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Gülhane Medical Journal (GMJ) is an international, multidisciplinary and peer reviewed journal for researchers and health-care providers. It is published four times a year, and accepts submissions in English. It is the official journal of the Gülhane Faculty of Medicine, University of Health Sciences Turkey.

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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

GMJ has gone a change in Editor-in-Chief following retirement of Prof. Dr. Omer Azal.

During the years Prof. Azal has served as the chief editor, GMJ has shown substantial improvements by increasing the number of prestigious indexes covered, annual submissions, and global citations. With the efforts of his team, GMJ has become a prestigious publication by increasing its domestic and international recognition.

The decision to continue with English language only was also taken during his term.

On behalf of the readers, authors and referees, I sincerely thank Prof. Azal and his editorial board for their substantial contributions to the institution, country and the global scientific community.

In the last issue of 2020, there are a number of interesting original articles, review articles and case reports from a wide range scientific disciplines in GMJ.

I would like to express my gratitude to all submitting authors, reviewers, and editors for their contributions so far.

Prof. Dr. M. Ali Gülçelik
Editor-in-Chief

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Osteoradionecrosis - a review of clinical features and management

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Keywords: Osteoradionecrosis, mandible, radiotherapy

ABSTRACT

Radiotherapy is an important part of oral cancer management. A significant complication of radiotherapy to the head and neck is osteoradionecrosis (ORN). The present report reviews the risk factors, clinical features, and management of ORN affecting the maxilla and mandible. A "PubMed" database search was done to identify "case reports" of ORN that were published, using the keywords "osteoradionecrosis", "jaw"', "mandible" and "maxilla". Data on ORN published within the past 10 years from 2008 to 2018 were collected and analyzed. A total of 23 full text articles reporting 27 cases of ORN were identified. Males constituted 84% of the cases. The mandible was affected in 96% of cases with bilateral involvement in 26.9% of cases and posterior mandibular involvement in 53.8% of cases. The amount of radiation received ranged from 50 Gy to 77 Gy. ORN occurred in 3.87 years on average after radiotherapy. The highest risk of developing ORN was associated with extraction of mandibular teeth within the radiation field in patients who received a radiation dose greater than 60 Gy. ORN was managed using varied methods such as surgical therapy, reconstruction with free fibular graft, low level laser therapy, and platelet rich gel. The recurrence of ORN was reported in 22% cases ranging from three weeks to one year later. In conclusion, the present review highlights the clinical features and risk factors associated as well as the various methods used in the treatment of ORN. The use of preventive strategies and advanced methods of management can decrease the incidence of ORN.

Introduction

Osteoradionecrosis (ORN) is a severe complication of external beam radiotherapy (RT) for malignancies affecting the head and neck (1,2). It is defined as 'A potentially severe, delayed radiation-induced injury, characterized by bone tissue necrosis, failure to heal, and exposed bone for at least three months' (3). The incidence of ORN in the head and neck region varies from 2% to 22% in subjects with a history of radiotherapy (3).

Various mechanisms have been proposed to explain the occurrence of ORN. These include the most commonly accepted hypoxic-hypocellular-hypovascular concept where radiation causes hypoxia of the bone, death of bone cells and long term damage to vascular supply as a result of endothelial cell damage ultimately leading to bone death (4). Another theory suggests that radiotherapy results in decreased soft tissue matrix which gets replaced with fibrous tissue, thereby increasing the tendency to develop ORN (5). Another suggested cause is the suppression of osteoclast related bone turnover. Some authors have proposed that radiation leads to a local inflammatory process which causes osteoblastic cell death, thereby preventing the repopulation of cells (6). The most recent theory of ORN is the fibroatrophic theory. According to this theory, vascular changes in the bone lead to endothelial changes along with an inflammatory response. This is followed by abnormal fibroblastic activity and altered bone healing which is more susceptible to infection (6).

Among the various classifications, the one given by Notani et al. (7), which is based on the amount of bone involvement, is

simple and preferred by many authors (8). ORN is a progressive condition which is difficult to treat. Various management strategies include sequestrectomy, resection, segmental mandibulectomy, and hyperbaric oxygen (HBO) therapy with varied results. Recent methods include the use of Pentoxifylline, Tocopherol and Clodronate, "PENTOCLO" (8).

The present report reviewed the current literature of the demographic characters, clinical features, and latest management techniques employed in the treatment of ORN.

A "PubMed" database search was done to identify case reports on ORN, published using the keywords "osteoradionecrosis", "jaw", "mandible", and "maxilla". Data on ORN published within the past 10 years from 2008 to 2018 were collected and analyzed. Only those case reports for which full text was available were considered in the review. Demographic characters, clinical features, and management were tabulated. Descriptive statistics were calculated using means and percentages.

A total of 23 full text articles reporting 27 cases of ORN were identified. The age range of the subjects was from 18 years to 84 years with a mean of 49 years. Males constituted 84% of the cases while females accounted for 16%. In 96% of the cases, the mandible was affected while 4% involved both the maxilla and mandible. The right and left mandible were equally affected in 34.6% of cases; and ORN was present bilaterally in 26.9% of cases. The posterior mandible was the most common site in 53.8% of cases.

