR) baseline QTc of 74 patients was 400 (375-421) milliseconds, the median (IQR) post-treatment QTc was 418 milliseconds (391-432), and the change was statistically significant ($P < .001$). There was no statistically significant difference in QTc prolongation between treatment groups. In the linear regression model, moderate disease activity, higher Modified Early Warning Score (MEWS) score ($\geq$2), and heart rate were independent predictors. QTc prolongation of more than 60 milliseconds was observed in five patients (6.7%). Post-treatment QTc value of over 500 milliseconds was observed in three patients (4%), and the drugs were discontinued.

Conclusions: This is the first study that demonstrates that MEWS score and disease severity are related to higher QTc prolongation values. HCQ, AZ, and FAV should be safely used in patients with lower MEWS score and without the severe disease, in conjunction with QTc follow-up.

Keywords: COVID-19, corrected QT, hydroxychloroquine, azithromycin, favipiravir

INTRODUCTION

Coronavirus disease-2019 (COVID-19), first reported in Wuhan, China, on December 8, 2019 and declared a pandemic by the World Health Organization (WHO) on March 11, 2020, has infected over 110 million people globally to date.[1]

There is still no valid treatment known for COVID-19 patients. In the beginning of pandemic, hydroxychloroquine (HCQ), often in combination with azithromycin (AZ), is being widely used for the treatment of COVID-19.[2–4] HCQ is an antimalarial drug, which has also been used in the treatment of systemic lupus erythematosus, rheumatoid arthritis, and other connective tissue disorders.[5] AZ is a macrolide antibiotic used to treat a wide variety of bacterial infections and also has antiviral activity. AZ also has immunomodulatory effects by inhibiting proinflammatory interleukins (IL)-5, IL-6, IL-8, IL-1β, and IL-10 and producing IL-13 and tumor necrosis factor alpha.[6] Favipiravir

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(FAV), an RNA-dependent RNA polymerase inhibitor, is an another antiviral used in the treatment of COVID-19.[7]

Although HCQ and AZ are frequently used in clinical practice and generally well tolerated before the COVID-19 pandemic, their cardiotoxic effects are known in advance. Concerns have been reported about QT prolongation, torsade de Pointes (TdP), and the risk of sudden cardiac death induction after extensive use of these drugs.[8,9] Prolonged QT interval due to FAV, which is now being used for the treatment of COVID-19 in some regions, has also been reported.[10] Although WHO discontinued HCQ treatment arms,[11] many countries, especially Asians, still use HCQ for COVID-19.[12]

In this study, we aimed to evaluate the degree of QT prolongation and associated factors in patients with COVID-19 in association with their usage of HCQ with or without combination AZ and/or FAV.

METHODS

Study Design and Population

This single-center, retrospective study was conducted in a tertiary care university hospital. We retrospectively examined the electrocardiogram (ECG) records of 223 probable or confirmed COVID-19 adult patients (≥18 years old) hospitalized to COVID-19 wards between March 20, 2020, the first case admitted to our center, and May 20, 2020.

The "confirmed case" was a patient with positive SARS-CoV-2 RT-polymerase chain reaction (PCR) from nasopharyngeal swab or a positive SARS-CoV-2 antibody test. The "probable case" was further divided into "clinically suspected" and "radiologically diagnosed" categories. A "clinically suspected case" was defined as a patient with sudden onset of fever, cough, or dyspnea, who had acute respiratory symptoms that cannot be explained with any other cause and who tested negative for SARS-CoV-2 RT-PCR plus a negative pulmonary imaging test.[13] The "radiologically diagnosed" patient was a clinically suspected case who also had chest imaging findings compatible with COVID-19. In this study, all patients were treated.

Main Points

- Although hydroxychloroquine and azithromycin are frequently used in clinical practice and generally well tolerated before COVID-19 pandemic, their cardiotoxic effects are known in advance.
- A statistical difference was found in terms of QTc prolongation in ECGs taken before and after treatment in patients using azithromycin and/or favipravir in addition to hydroxychloroquine. However, there was no statistically significant difference in QTc prolongation between treatment groups.
- Predictors of QTc prolongation were pretreatment heart rate, disease severity, and Modified Early Warning Score (MEWS) score.
- Hydroxychloroquine, azithromycin, and favipravir should be safely used in patients with lower MEWS score and without severe disease, in conjunction with QTc follow-up.
- This is the first study that demonstrates that MEWS score and disease severity are related to higher QTc prolongation values.

We further classified patients in three categories based on the severity of the clinical presentation according to WHO classification: mild, moderate, and severe.[14] Severe patients with sepsis and/or acute respiratory distress syndrome requiring intensive care unit (ICU) at the time of admission or those who were transferred to the ICU during the hospital stay or those who were transferred from the ICU to the COVID-19 wards were excluded considering that critically ill patients with COVID-19 might have different effects on ECG. So, we analyzed mild or moderate patients ECGs.

Hospitalization, treatment, and discharge decisions of the cases were held by the Infectious Diseases Department or consultant physicians (A.Ç.İ.) of the wards according to the guidelines composed and regularly updated by the Scientific Board of the Ministry of Health of the Republic of Turkey.[13] The standard regimen of HCQ was 400 mg twice on the first day, and then 400 mg day^{-1} for 4 days, and AZ was 500 mg on the first day, and then 250 mg day^{-1} for 4 days. The standard regimen of FAV was 1,600 mg twice (2 × 1,600) on the first day, and then 1,200 mg day^{-1} (2 × 600 mg) for 4 days.

We routinely took the initial ECG from all patients on the admission day before any treatments. The ECGs taken were automatically transferred to the hospital computer system. However, 47 patients' ECGs were not recorded in the hospital computer system. We reached the control ECGs of only 74 of the remaining 176 patients after treatment was initiated. Unfortunately, ECGs were not routinely taken at certain hours (e.g., 72 hours later) after treatment was initiated. In the evaluation phase, we calculated the median withdrawal time of 74 control ECGs taken after treatment was initiated. The comparison of the control ECGs of the patients at the beginning and after the initiation of treatment was made. ECGs were manually evaluated by cardiologists (Y.Z.Ş., U.P., and H.Y.) to calculate QTc intervals using the Bazett formula and so-called excess correction method for QRS values greater than 120 milliseconds.