ORN occurred three months -13 years later following radiotherapy, with an average time of 3.87 years. Associated malignancies varied with maximum cases having received radiotherapy for tonsillar carcinoma (Figure 1).

Radiotherapy was the primary treatment given in 25.9% of cases; surgery and radiotherapy were given in 40.7% of cases; subjects received adjuvant chemotherapy in 25.9% of cases while a combination of surgery, chemotherapy and radiotherapy was given in 7.4% of cases (Figure 2).

The amount of radiation received ranged from 50 Gy to 77 Gy.

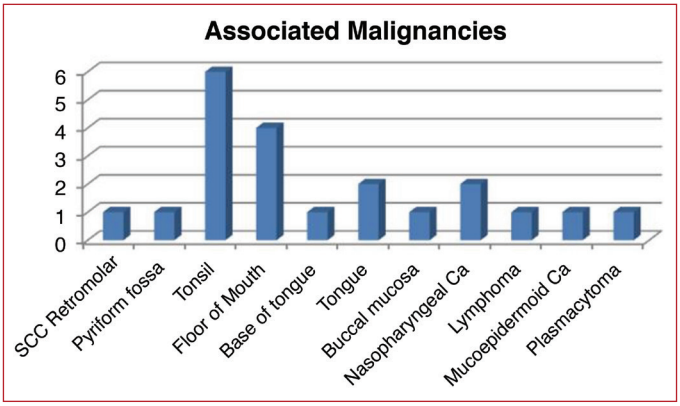

Figure 1. Graph showing the site of reported malignancies
SCC: Squamous cell carcinoma, Ca: Carcinoma

The presenting features of ORN included pain and discharge in 25.9% of cases, pathological fracture in 14.8% of cases, dysphagia and swelling in 7.4% of cases and anesthesia of the inferior alveolar nerve in 7.4% of cases.

Risk factors for ORN were tooth extraction, tobacco and alcohol abuse, and underlying medical conditions.

Management included surgical resection with fibular graft in 37% of cases, HBO therapy in 29.6% of cases, and segmental resection in 18.5% of cases. Other methods of ORN management included the use of leukocyte platelet-rich plasma (PRP), sequestrectomy, surgical debridement with Integra skin regeneration system and vacuum-assisted closure (VAC) system.

Recurrence of ORN was reported in 22% of cases, which ranged from three weeks to one year later. Table 1 (6,9-27) summarizes the details of subjects with ORN as reported by the various authors.

Discussion

Regaud first described post radiation ORN of the jaw in 1922 (13). Ewing, in 1926, reported the bone changes after radiotherapy as radiation osteitis (11).

Early bone changes after radiotherapy includes hyperemia, endarteritis, and cell death, while late changes include thrombosis, hypovascularization, and fibrosis (5).

ORN is a late effect of radiotherapy. RT for cancer in the head and neck has an increased chance of causing mandibular ORN. Recent reports suggest that the incidence of ORN has decreased from 20% to around 4-8%. This decrease is related to the elimination of all risk factors prior to radiotherapy and

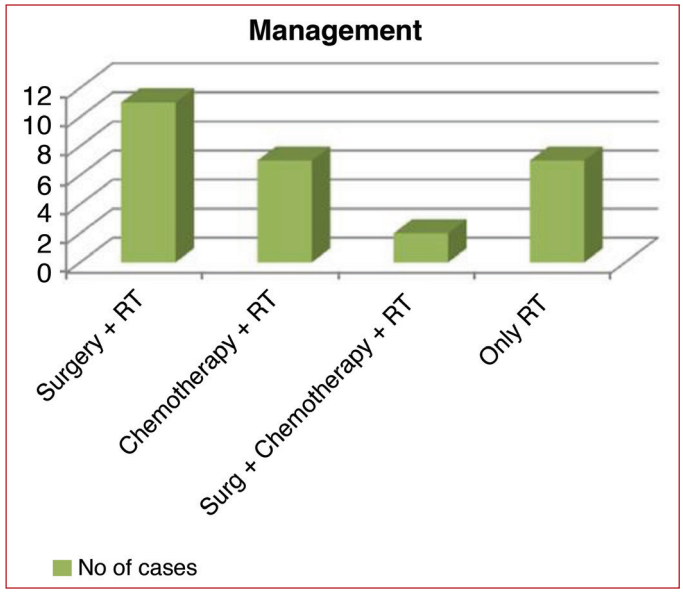

Figure 2. Graph showing the management strategies used in the reported cases
RT: Radiotherapy

recent advances in radiotherapy such as intensity modulated radiotherapy (IMRT) (28). The incidence of occurrence of ORN in the mandible is between 2% and 22% with most cases occurring in the mandibular body (9). This is in accordance with the present report where the mandible was the most affected, predominantly the posterior mandible. This increased predilection for the mandible is due to the richer vascularity in the maxilla and also because the mandible is irradiated more often. Also, since the mandibular bone is denser, the amount of radiation absorbed by the bone is more (6,29).

Around 70-90% of ORN cases are reported to occur within the first three years after radiotherapy. In the present report, ORN occurred from three months to 13 years following radiotherapy. However, the majority of cases occurred within the first five years. This variability could be because of the size and nature of the tumor, the type of radiotherapy used or individual patient risk factors (28).

The amount of radiation received ranged from 50 Gy to 77 Gy. The risk of developing ORN is medium at a radiation dosage of 40-60 Gy and high at a dose above 60 Gy (23). This is in conformity with our results.

The subjects may be asymptomatic in the initial stages. The main diagnostic feature is the presence of exposed bone in the mucosa or skin which can get secondarily infected. Other features include pain, dysesthesia, halitosis, and dysgeusia. Severe cases may lead to fistula formation from the oral mucosa or skin and pathological fractures (9). Diagnosis of ORN is made on the basis of patient history and the presence of exposed bone for more than three months. Radiological investigations such as panoramic radiographs and computed tomography are used to assess the extent of bone changes (17,23,30). This is similar to the clinical features reported by ORN cases in the present review.

Chemoradiotherapy (CRT) is linked to better locoregional control and overall survival and eradicates micrometastases. Although CRT is associated with an increase in early toxicity such as mucositis, the role of CRT in late toxicity is not clear. Recent studies have concluded that CRT does not increase the risk of ORN. In the present review, 25.9% of the cases received CRT. However, previous studies show difference in the incidence of ORN after RT and CRT (31).

Conventional management of ORN includes surgical debridement, sequestrectomy, oral hygiene maintenance with oral antiseptics, and the use of medications such as analgesics, antibiotics and corticosteroids (11). Segmental mandibulectomy is the next option followed by a complex reconstruction. In accordance with the fibro atrophic theory, a recent regimen for ORN recommends the use of vascular directed therapy using alpha – tocopherol (Vitamin E) and pentoxifylline (PENTO). Addition of clodronate to PENTO was found to be beneficial but carried the risk of bisphosphonate induced osteonecrosis (9,26). Delanian et al. (30,32) reported that PENTOCLO resulted in spontaneous sequestrectomy within the first six months of therapy leading to bone healing. PENTOCLO is not recommended in patients with recurrent or residual tumor. HBO therapy has been used along with surgery due to its ability to promote vascularity. HBO therapy includes the use of 100% oxygen for 90 mins at 2.4 atm pressure (24). However, recent trials have failed to demonstrate definite benefits. HBO is advised as an adjunct when resection or reconstruction surgery is needed (26). In the present report, HBO therapy was used in 29.6% of cases, usually in association with surgical debridement and resection with good results.

ORN can be of two types-spontaneously occurring and trauma induced (5). Spontaneously occurring ORN depends on the radiation dose that is received while ORN after dental treatments is categorized as trauma-induced ORN (5,27). Around 5% of cases occur following dental extraction (8). This is reflected in the present results where only two cases of ORN were reported after tooth extraction.

Spontaneous ORN commonly occurs between 6 months and 2 years after radiotherapy while the possibility of trauma-induced ORN is for long term. Thus, the risk of trauma induced ORN is higher in the dentate subjects due to extraction or dental and periodontal infection (9). Other factors include the grade and site of tumor, amount of radiation, immune deficiencies and any comorbidities (14). Moon et al. (28) found that pre-radiotherapy extractions were an independent risk factor for ORN but mentioned that it might be a reflection of the poor oral hygiene of the subjects. The use of IMRT has decreased the incidence of ORN especially in combination with good oral hygiene measures and decreased radiation to the mandible and parotid salivary glands (8). Contributing factors noted in the present review included tobacco and alcohol abuse and underlying medical conditions.

Marx's staging of ORN as stage 1, stage 2 and stage 3 is still widely followed (21). Stage 3 ORN requires surgical intervention (23). Kraeima et al. (23) used a novel method of combining the chemotherapy with the radiotherapy isodose curves in order to accurately predict the areas of ORN risk, and plan exact resection of affected bone and screw locations for reconstruction plates which are outside high dose areas.

Management of ORN in the present review was done using various methods. Most management strategies involved surgical treatment with the debridement of non-viable tissue and subsequent reconstruction. Successful management strategies included the use of allogeneic platelet gel (1) and skin regeneration systems for the repair of minor to moderate intraoral defects (3). Schepers et al. (10) described successful prosthetic rehabilitation with fibular graft using virtual implant planning. PRP was used to regain mandibular integrity and continuity of bone following