Local ethical committee approval (approval number: GO 20/353, date: March 31, 2020) and permission of the Health Ministry of Turkish Republic were obtained.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25 (IBM SPSS Corp.; Armonk, NY, USA). In descriptive statistics, number and percentage were used for categorical variables. For continuous variables with normal distribution, mean and standard deviation were used, and for continuous variables that do not show normal distribution, median, interquartile range (IQR), and percentiles (25-75) were preferred. The suitability of variables to normal distribution was examined using visual and analytical methods. Non-normally distributed numerical data were analyzed using the Mann–Whitney U test and Wilcoxon test. The

Table 1. Demographic Characteristics of the Patients

	Total: 74 n (%)	QTc Differences, Median (IQR)	*P*
Age, Median (IQR), Year	44 (27)		
<60 years		13.5 (49)	.900
≥60 years		13 (30)	
Sex, n (%)			
Female	34 (45.9)	12.0 (29.25)	.770
Male	40 (54.1)	15.0 (36)	
Underlying Medical Illnesses, n (%)			
Diabetes mellitus	14 (18.9)	1.0 (28.75)	**.052**
Hypertension	17 (23)	18.0 (33.5)	.923
Coronary artery disease	7 (9.5)	18.0 (55.0)	.971
Chronic heart failure	4 (5.4)	33.0 (50.25)	.300
Obstructive pulmonary disease	9 (12.2)	4.0 (28.5)	.120
Malignancy	5 (6.8)	23.0 (41.0)	.211
Chronic kidney disease	6 (8.1)	8.5 (52.75)	.507
Hypo/hyperthyoidism	5 (6.8)	18 (28)	.643
Smoking	17 (23)	22.0 (35.0)	.115
Alcohol	8 (10.8)	8.5 (28.0)	.297
Drugs, n (%)			
ACEI/ARB	7 (9.5)	16.0 (35)	.664
Metformin	14 (18.9)	1.0 (28.75)	**.052**
Acetylsalicylic acid	3 (4.1)	13.6 (40.2)	.603
Beta blockers	6 (8.1)	26.5 (51)	.342
Calcium channel blockers	3 (4.1)	28.6 (21.8)	.275
Steroid	5 (6.8)	16 (73)	.917

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

parameters affecting ΔQTc were investigated using the Spearman correlation test. A multiple linear regression model was used to identify independent predictors. The model fit was assessed using appropriate residual and goodness-of-fit statistics. For all comparisons, *P*-values less than .05 were considered as statistically significant.

RESULTS

Demographic Characteristics

Seventy-four patients were diagnosed with probable/confirmed COVID-19. Fifty-one cases (68.9%) were confirmed by PCR, and the remaining part were diagnosed clinically and radiologically.

The median age was 44 (IQR 27), and 34 (45.5%) of them were woman.

The most common comorbidities were hypertension (n = 17, 23%) and diabetes mellitus (n = 14, 19%).

There were only mild (n = 13, 17.6%) and moderate (n = 61, 82.4%) COVID-19 pneumonia cases since severe cases were admitted to ICU, exclusively.

See Tables 1–3 for demographic characteristics, symptoms, signs, diagnostic criteria, and treatments of patients on admission.

ECG Evaluation of ECGs

The median duration between baseline and post-treatment ECGs was 62 (IQR = 20) hours. All baseline and post-treatment ECGs were in sinus rhythm. The median (IQR) baseline QTc of 74 patients was 400 (375-421) milliseconds, the median (IQR) post-treatment QTc was 418 milliseconds (391-432), and the change was statistically significant ($P < .001$) (see Table 4).

All these 74 patients were treated with HCQ that QTc was significantly increased. Sixty-three of them (83.2%) were treated plus with AZ, and eight patients (10.8%) also were treated with plus FAV to HCQ plus AZ. There was no statistically significant difference in QTc prolongation between treatment groups (see Table 3).

Six patients had (8.1%) longer baseline QTc than 450 ms, and nine patients (12.2%) had longer post-treatment QTc than 450 ms. Arrhythmia was not developed in any patients. QTc prolongation more than 60 milliseconds was observed in five patients (6.7%). The biggest ΔQTc was 80 milliseconds. Post-treatment QTc value of over 500 milliseconds was observed in three patients (4%), and the drugs were discontinued. One of the three patients was using only HCQ, one was using HCQ plus AZ, and the other was using HCQ plus AZ plus FAV. AZ was seen to prolong the ΔQTc; however, there was no statistically difference ($P = .5$).

Diabetes mellitus, metformin use, myalgia, heart rate, higher Modified Early Warning Score (MEWS) score (≥2), and

Table 2. Symptoms, Signs, and Diagnostic Criteria of Patients on Admission

	Total: 74 n (%)	QTc Differences Median (IQR)	*P*
Symptoms, n (%)			
Fever	41 (55.4)	13.0 (28.5)	.663
Fatigue	51 (68.9)	14.0 (29.0)	.944
Cough	53 (71.6)	12.0 (29.0)	.666
Myalgia	40 (54.1)	10.0 (24.75)	.099
Dyspnea	18 (24.3)	9.5 (26.75)	.364
Sore throat	21 (28.4)	14.0 (39.0	.569
Heart rate, mean (SD)	88 (19)		
Heart rate, n (%)			
60-100	56 (75.7)	18.5 (27)	**.003**
>100	18 (24.3)	0.5 (70)	
Respiratory rate, median (IQR)			
Respiratory rate, n (%)	20 (2)		
<24 min^{-1}	65 (87.8)	12.0 (31.5)	.811
24-30 min^{-1}	7 (9.4)	18.0 (11)	
>30 min^{-1}	2 (2.7)	22.5 (40.3)	
Saturation, mean (SD)	96 (3)		
Oxygen support, n (%)			
Not required	65 (87.8)	12.0 (31)	.325
Nasal oxygen	9 (12.2)	18.0 (30)	
MEWS, n (%)			**.016**
0-1 points	60 (81.1)	10.5 (30.25)	
>2 points	14 (18.9)	25.5 (33.25)	
Disease severity, n (%)			**.003**
Mild	13 (17.6)	-2.0 (26.5)	
Moderate	61 (82.4)	18.0 (24)	
Diagnosis, n (%)			.559
PCR positivity	51 (68.9)	12.0 (32)	
Radiologic (PCR negative)	14 (18.9)	17.0 (34.5)	
Clinical (negative PCR normal CT)	9 (12.2)	27.0 (36.5)	

MEWS, Modified Early Warning Score; PCR, polymerase chain reaction; CT, computed tomography.