Table 1. Table showing details of subjects with osteoradionecrosis

Authors	Site of ORN	Associated malignancy with staging	RT cycles	Any other concurrent therapy	Age/ Sex	Duration after RT
Curi et al. (5) 2017	Bilateral posterior mandible	Retromolar trigone Ca (T2 N2 M0)	Postoperative fractionated RT (5 fractions/week; 2.0 Gy/fraction; 34 sessions total of 68 Gy)	Surgery right radical neck dissection (lymph nodes levels 2 to 4) without ligation of the external carotid artery	56/M	8 yrs
Piccin et al. (1) 2016	Right posterior mandible	Right piriform sinus poorly differentiated adenocarcinoma	RT 7,000 cGy were given over 35 sessions	Chemotherapy (cisplatin 100 mg/ m^2 intravenous)	61/M	9 yrs
Beech and Farrier (3) 2016	Right posterior mandible	Left-sided tonsillar carcinoma	RT	Surgical excision	54/M	5 yrs
Schepers et al. (10) 2013	Right anterior mandible	Squamous cell carcinoma of the anterior floor of the mouth	RT 66 Gy	Surgical excision	54/M	1 yr
Reiffel et al. (11) 2012	Left posterior mandible	Cancer of base of tongue stage 4	RT	Chemotherapy	55/M	2.5 yrs
Rao et al. (4) 2012	Right posterior mandible	Low grade mucoepidermoid carcinoma	RT	Surgical excision	38/F	5 yrs
Poglio et al. (12) 2011	Right posterior mandible	Unknown	RT		41/M	2 yrs
Man et al. (13) 2015	Right posterior mandible	Malignant lymphoma	RT 60 Gy	Chemotherapy	18/M	1 yr
Scala et al. (14) 2010	Bilateral anterior and posterior mandible	Squamous cell carcinoma of the left half of tongue PT1pN0	RT 33 visits, 5 visits per week; each consisted of a dose of 200 cGy with a total dose of 6,600 cGy with Lonidamine	Partial left glossectomy with conservative neck dissection (CND) and bilateral suprahyoid lymph node dissection	44/M	4 yrs
Khatami et al. (15) 2010	Bilateral anterior and posterior mandible	Cancer of unknown primary	RT		62/M	

Clinical features	Management	Any other	Risk factor
Dysphagia caused by a painful, swollen, and discolored tongue	Hyperbaric oxygen therapy (30 sessions: 20 sessions before surgery and 10 sessions after surgery; 2.4 ATA; 90-minute session in a monoplace chamber. Bilateral marginal bone resections	Associated tongue necrosis	Tooth extraction under local anesthesia using vasoconstrictor
Severe dysphagia, fever >38 °C, rigor swelling of the right jaw and right sternocleidomastoid muscle	Leukocyte platelet-rich plasma (PRP) every 3 days for a total of 7 weeks (22 applications in total)		Alcohol abuse
Pain, difficulty eating, foul taste. Anesthesia of right inferior dental nerve; pathological fracture	Surgical debridement and Integra skin regeneration system		
Oral dehiscence and necrotic mandibular bone	Surgical resection followed by reconstruction with a free osseous flap with the planning of an implant-based prosthesis		
Necrotic left mandibular body	Segmental mandibulectomy followed by free fibular graft		
Pain, restricted mouth opening and discharge from ear; discoloration of overlying skin	Hyperbaric oxygen therapy	Mastoiditis	
Lower jaw defect involving the oral mucosa, mandibular bone, external skin, and soft tissue, communication between the oral cavity and the exterior	Subtotal mandibulectomy, fibular graft and vacuum-assisted closure system		
	Hemimandibulectomy, debridement of necrotic soft tissue, repair of the orocutaneous defects with thigh flap	Recurrent ORN 2 yrs later repaired using stereolithographic 3-Dimensional Printing modeling technology osteomyocutaneous flap	
Stomatitis, purulent abscesses and exposed alveolar process H/o tooth exfoliation	Moxifloxacin hydrochloride 600 mg daily dose for 20 days, regenerative surgery with autologous platelet rich plasma		
	Mandibulectomy and reconstruction with vascularized fibula flap		

Table 1. Continued

Authors	Site of ORN	Associated malignancy with staging	RT cycles	Any other concurrent therapy	Age/ Sex	Duration after RT
Mendonça and Juiz-Lopez (16) 2010	Mandibular and maxillary anterior and posterior	Tonsillar cancer	RT		63/M	
Pautke et al. (17) 2010	Right anterior and posterior mandible	Extramedullary plasmocytoma	RT chest at 50 Gy	Adenectomy and lobectomy of the right lower lobe Bisphosphonate therapy	72/M	11 yrs
Pautke et al. (17) 2010	Left anterior and posterior mandible	Carcinoma of the left margin of the tongue pT1, pN1, Mx	RT 68.7 Gy; brachytherapy 62.5 Gy 9 yrs later	Bilateral neck dissection and partial glossectomy; chemotherapy (cisplatin and 5-fluorouracil) 9 yrs later	68/M	11 yrs
Le Stanc et al. (18) 2009	Left posterior mandible	Left tonsil squamous cell carcinoma extending to tongue and skull base cT4N1M0	RT 70 Gy	Chemotherapy (Carboplatin-Paclitaxel)	48/M	2 yrs
Jacobson et al. (19) 2010	Bilateral posterior mandible	Cancer of the tonsil	Opposing fields of external beam RT		72/M	4 yrs
Tursun and Green (20) 2017	Bilateral posterior mandible	Base-of the-tongue squamous cell carcinoma	7,000 cGy of radiation		72/M	13 yrs
Kakarala et al. (21) 2011	Bilateral mandible	Squamous cell carcinoma of the anterior floor of the mouth	RT	Resection and neck dissection	36/F	
Horta et al. (22) 2014	Mandible		RT		41/F	
Kraeima et al. (23) 2018	Left hemimandible	Squamous cell carcinoma in the floor of the mouth stage pT4N0	RT 56 Gy	Marginal mandibular resection.		3 months