Table 3. Treatments of Patients

	Total: 74 n (%)	QTc Differences Median (IQR)	*P*
Treatments, n (%)			.174
Hydroxychloroquine (HCQ)	11 (14.9)	5.0 (36)	.224
HCQ + azithromycin (AZT)	55 (74.3)	16.0 (30)	.490
HCQ + AZT + favipiravir (combination/sequential)	8 (10.8)	16 (53.75)	.123
Oseltamivir	46 (62.2)	12 (25)	.36
Enoxaparin Treatment			
No	19 (25.6)	13.0 (30)	.901
Yes	55 (74.4)	14.0 (30)	

Table 4. Characteristics of ECGs

	Baseline ECG	Post–Treatment ECG	Δ(Delta)	*P*
Heart rate, mean (SD), pulse/minutes	89.6 (14)	80.2 (8)	–8 (13.75)*	**<.001**
PR, median (milliseconds) (IQR)	140 (21.5)	140 (33.5)	2 (16)	.143
QRS, median (milliseconds) (IQR)	80 (11.75)	82 (14)	4 (9.5)	**.002**
QTc, median (milliseconds) (IQR)	400 (25–85) (45)	418 (25–75) (41)	13.5 (29.75)	**<.001**

Δ(Delta); post-treatment—baseline.
*Median (IQR).

Table 5. Linear Regression Model for QTc Prolongation

	Unstandardized Coefficients		Standardized Coefficients		
	B	SE	β	*t*	*P*
Heart rate	–.314	0.180	–0.188	–1.74	.086
MEWS score (≥2 score)	17.350	6.421	0.292	2.702	.009
Moderate disease activity	18.530	6.554	0.303	2.827	.006

R^2: 0.230, ANOVA F = 6.989, $P < .001$.

moderate disease activity seemed to influence ΔQTc (see Tables 1 and 2). However, in the linear regression model, only moderate disease activity, higher MEWS score (≥2), and heart rate were independent predictors (see Table 5).

We also performed statistical analysis in terms of laboratory values that would affect disease activity and ECG changes (hemoglobin, white blood cell count, neutrophil, lymphocyte, platelet count, C-reactive protein, sedimentation, procalcitonin, ferritin, creatine cinase, lactate dehydrogenase, d-dimer, troponin, creatine kinase myocardial band (CK-MB), myoglobin, sodium, potassium, corrected calcium, phosphorus, low-density lipoprotein, and triglycerides), but we could not find any statistically significant result.

DISCUSSION

The main findings of this study are as follows: a statistical difference was found in terms of QTc prolongation in ECGs taken before and after treatment in patients using AZ and/or FAV in addition to HCQ. However, there was no statistically significant difference in QTc prolongation between treatment groups. Predictors of QTc prolongation were pretreatment heart rate, disease severity, and MEWS score. No arrhythmic episodes were developed, and drug cessation due to severe QTc prolongation was required in only three patients (4%) as consistent with literature.

Treatment strategies against COVID-19 include combination of several drugs that have synergistic effects. Chloroquine/HCQ, AZ, protease inhibitors (like lopinavir-ritonavir or darunavir-cobicistat), remdesivir, and FAV are used "off-label" despite the lack of definitive evidence on their efficacy.[15,16] Major concern with these drugs (especially with chloroquine/HCQ and AZ) is QTc prolongation and development of TdP/sudden cardiac death, despite it is a rare manifestation of the treatment.[17] There are several known risk factors for QTc prolongation such as electrolyte disorders (hypokalemia, hypocalcemia, hypomagnasemia, etc.), co-administration of QTc prolonging drugs (antihistaminic drugs, antipsychotic drugs, antiarrhythmic drugs, etc.), use of diuretics, bradycardia, structural heart disease, and channelopathies causing congenital long QT syndromes.[18] It is reported that concomittantly use of diuretics or AZ and higher baseline QTc values (>450 milliseconds) are associated with more QTc prolongation in COVID-19 patients treated with HCQ.[18] In another study, the presence of atrial fibrillation, heart failure, and chronic kidney disease was found to be related to more QTc prolongation in HCQ-treated patients with COVID-19.[19] In our study, we found that baseline heart rate, disease severity, and MEWS score were predictors of QTc prolongation. Patient population in this study is younger than other trials and has lower burden of chronic diseases due to severe patients treated in ICU were excluded. Therefore, significant electrolyte disorders and frequency of chronic diseases were rare as compared with general population. However, this situation provides the advantage of the assessment effects of COVID-19 disease-related physiologic changes and disease severity on QTc prolongation.

In previous studies, it is reported that severe QTc prolongation (>500 milliseconds) was observed in 9-11% of the cases,

leading drug discontinuation in 2.5-3.5% of the patients.[20] Hooks et al.[21] reported that QTc prolongation more than >15% or QTc >500 ms after treatment was occurred in 3.9% of the COVID-19 patients treated with HCQ. In another study including 201 COVID-19 patients treated with HCQ or AZT, drug discontinuation due to QTc prolongation was established in 3.5% of the cases, and arrhythmia-related death did not occur in any patients.[22] In the present study, severe QTc prolongation (>500 milliseconds) was developed in three (4%) patients and the drugs. The lower rates might due to exclusion of severe patients in our study.

Baseline heart rate was found to be negatively correlated with ΔQTc in our study. Despite this finding is statistically significant, it may not have clinical significance due to the possible correction mistakes of Bazett formula in patients with abnormal heart rates. There are several formulas including Bazett, Frederica, Framingham, and Hodges formulas for QT correction according to heart rate, and Bazett formula is the most common used formula even it has disadvantages in patients with heart rates <60 bpm and >100 bpm. Bazett and Fridericia are logarithmic corrections, whereas Hodges and Framingham are linear correction formulas. Bazett formula overcorrects QT interval in patients with heart rates higher than 100 bpm.[23,24] As pretreatment heart rates are significantly higher than the heart rates during or after treatment, pretreatment QTc values should have been overcorrected in our study resulting in underestimated ΔQTc.

MEWS includes parameters of heart rate, respiratory rate, body temperature, systolic blood pressure, and level of consciousness, and it can be obtained within minutes after the patient is admitted, providing a rapid evaluation for clinicians to enable timely treatment to high risk patients.[25] Wang et al.[26] reported that MEWS is an efficient tool for rapid assessment of elderly COVID-19 patients, and it predicts in-hospital mortality. In our study, higher MEWS scores were related to higher ΔQTc values.

Severity of COVID-19 pneumonia is classified by WHO into three categories, and severe disease is associated with increased mortality rates and increased need of ICU admissions.[14] In this study, we demonstrated that moderate disease severity is associated with higher ΔQTc than mild disease severity. Despite our study population includes patients without severe disease and younger patients with lower burden of comorbidities, association between ΔQTc and both MEWS score and disease severity indicates that COVID-19 disease-related physiologic changes are predictors of QTc prolongation even absence of other risk factors for QT prolongation.

First limitation of this study is the exclusion of severe cases from the study. Therefore, effects of MEWS score and diseases severity on ΔQTc could not be generalized into general population. However, this condition provided advantage to evaluate the pure effects of COVID-19-related physiologic alterations on QTc prolongation by excluding confounding factors such as chronic diseases, used medications, and electrolyte disorders. Second limitation is the heterogenous time duration between the baseline ECG and second ECG due to the retrospective nature of the study. Finally, Bazett formula has disadvantages on QT correction in patients with heart rates more than 100 bpm and lower than 60 bpm. However, all of the QT correction formulas have similar disadvantages in different heart rates.

CONCLUSION

Although it is rare, drugs used for COVID-19 treatment may lead to QT prolongation and development of arrhythmias. HCQ, AZ, and FAV should be safely used in patients with lower MEWS score and without severe disease, in conjunction with QTc follow-up. This is the first study that demonstrates that MEWS score and disease severity are related to higher QTc prolongation values. Future large-scale studies are needed to evaluate the role of MEWS score to predict QTc prolongation in COVID-19 patients.

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Review

Gaucher Disease and Dental Approaches

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ABSTRACT

Gaucher disease (GD) is a lysosomal storage disease that results in glucocerebroside accumulation in the lysosomes due to deficiency of the enzyme glucocerebrosidase (GBA). GD, inherited as an autosomal recessive disorder, is a panethnic disease. However, it is most common in Ashkenazi Jews with a rate of 1/13. GD typically presents organomegaly and multiple organ involvement, in which the bone marrow is infiltrated by lipid-laden macrophages. Three clinical types have been identified based on whether neurological involvement of GD is observed. Type I GD is non-neuronopathic and the most common clinical type. The diagnosis of GD is determined by detecting low levels of GBA enzyme in peripheral blood leukocytes. Mutation analysis should be performed in patients with low enzyme levels. Specific treatment of GD includes enzyme replacement therapy (ERT) as a first step and substrate reduction therapy that can be tried in patients who cannot tolerate ERT. Bisphosphonates can be used as supportive therapy in patients with osteoporosis when there is no response to specific therapy. It is extremely important for dentists to be familiar with the maxillofacial abnormalities such as generalized osteopenia, enlarged bone marrow spaces, pseudocystic lesions, cortical thinning, and mental demineralization observed in the patients with GD, as well as multiple organ involvement, and hematological and skeletal involvement of GD. The aim of this review is to comprehensively point out the general involvement of GD and to illuminate the dentomaxillofacial findings of this disease, leading dentists on possible oral and dental complications that may develop in dental and surgical procedures of the patients with GD.

Keywords: Gaucher disease, maxillofacial abnormalities, dental approaches

INTRODUCTION

Gaucher disease (GD) is a lysosomal storage disease that results in glucocerebroside accumulation in the lysosomes due to deficiency of the enzyme glucocerebrosidase (GBA).[1] Lipid-laden macrophages, called Gaucher cells, present a typical morphology as large size cells with eccentric nucleus, condensed chromatin, and heterogeneous cytoplasm under the light microscope. The fine lines created by the accumulated substances in the cytoplasm are called "crumpled tissue paper appearance." Although these cells can be seen wherever macrophages are normally found, they are mostly found in the liver, spleen, bone marrow, and lymph nodes.[2]

GD was first described in 1882 by the French physician Phillippe Ernest Gaucher.[3] The disease was named "Gaucher Disease" by N. E. Brill, the medical doctor who made the first premortem diagnosis of the patient with this pathology in 1905.[4] GD is an autosomal recessive inherited disease that can be seen in many ethnicities. It is seen as one in 40,00-50,000 live births. The most common form is Type I without neurological involvement. It constitutes approximately 90% of the patients. It is common in Ashkenazi Jews, and the carrier rate is known as 1/13.[5] Although there is no study about the prevalence of GD in Turkey, it is estimated that it is above the general average due to the prevalence of consanguineous marriage. Neuronopathic GD (Type II and Type III GD) is less common. It is known that less than 1% of 1,698 patients reported to the Gaucher registry unit, which has the largest Gaucher patient database in the world, were Type II GD and 5% were Type III GD.[6]

The most effective and reliable way to diagnose GD is to measure the level of GBA enzyme in peripheral blood leukocytes. Although there is usually 10-15% enzyme activity in Type I GD patients, there is almost no enzyme activity in Types II and III GD patients. Those whose enzyme level is lower than 4.2 IU mL^{-1} are considered GD. It is thought that people with an enzyme level greater than 10 IU mL^{-1} do not have GD. Individuals in the intermediate group may have difficulty in diagnosis. Besides, genetic tests can be used in the differential diagnosis of groups with an enzyme level between 4.2 and 10 IU mL^{-1}. The diagnosis is confirmed in patients with biallelic pathological mutations. The presence of Gaucher cells in bone marrow

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biopsy is a key finding for diagnosis but may not be necessary for most patients who have characteristic clinical and biochemical features.[7] Mutation analysis can also be useful in terms of giving genetic counseling to the family of the affected person and family screening, as well as obtaining information about the phenotypic characteristics for specific cases whose mutations have been studied and determining the severity of the disease.