Clinical features	Management	Any other	Risk factor
Tooth extraction, pathologic fracture, life-threatening infection, prolonged hospitalization, and severe chronic pain	Surgical debridement, 45 dives in hyperbaric oxygen, antibiotic therapy	Recurrent ORN after 1 year, suppuration from two fistulas, severe trismus, total lip anesthesia, treated with cultures stem and progenitor cells using bone marrow aspirate	
Submental abscess and an extraoral fistula in the anterior right chin region	Abscess was incised, extraction from the left lower first incisor to the right lower canine	Recurrence occurred twice mandibulectomy was done	Peripheral artery disease, coronary artery disease, arterial hypertension, diabetes mellitus, and a smoking habit
Exposed bone in the left lower jaw, fetor ex ore, and intensive, therapy-resistant pain	Partial resection of the left mandible and immediate reconstruction with fibular graft		Hypertension, glaucoma, and hyperthyroidism
Left submandibular fistula and pain; later pathological fracture	Surgical treatment	ORN with recurrent tumor	Alcohol and tobacco consumption
Bone exposure	Hyperbaric oxygen, antibiotics, and local debridements	Marx stage 3 ORN 6 months later; segmental mandibulectomies, with preservation of the native symphysis, and a reconstruction using a single fibular free flap	
Exposed bone in the right mandible with pain, purulent discharge, and severe hypoesthesia in the distribution of the inferior alveolar nerve	Antibiotics in addition to chlorhexidine mouth rinses 3 times daily to control the localized infection. The patient underwent hyperbaric oxygen therapy; ultimately surgical resection and fibular graft		
ORN	Resection and fibular graft	Wound infection and free flap loss; revision fibular free flap reconstruction was done with VAC	
	Resection and fibular graft	Chimeric anterolateral thigh flap	
Intraoral exposed necrotic bone (ORN) and a fractured mandible with an orocutaneous fistula	HBO treatment; reconstruction with iliac graft (30 sessions)	Repeat ORN in three weeks; reconstruction with fibular graft	

Table 1. Continued

Authors	Site of ORN	Associated malignancy with staging	RT cycles	Any other concurrent therapy	Age/ Sex	Duration after RT
Kraeima et al. (23) 2018	Bilateral mandible	Squamous cell carcinoma floor of the mouth	RT 56 Gy	Surgical resection including a marginal resection of the mandible		11 months
Kraeima et al. (23) 2018	Left mandible	Squamous cell carcinoma in the buccal mucosa of the left mandible (pT4N1)	RT 66 Gy	3D guided surgical resection, including neck dissection, and the defect was reconstructed with a free vascularized fibula flap	84/M	20 months
Jeyaraj and Bandyopadhyay (24) 2016	Left mandible	Carcinoma of the left tonsil and faucial pillar and the left lateral and posterior pharyngeal wall	RT 76.8 Gy		60/M	10 months; One month after tooth extraction
Badeau and Deleyiannis (25) 2013	Left mandible	Left basaloid squamous cell carcinoma with recurrence	RT	Chemotherapy	59/M	3 yrs
Rathy et al. (9) 2013	Right mandible	Squamous cell carcinoma	RT	Surgery	65/M	4 yrs
Etezadi et al. (26) 2013	Left mandible	Left tonsillar squamous cell carcinoma stage T4bN3	RT 7,000 cGy	Radical tonsillectomy and modified neck dissection; chemotherapy	46/F	
Shimizu et al. (27) 2012	Right mandible	Nasopharyngeal cancer	RT 60 Gy to bilateral mandible	Chemotherapy	74/M	5 yrs
Shimizu et al. (27) 2012	Left mandible	Nasopharyngeal cancer	RT 66 Gy to bilateral mandible	Chemotherapy	69/M	3 yrs

Yrs: Years, Yr: Year, ORN: Osteoradionecrosis, HBO: Hyperbaric oxygen, RT: Radiotherapy

ORN (14). The most commonly reported treatment in large defects involved mandibular resection followed by free fibular graft and implant supported prosthesis (15). Tursun and Green (20) reported the use of processed allogeneic nerve allograft during surgical treatment for regaining neurosensory function in patients with ORN. Iliac marrow aspirate was used successfully for bone regeneration in one case (16). Kakarala et al. (21) used VAC dressing over free flap muscle to assist the closure of cutaneous defects in ORN. Horta et al. (22) reported a case where the failure of fibular graft was managed using chimeric anterolateral thigh flap and a dural substitute membrane with acceptable results.