The purpose of the treatment of GD is to reduce the symptoms and complications of the disease and to increase the quality of life. It is aimed to improve organomegaly and symptomatic cytopenia in visceral and hematological involvements, to prevent bone pain, bone crises, and osteonecrosis in patients with skeletal involvement, and to increase the mineral density of trabecular bone. Specific treatment of GD includes enzyme replacement therapy (ERT) as a first step and substrate reduction therapy (SRT) that can be tried in patients who cannot tolerate ERT. Bisphosphonates can be used as supportive therapy in patients with osteoporosis when there is no response to specific therapy.[7]

The purpose of this review is to discuss the general involvement of GD comprehensively and to guide dentists about the issues that should be taken into consideration in the dental treatments of GD patients by shedding light on the dentomaxillofacial findings of this disease.

CLINICAL AND RESEARCH CONSEQUENCES

Clinical Sub-Types of Gaucher Disease

Three clinical types of GD have been defined according to the presence of neurological findings and the progression rate of these neurological findings.

Type I Gaucher Disease

Type I GD is the most common clinical type, which neurological findings are not observed. The clinical manifestation can vary significantly. The disease is classically characterized by splenomegaly as a result of glucosylceramide accumulation in splenic macrophages. Apart from the spleen, lipid-rich macrophages called "Gaucher cells" can be observed in the liver and bone marrow. For this reason, damage in GD is mostly observed in organs that are rich in macrophages.[8] Cytopenia, splenomegaly, and hepatomegaly are common in patients due to spleen, liver, and bone marrow involvement. In addition, orthopedic complications and other hematological changes can be observed.

Although it is generally thought that late-onset Type I GD has a slow course and shows little progression in the long term, recent studies have shown that this group of patients may have significant visceral, hematologic, and skeletal system disorders in the long-term follow-up, and also, late-onset patients may have an increased risk of malignancy.[9] According to the Gaucher report data of the International Gaucher Group (ICGG: International Collaborate Gaucher Group), the life expectancy in late-onset Type 1 Gaucher patients was found to be decreased by approximately 8.9 years compared to the population.

Type II Gaucher Disease

Type II GD is the clinical type characterized by the onset of symptoms in early infancy and the rapid progression of neurological symptoms. Typically, patients die within the first 3 years of life. There are hepatosplenomegaly, anemia, thrombocytopenia, and significant brainstem involvement findings. Pyramidal involvement and cognitive disorders may accompany. Brainstem manifestations include dysphagia, stridor pyramidal signs, spasticity, retroflection of the neck, trismus, and opisthotonus.[10]

Type III Gaucher Disease

Type III GD is called the chronic progressive neuronopathic type and may present in infancy, childhood, adolescence, or adulthood. Type III GD exhibits a more heterogeneous clinic than Type II. This clinical type was previously thought to be limited to people living in the Norbotten and Vasterbotten regions of Northern Sweden.[11] However, it was later understood that it was more common than thought and was seen in all ethnic groups.

Tissue and Organ Systems Affected by Gaucher Disease

GD is a disease with a wide clinical variety. Symptoms of the disease may differ even in patients with the same genetic mutation and enzyme level. Symptoms of the disease usually occur due to local effects of accumulated substances, organomegaly, and organ dysfunction. The main symptoms of the disease are hepatosplenomegaly, osteopenia, bone pain, cytopenias, bleeding, fatigue, easy bruising, and oculomotor apraxia. Table 1 reveals the clinical conditions and symptoms frequently detected in GD subtypes. Splenomegaly is seen in approximately 90-95% of GD patients. It plays a key role in diagnosis. Hepatomegaly is seen in approximately 75-80% of all patients. This rate is higher in patients who have undergone splenectomy.[6]

The majority of patients have clinical or radiological bone involvement. These involvements can vary from asymptomatic osteopenia to osteonecrosis. There may be acute and chronic bone pain, pathological fractures, and degenerative disorders due to subchondral resorption. Some patients may have painful bone crises, usually involving a single limb or joint. During a

Main Points

- The main symptoms of Gaucher disease are hepatosplenomegaly, osteopenia, bone pain, and cytopenias.
- Radiographic findings of dentomaxillofacial involvement in Gaucher patients include generalized rarefaction, loss of trabecular structure, enlarged marrow spaces, cortical thinning, osteosclerosis, pseudocystic radiolucent lesions, and loss of the anatomical structures.
- The radiographic appearance of the jawbones in Gaucher disease may be confused with other jaw lesions, and incorrect surgical procedures may be applied.
- The increase in osteopenia, which is present in almost all Gaucher patients, may cause pathological fractures and osteomyelitis in the jaws.

Table 1. Clinical Sub-Types and Symptoms of Gaucher Disease

Sub-Types	Primary CNS Involvement	Bone Disease	Others
Type I GD	Absent	Present	• Splenomegaly • Hepatomegaly • Cytopenia • Pulmonary disease
Type II GD (acute or infantile)	• Bulbar signs • Pyramidal signs • Cognitive impairment	Absent	• Splenomegaly • Hepatomegaly • Cytopenia • Pulmonary disease • Dermatological changes
Type III GD (subacute, juvenile)	• Oculomotor apraxia • Attack • Progressive myoclonic epilepsy	Present	• Splenomegaly • Hepatomegaly • Cytopenia • Pulmonary disease

GD, Gaucher disease; CNS, central nervous system.

bone crisis, there may be tenderness, heat increase, and edema in the joint. Fever and leukocytosis are also observed. Clinical, radiological, and laboratory findings can be confused as osteomyelitis or septic arthritis. Therefore, unnecessary surgeries can be performed.[12]

Among the main findings of hematological involvement of GD, anemia, thrombocytopenia, neutropenia, and coagulopathy are the most common findings.[13] Hematological involvement usually manifests itself with symptoms such as weakness, fatigue, epistaxis, and easy bruising. Some patients may present with anemia severe enough to be transfusion dependent. Leukopenia is less common. In GD, thrombocytopenia is prominent in the early period, but pancytopenia can be seen in progressive cases.[12]

Dentomaxillofacial Findings of Gaucher Disease

The underlying pathology of bone involvement in GD is associated with the accumulation of Gaucher cells that infiltrate the bone marrow compartment and directly/indirectly lead to local bone defects including cortical thinning, osteonecrosis, and lytic lesions.[14] Maxillofacial bone involvement is less commonly seen, while long bone involvement is common in GD. However, the mandible is considered to be a long bone that, unlike the maxilla, appears to be potential reservoir areas for Gaucher cells. Therefore, the mandible is also likely to be a focus of bone involvement.[15] Jawbone involvement is generally asymptomatic[15,16] and is detected as incidental findings in routine dental radiographs.[17] These radiographic findings include generalized rarefaction of the bone (osteopenia), loss of trabecular structure, enlarged marrow spaces, cortical thinning, osteosclerosis, pseudocystic radiolucent lesions, demineralization of the mental region, thinning of the lamina dura, displacement of the mandibular canal, and the root resorption in the teeth adjacent to the lesions.[18–21] There are only a few case reports reporting maxillary sinus involvement.[20,22,23] Several case reports have also reported that the mandible is a nidus of Gaucher cell infiltration and/or bone crisis.[22,24–27] In Table 2, studies reporting maxillofacial involvement of GD published from 1938 to 2020 are summarized.[28–34]

Dentist's Approach in Gaucher Disease

There are studies in the literature reporting that bone regeneration is observed after tooth extraction in patients with GD, and normal trabecular appearance is retrieved.[20,35,36] Besides, it is very important for dentists to know the jaw bone changes such as generalized osteopenia, enlarged marrow cavities, pseudocystic lesions, cortical thinning, and mental demineralization. These findings are of critical clinical importance in surgical procedures such as implant placement, bone graft removal, and orthognathic surgery.[37] Also, the increase in osteopenia, which is present in almost all GD patients, is associated with an increased risk of bone fractures in both adult and pediatric patients.[38] A soft diet should be recommended to patients to avoid the possibility of pathological fractures in the jaws.

In GD, osteomyelitis may occur in the mandible as a result of trabecular bone loss in the jaws, and owing to GD, the susceptibility of the bone to infection may increase.[39] The importance of oral hygiene to prevent odontogenic infections and secondary osteomyelitis should be emphasized if any findings related to GD in the jawbones are detected on panoramic radiographs or cone-beam computed tomography images. Clinical and radiological examinations of patients in terms of mandibular involvement are recommended to be performed periodically.[40,41]

Diffuse sclerotic radiopaque appearance seen in patients with GD may resemble Paget's disease or fibrous dysplasia.[20] Radiographic appearance may be confused for plasma cell myeloma or cancer metastasis, especially when accompanied by acute bone pain.[35] According to the radiological features associated with jaw lesions, the differential diagnosis of gnathic changes in GD is considerably extensive and includes bone marrow defects,[26] thalassemia, and sickle cell anemia[20,35] for generalized osteopenia. The "dome phenomenon" due to

Table 2. Compilation of Published Studies and Case Reports on the Dentomaxillofacial Manifestations of GD

Author, Year	Age/ Gender	Region	RG	Findings	Treatment
Bender, 1938[24]	13/F	md and mx	Periapical and extraoral X-ray	Cyst-like radiolucency, loss of trabecular structure in the premolar-molar region, generalized osteoporosis in the mandibular region	Extraction of the lower first molar tooth
Bender, 1959 (follow-up)[28]				Different RL areas—further loss of trabecular structure, endosteal bone degeneration and reduction in thickness, episodes of spontaneous bleeding in the hard palate region	Extraction of the lower first molar tooth
Bender et al., 1996 (follow-up)[35]				Significant improvement in radiolucency with regeneration of trabeculae	Uncomplicated extraction of posterior teeth, ERT since 1991
Moch et al., 1953[33]	39/F	md	Extraoral X-ray	Pseudocystic RL areas on both sides of the mandible, alveolar abscess of the right upper second premolar	Abscessed tooth extraction and curettage of apical area (penicillin + 500 cc complete blood)
Spiegel, 1957[34]	19/F	md and mx	Periapical and extraoral X-ray	Radiolucency in the premolar and molar regions, and loss of trabecular structure, osteolysis in the left maxillary premolar region, prolonged bleeding after minor surgeries	Removal of the tissue flap on the right lower third molar
Michanowicz et al., 1967[36]	21/M	md	Periapical X-ray	Small and large carious lesions in most mandibular and maxillary teeth, radiolucency in the right third molar and first molar, generalized osteoporosis, and cavities in the mandible	Extraction of right lower third molar, left lower first molar and left upper second molar teeth
Weigler et al., 1967[48]	28/M	md	Periapical X-ray	A large RL area from the first premolar to the third molar, enlargement of bone marrow spaces, loss of lamina dura at the lower-left second premolar and first molar root	Extraction and curettage of the lower left first molar
Bildman, 1972[17]	16/F	md	Periapical x-ray	Bilateral radiolucent areas in the body of the mandible	The extraction of the upper and lower first molars
Sela, 1972[25]	67/F	md	Autopsy examination	Histologically, tumor-like accumulation of Gaucher cells replaced by the bone marrow in the mandible, nodular reddish and yellowish tumor-like masses	-
Browne, 1977[46]	39/F	md	Periapical X-ray	Poor oral hygiene, yellow pigmentation of the oral mucosa, root resorption at the apical of the mandibular molars on radiographs, generalized trabeculation loss	Periodontal treatment and uncomplicated tooth extraction
Hall et al., 1985[39]	47/M	md	Panoramic X-ray	A large RL lesion with secondary infection in the left mandible	Debridement of the left mandibular corpus and ramus, lower second premolar, first and second molar extraction, IV and oral penicillin

Table 2. Compilation of Published Studies and Case Reports on the Dentomaxillofacial Manifestations of GD (Continued)