Based on the fibroatrophic theory of ORN, a combination of pentoxifylline, tocopherol and clodronate is being tried as medical management in ORN cases refractory to surgery and HBO therapy. This protocol included antibiotic and corticosteroid treatment for one month to control infection followed by pentoxifylline, tocopherol and clodronate for at least six months. The authors reported a resolution rate of around 89% (33,34). In the present review, Garg et al. (6) was able to achieve good results with a combination of PENTOCLO therapy and sequestrectomy. An additional finding in the study was the incidence of ORN recurrence. As much as 22% of cases reported the recurrence ranging from

Clinical features	Management	Any other	Risk factor
	Reconstruction using isodose curves		
An intraoral fistula with exposed bone	HBO with soft tissue nasolabial flap; reconstruction using isodose curves		
Inability to open his mouth, difficulty in consuming even semisolid food and a persistent dull aching pain in the left side of his lower jaw	Segmental mandibular resection followed by Titanium reconstruction plate		Smoker, microvascular thrombosis, bronchiectasis of lung
Anterior submental draining sinus tract extending to the bone	Antibiotics and hyperbaric oxygen; surgical resection with fibular free flap		
Sharp bony projection in the mouth and pus discharge on right cheek	Sequestrectomy		
Exposed bone pain, trismus, and intraoral drainage	HBO; Segmental resection of the affected bone of the mandibular body, bilateral coronoidectomies, and placement of an external pin fixator	Dehiscence of the skin at the incision site with orocutaneous fistula after three months. Reconstruction with fibular flap	
Cheek skin was stiff, orocutaneous fistula, limited mouth opening	Surgical resection with fibular osteoseptocutaneous flap	ORN of left mandible occurred 3 yrs later; treated similarly	
Cheek skin was stiff, orocutaneous fistula, limited mouth opening	Surgical resection with fibular osteoseptocutaneous flap	ORN of right mandible occurred 2 yrs later; treated similarly	Extraction of left mandibular molar

three weeks to one year later; thus highlighting the recalcitrant nature of ORN.

The present review has certain limitations. In the reviewed case reports, data regarding newer methods of surgical management are highlighted. Pharmacologic management using pentoxifylline, tocopherol, and clodronate “PENTOCLO” has shown promise in treating patients with ORN. However, none of the reviewed case reports had data regarding the pharmacologic management of ORN. The incidence of ORN can be decreased through the use of new RT protocols such as 3D conformational radiotherapy and IMRT, which are able to deliver maximum radiation to the affected area while sparing the normal surrounding tissue as far as possible. However, data regarding the use of these methods were not available in the reviewed articles.

Conclusion

ORN is an important late complication of RT for head and neck cancer. The present review highlights the predilection of ORN to occur in the posterior mandible in subjects who have received radiation doses greater than 60 Gy. Tooth extraction, tobacco and alcohol use, and patient comorbidities are the risk factors for the development of ORN. All patients should undergo prophylactic oral care before, during and after the completion of radiotherapy.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: V.A., S.H., Design: V.A., S.H., Data Collection or Processing: V.A., Analysis or Interpretation: V.A., S.H., Literature Search: V.A., Writing: V.A., S.H.

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The relevance of antibiotic supplements in mammalian cell cultures: Towards a paradigm shift

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ABSTRACT

Antibiotic supplements remain a key component of mammalian cell culture systems, providing simple and cost-effective preventive measures as well as treatment for bacterial contamination. However, to a certain extent, antibiotic supplements may also have undesirable activities that are not consciously recognized. In fact, customary antibiotic supplements in cell cultures exhibit cytotoxic and cytostatic activity at standard concentrations, as well as altering the biological patterns of cultured mammalian cells. On the other hand, acquired resistance is a matter of great concern that may arise as a result of routine and long-term use of antibiotic supplements. This review addresses the relevance of the use of antibiotic supplements in mammalian cell culture systems, by highlighting their advantages and disadvantages and providing insight into the practices of antibiotic-free culture media.

Introduction

Cell culture is a method by which eukaryotic cells are grown and propagated *in vitro* with enriched fluid media under controlled conditions. The method was first introduced by Harrison et al. (1), where a small piece of neural tissue isolated from frog embryos placed in a drop of fresh adult frog lymph on a sterile cover slip was observed to grow and form nerve fibers. Since then, the method has been improved and has enabled various cell-based applications through the use of sterile plastic consumables, artificial growth media, and antimicrobial agents such as antibiotics and antifungals (2,3). One of the earliest uses of cell culture was the propagation of poliovirus for vaccine production in the 1950s (4), and in the decades since, the method has been extensively utilized in research and industry, especially in the field of biomedical and pharmaceutical sciences.

Cell culture-based assays are usually performed using primary cells or cell lines-derived from organisms such as humans, rats, and mice. Cells isolated directly from these organisms are called primary cells, while permanently established cells are called cell lines, and these cells are either adherent or suspension. The primary cells have a limited lifespan, but the cell lines are usually indefinite. Presently, mammalian cell culture systems are either two-dimensional (2D), three-dimensional (3D) or co-culture (3). In 2D cultures, cells grow on a flat, rigid surface of standard culture flasks or plates. On the other hand, 3D cultures involve either the use of scaffolds or liquid cultures on low-attachment plates, in hanging

drops or in rotation, and these methods can be carried out in co-cultures of with different cell types or cellular components.

In *in vitro* mammalian cell-based studies, bacterial contamination is a major threat and the culture media are usually supplemented with antibiotics as a preventive measure. In particular, the identified contaminated cells will be discarded rather than treated in order to prevent the risk of persistent contamination. However, in some circumstances, including limited cell resources, antibiotic treatment is the ideal way to rescue contaminated cells. Markedly, although antibiotic use has been shown to be an effective method for eliminating bacteria from contaminated cells, it is important to emphasize that their presence in culture media is not inert (Figure 1). The aim of the present review is to discuss the relevance of antibiotic-supplemented culture media because mammalian cells are adversely affected by antibiotic supplements, thereby wreaking an error discovery and further fueling concerns about the rise of antibiotic-resistant bacteria over routine and continuous use.

Threats to Mammalian Cell Cultures

There are three constant threats in mammalian cell culture systems, namely, microbial contamination, cross-contamination, and chemical contamination. These threats can be persistent, hidden, overlooked, and unrecognized (5). In general, all contaminants are hazards to the cell culture system and will affect the reliability and reproducibility of the scientific findings of a particular experiment.

Microbial contamination is most commonly due to the presence of microorganisms such as bacteria and fungi that flourish in cultures (6). These microbes compete for nutrients and cause a shift in the pH value of the culture media, alter cell metabolism, hinder cell growth, and often lead to cell death. On the other hand, cross-contamination is referred to as the condition of one type of cell contaminated with another type of cell. The widely known cross-contamination is human cervical adenoma cells cross-contaminated with many mammalian cell lines. The gold standard method for authenticating this type of contamination is DNA profiling based on short tandem repeat (7). In addition to microbial and biological sources, contamination may also occur due to chemical residues of disinfectants or detergents in glassware and impurities or toxins in water, media, or other reagents used in cell cultures (8).

It should be noted that microbial contamination is a major and persistent challenge in mammalian cell culture systems, and most cases are due to mycoplasmas (6,9,10). They are the smallest prokaryotes and are difficult to detect either macroscopically or microscopically. Mycoplasma-contaminated cell cultures do not cause the culture media turbidity and pH changes with no apparent effect on cell growth and cell morphology, and hence remain undetected for many passages (6,11). In point of fact, mycoplasmal contamination alters the biological features of host cells. Sokolova et al. (12) discovered that *Mycoplasma bovis* sensitized murine T-cell hybridoma 2B4 and several different human cell lines to apoptosis induction. However, *Mycoplasma fermentans* has been found to cause choline deficiency-induced apoptosis in primary rat astrocytes (13). The impact of *Mycoplasma fermentans* was also evident

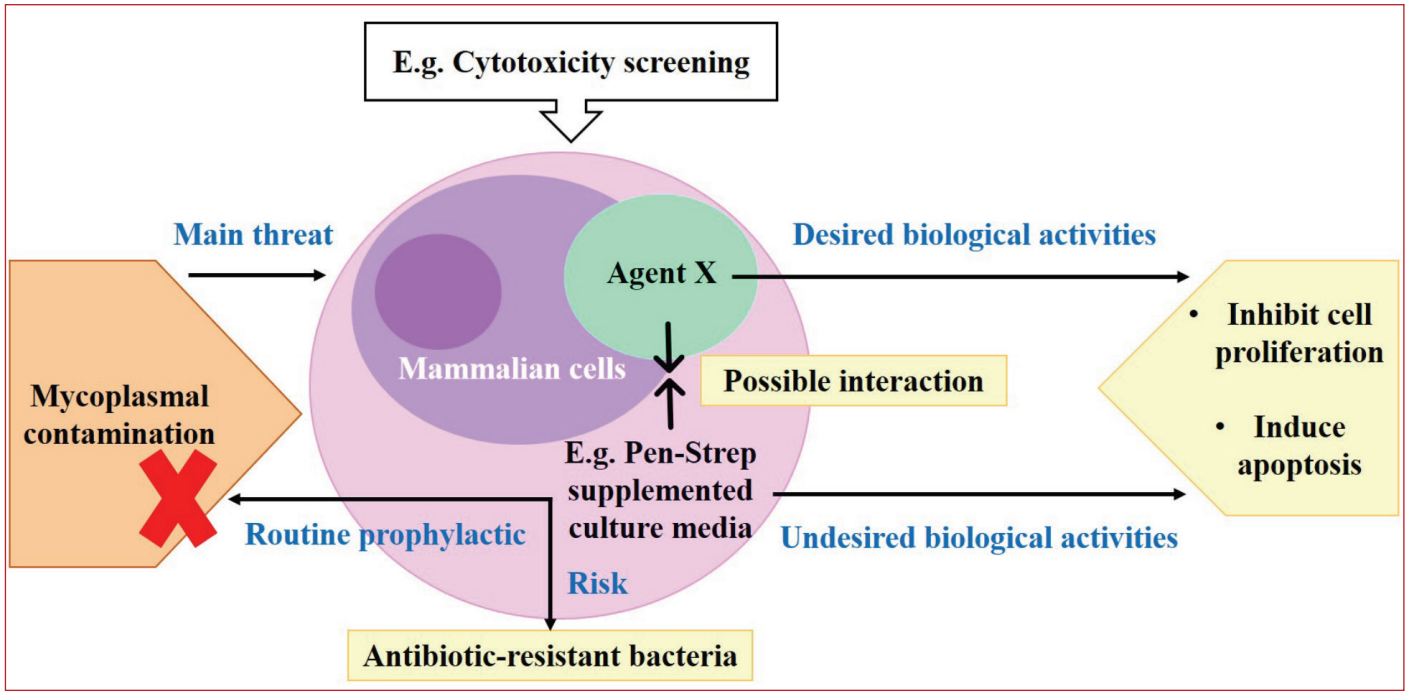

Figure 1. Overview and downside of the customary antibiotic supplements in mammalian cell cultures

Pen-Strep: Penicillin-streptomycin, E.g.: For example

across cytotoxicity as it exerted cytokines-inducing activity in human monocytes and myelomonocytic cell lines (14).