Author, Year	Age/ Gender	Region	RG	Findings	Treatment
Schwartz et al., 1988[22]	46/M	maxillary sinus and sphenoid sinus	Extraoral sinus X-ray and CT	Radiographic opacification of the maxillary sinus and sphenoid sinus, thinning of the posterolateral walls of the sinuses and mild enlargement of the maxillary antrum	Irrigation of the bilateral maxillary sinuses and medical treatment for the sinusitis-like condition
Heasman, 1991[19]	40/F	md	Periapical and panoramic X-ray	Hemorrhagic lesions on the face and lips; Bilateral RO areas seen in the premolar and molar regions of the mandible, generalized edematous gingivitis	-
Lustmann et al., 1991[26]	50/M	md and mx	Periapical and panoramic X-ray	Moderate periodontal disease and poor oral hygiene, four RL lesions characterized by reduced trabeculation and uncertain borders, two in the body of the mandible and two in the maxillary canine-premolar region, advanced apical resorption in canines, premolar and molars on both sides	-
Regenye et al., 1992[47]	23/M	mandibular trauma	Periapical, occlusal, panoramic X-ray and CT	There is mandibular fracture as a result of a motor vehicle accident, postoperative infection, no excessive bleeding during surgical procedures, a decrease in bone remodeling was detected	Stabilization of mandibular fractures, treatment of postoperative infection with clindamycin
Karabulut et al., 1997[23]	14/F	md, mx and sphenoid bones	Posteroanterior lateral radiography and CT	Diffuse osteopenia, trabecular loss in both mandible and maxilla, opacification of the sphenoid and maxillary sinuses due to widening of the medullary spaces	-
Carter et al., 1998[18]	28 patients	md and mx	Panoramic X-ray	Twenty-five of 28 patients have radiographic evidence of jaw involvement, the most common findings: enlargement of the bone marrow spaces, cyst-like lesions, cortical thinning, root resorption, displacement of the mandibular canal, and delayed permanent tooth eruption	-
Wasserstein et al., 1999[41]	12/F	md	Panoramic X-ray and CT	Large multilocular RL lesions extending to the lower cortical borders of the left and right mandible and invading between the teeth from above, the symmetric large RL lesion with ill-defined borders in the mandibular incisor region	A soft diet recommendation to reduce the risk of pathological fractures
Fischman et al., 2003[29]	87 patients and 31 carriers	-	Clinical examination only (DMFS index and GI)	Despite the prevalence of thrombocytopenia, there is no gingival bleeding, although there is radiological evidence of bone involvement, no tooth loss or mobility was found	-

Table 2. Compilation of Published Studies and Case Reports on the Dentomaxillofacial Manifestations of GD (Continued)

Author, Year	Age/ Gender	Region	RG	Findings	Treatment
Horwitz et al., 2007[20]	47/F	md	Periapical and panoramic X-ray	On clinical examination, petechiae, large plaque, and calculus deposits on the right buccal mucosa, acute generalized gingivitis, spontaneous bleeding and swelling, cauliflower-like papillae, bilateral cyst-like lesions on RG examination, severe root resorption in the premolar molar region, enlargement of the bone marrow cavities, loss of cortical margins of the mandibular canal	Detertrage and curettage, open flap surgery, extraction of three teeth on the right maxilla
Lisboa et al., 2011[32]	24/F	-	Periapical X-ray	History of excessive bleeding in previous extractions of the patient, deep carious lesion affecting the pulp of left maxillary first molar, and excessive crown destruction	Extraction of the left maxillary third molar, postoperative bleeding, pre- and postoperative prophylactic antibiotic and antifibrinolytic drug protocol due to the risk of infection
Givol et al., 2011[30]	Seven patients	-	-	A study investigating thrombocytopenia and bleeding in dental procedures, all patients were thrombocytopenic and coagulation tests were normal for most patients, the need for hematological replacement therapy during the procedures according to the total bleeding risk score and hematological (platelet count, dysfunction, coagulopathies, prolonged PT and PTT, and decreased fibrinogen level) risk score of the dental procedure	Detertrage, crown lengthening, surgical tooth extraction, root canal treatment, and cyst enucleation
Kumar et al., 2012[31]	47/M	mx	CT	Whitish necrotic bone not covered with mucoperiosteum from the right canine tooth to the third molar, bone destruction of the entire hard palate containing the right maxillary alveolus, and erosion of the right maxillary sinus floor	Surgical removal of necrotic bone including right-sided alveoli, maxillary sinus floor, and hard palate
Nobre et al., 2012[37]	Ten patients and 20 control	md and mx	Panoramic X-ray and CBCT	In CBCT images, mandibular involvement in all cases, both mandible and maxilla involvement in six, generalized rarefaction and enlarged marrow spaces in all patients, cortical thinning and osteosclerosis in five, pseudocystic RL lesions in nine, mental demineralization in seven, flattening of the condyle head in one, loss of the anatomical structures in eight, and thickening of the maxillary sinus mucosa in three patients, no pathological fracture, root resorption or delay in tooth eruption	-

Table 2. Compilation of Published Studies and Case Reports on the Dentomaxillofacial Manifestations of GD (Continued)

Author, Year	Age/ Gender	Region	RG	Findings	Treatment
Zeevi et al., 2013[16]	30/M	md	Panoramic X-ray and CT	Large, multilocular, well-defined asymptomatic bilateral RL lesion with scallop-like cortical margins in panoramic radiography, reduced trabecular structure, bone expansion and buccal bone perforation on axial CT images, loss of bilateral mandibular canal borders, tooth displacement, and extensive postoperative bleeding complication	Biopsy taken from the area of the lesion
	37/F	md and mx	Panoramic X-ray and CT	Rarefaction of bone trabeculae in the mandible and maxilla, asymptomatic unilocular RL lesion in the left posterior mandible, bilateral loss of mandibular canal margins and obliteration of maxillary sinuses, obliterated maxillary sinus on axial CT, enlarged bone marrow cavities in the maxilla, rarefaction of the mandibular bone and well-defined lesion of the left posterior mandible	Biopsy taken from the area of the lesion
Ahmadieh et al., 2014[21]	46/F	md	Periapical and panoramic X-ray and CT	Severe and persistent throbbing pain in the posterior left mandible, relatively well-circumscribed pseudocystic multilocular RL lesions in many regions of the mandible in the panoramic image, decreased trabeculation, effacement of the mandibular canal, and mild opacification of the maxillary sinus, a large multilocular lytic lesion and enlarged bone marrow cavities in the left mandible with the patient's complaint in CBCT images, thinning of periodontal ligament space with loss of the lamina dura in the affected molars	Use of oral bisphosphonates, a surgical biopsy to exclude other pathologies in the area of pain, surgical removal of pathological tissue
Mohamed et al., 2020[14]	42 pediatric patients (16 Type I GD and 26 Type III GD)	md	Panoramic X-ray	Delayed permanent tooth eruption in five patients in intraoral examination. The most common findings: thinning in the inferior cortex of the mandible, localized and generalized rarefaction, generalized rarefaction with a similar frequency in Type 1 and Type III GH, enlargement of the bone marrow spaces is more common in Type I GD, pseudocystic RL lesions, cortical thinning, anodontia, and dental anomalies are more common in Type III GD, no difference was found between dental age and chronological age	Bisphosphonate and enzyme replacement therapy

GD, Gaucher disease; RG, radiography; F, female; M, male; Md, mandible; Mx, maxilla; CT, computed tomography; CBCT, cone-beam computed tomography; RL, radiolucent; RO, radiopaque; PT, prothrombin time; PTT, partial thromboplastin time.

preprosthetic maxillary sinus augmentation may also resemble sinus devastation associated with GD.[16] Well-defined radiolucent osteolytic lesions, such as a keratocystic odontogenic tumor, central giant cell granuloma, aneurysmal bone cysts,[42] and even traumatic bone cysts,[16] which are thought to be more similar, should also be considered in the differential diagnosis. Gaucher lesions may also resemble alveolar bone loss associated with periodontal disease.[43] When GD is suspected, the least invasive method for diagnosis is reduced b-GBA enzyme activity in blood samples.[43] Jaw biopsy is not recommended unless another condition such as malignancy is suspected. To diagnose GD, an enzymatic evaluation is required, not a biopsy or a bone marrow sample.

Some studies have reported the use of bisphosphonates in osteopenia/osteonecrosis therapy as a supportive treatment for ERT in GD.[14,44] It has been reported that bisphosphonates preserve bone density by proving an antiresorptive effect; however, prolonged IV bisphosphonate treatment rarely causes osteonecrosis of the jaw that is triggered by exposed bone after tooth extraction and subsequently bacterial contamination.[45] Therefore, the use and duration of bisphosphonates should be investigated in Gaucher patients before tooth extraction or dental surgeries.

There is a possibility of complications like excessive bleeding due to thrombocytopenia during surgical procedures, especially in patients who do not undergo splenectomy.[35,46,47] Horwitz et al.[20] reported increased bleeding during tooth extraction and its local control in the case report they presented. However, in most of the other cases reported in the literature, it was stated that there was no abnormal bleeding, and the recovery was normal.[17,35,36,46–48] Nevertheless, in patients with GD, it is recommended to consult the patient's physician before invasive procedures and to check complete blood count including PT, PTT, bleeding time, and platelet count at the first examination. Local hemostasis should be applied according to the patient and procedure.

CONCLUSION

As a result, dental radiographs can play a role in the early diagnosis of GD, especially in the absence of clinical symptoms. The roadmap to be followed for the diagnosis of Gaucher lesions in the jawbones is a comprehensive medical history, and clinical and radiological examinations. Dentists should be familiar with the dentomaxillofacial findings of GD and be aware of possible oral and dental complications that may develop. Furthermore, when GD is suspected in undiagnosed patients, patients should be able to be referred to the necessary departments.

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Letter to the Editor

A Pilot Study Evaluating Antimicrobial Antagonism in Syphilis/*Chlamydia trachomatis* Co-Infection in Men Who Have Sex with Men

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Penicillins are bactericidal, whereas doxycycline is bacteriostatic; simultaneous use of penicillin and doxycycline has been associated with antimicrobial "antagonism," and treatment failure in clinical cases of pneumococcal meningitis, scarlet fever, and ocular syphilis.[1–4] There have been significant increases in early syphilis and *Chlamydia trachomatis* in men who have sex with men (MSM). Early syphilis is treated with a single injection of Benzathine penicillin (BPG) and chlamydia is treated with 7 days of oral doxycycline 100 mg BID.[5] The summary of product characteristics (SmPC) of both products recommend the avoidance of simultaneous use of BPG and doxycycline (www.medicines.org.uk/emc/product/11044/smpc#gref; www.medicines.org.uk/emc/product/4063/smpc#gref). There is little data on syphilis/chlamydia co-infection or associated antimicrobial antagonism.

We reviewed all cases of syphilis/chlamydia co-infection in MSM in our sexual health clinic in the UK which sees 6,500 attendances by MSM per year. At the time of this study, HIV Prep-exposure prophylaxis (PrEP) was not widely available.

In 2019, 6613 MSM attended for sexually transmitted infection testing and 155 MSM were diagnosed with early syphilis. Fifty-three (34%) were HIV positive, 26 of 102 (25%) HIV negative MSM were using PrEP, the median age was 43 years (interquartile range = 34-53), none had neurological syphilis and all were treated with BPG. Twenty-one (14%, 95% confidence interval = 8.6-20.1) were simultaneously diagnosed with chlamydia (rectal: 17/21 [81%], urethra: 4/21 [19%]). All MSM with rectal chlamydia were tested for Lymphogranuloma venereum: None were positive. MSM with syphilis/chlamydia co-infection were the same age (43 vs 44 years, $P = .426$), had similar baseline Venereal Disease Research Laboratory (VDRL) titers (1:32 vs 1:32, $P = .586$), were diagnosed at similar stages of syphilis, but were more likely to be HIV-positive than MSM diagnosed with syphilis alone (13/21 [62%] vs 40/134 [30%], $P = .004$). Thirteen out of 21 with co-infection were not treated simultaneously because of delays in laboratory results (N = 10) or clinician concerns about antimicrobial antagonism (N = 3). Eight out of 21 MSM were inadvertently treated simultaneously with BPG and doxycycline. There were no treatment failures: Overall 108/155 (70%) attended for at least one follow-up VDRL and all had at least a four-fold reduction in VDRL titer (median 1:1) at a median of 101 days. All eight who were treated simultaneously with BPG/doxycycline returned for follow-up VDRL.

We have shown that 14% of MSM diagnosed with syphilis have syphilis/chlamydia co-infection, mostly rectal chlamydia (81%). It is interesting that living with HIV MSM with syphilis were significantly more likely to have syphilis/chlamydia co-infection than HIV-negative MSM suggesting that their sexual networks remain relatively distinct or that immune responses to chlamydia differ in HIV patients. We treated 8 MSM simultaneously with BPG and doxycycline and there were no apparent treatment failures. There is a lack of guidance on the simultaneous

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treatment of syphilis/chlamydia co-infection with BPG and doxycycline despite concerns about antimicrobial antagonism, apart from the SmPC. Caution is needed with co-prescribing BPG/doxycycline for syphilis until further research is available demonstrating the safety and efficacy of simultaneous treatment. An option is to use 3 weeks of oral doxycycline BID for the treatment of syphilis/chlamydia co-infection; however, more research is needed.

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