Uphoff and Drexler (9) have shown that the most common mycoplasma species contaminating the cell lines is of human origin, of which about 47% identified by polymerase chain reaction-restriction fragment length polymorphism method was *Mycoplasma fermentans*. Other species have been found in mammalian cell lines, including *Mycoplasma arginini* (bovine), *Mycoplasma orale* (human), *Mycoplasma hyorhinis* (swine) and *Mycoplasma hominis* (human). Mycoplasmas are spread from mycoplasma-contaminated cell lines, cell culturist, animal-derived sera, origin of cells, and poor aseptic techniques, as well as cell culture equipment, culture media, and reagents used in the processing mycoplasma-contaminated cell cultures (6,11,15). Another potential source of mycoplasma contamination is the storage of cells in a liquid nitrogen tank in which mycoplasmas are able to survive in liquid nitrogen without cryopreservation and are capable of contaminating cryopreserved cells (16).

Antibiotic Supplements in Mammalian Cell Cultures

Antibiotics are classified according to their target on bacterial cellular components, which are either bactericidal or bacteriostatic. Bactericidal antibiotics kill bacteria, while bacteriostatic antibiotics inhibit the growth of bacteria. According to Perlman (17), there are seven basic requirements for antibiotic supplements in mammalian cell culture systems; (i) eliminate the microbial contaminants (bactericidal is preferred to bacteriostatic), (ii) do not inhibit growth and metabolism of mammalian cells, (iii) provide protection for the complete experimental period, (iv) do not affect any ultimate use intended for mammalian cells, (v) non-toxic and safe, (vi) compatible with other components in culture media and (vii) inexpensive and not contain excipients. In addition, Schafer et al. (18) suggested that the ideal antibiotic supplements should have broad-spectrum antibacterial and antimycoplasmal activities, but not cause cytotoxicity. It is important to know that antibiotics are stable in the cell culture media for three days at 37 °C and they are light-sensitive; therefore, stock and working antibiotics as well as cell culture media containing antibiotics must be protected from light (16,17).

At present, one of the most commonly used antibiotic supplements in mammalian cell cultures is a combination of penicillin (Pen) (100 U/mL) and streptomycin (Strep) (100 µg/mL) (1% v/v). Pen is a class of β-lactam antibiotics that works against Gram-positive bacteria, while Strep is a class of aminoglycoside antibiotic that works against both Gram-positive and Gram-negative bacteria. Both bactericidal antibiotics exhibit synergistic interactions, in which inhibition of bacterial cell wall synthesis by Pen facilitates the entry of Strep into bacteria that impair bacterial protein synthesis. Nevertheless, both antibiotics are sensitive to pH and temperature changes (18). Pen has a very short half-life at 37 °C and a rapid loss of activity at acidic and alkaline pH levels, while Strep has an optimum stability at 28 °C or below and a progressive loss of activity at alkaline pH (18-20). On the other hand, Pen activity has been shown to be decreased upon addition to the culture media containing serum and to be completely inactivated following autoclaving (18).

Gentamicin is the second most common antibiotic supplement used in mammalian cell cultures. According to Schafer et al. (18), the biological and biochemical properties of gentamicin are superior than that of Pen and Strep either given alone or in combination. Gentamicin belongs to the aminoglycoside group of antibiotics. It is a protein synthesis inhibitor with bactericidal activity against mycoplasma, Gram-negative, and Gram-positive bacteria. In terms of pH and temperature stability, gentamicin has been shown to be stable at 37 °C in both acidic and alkaline pH for 15 days and has not been affected by the presence of serum. In addition, gentamicin was found to be completely stable following 15 minutes of autoclaving at 121 °C with 15 lb of pressure (18). Gentamicin with the standard concentration (50 µg/mL) was demonstrated to have no noticeable effect on morphology, growth and metabolism of a number of mammalian cells (18,21). It is usually supplemented in cell culture media either alone or in combination with other antibiotics, mainly Pen-Strep.

Other antibiotics used for prophylaxis in mammalian cell cultures include ampicillin, erythromycin, and kanamycin, but are less popular. The recommended concentration for these antibiotics is 100 µg/mL (1% v/v). Ampicillin (β-lactam antibiotic) is a cell wall synthesis inhibitor with bactericidal activity against both Gram-positive and Gram-negative bacteria, while erythromycin (macrolide antibiotic) is a protein synthesis inhibitor with bacteriostatic activity against mycoplasma and Gram-positive bacteria. On the other hand, kanamycin (aminoglycoside antibiotic) is a protein synthesis inhibitor with bactericidal activity against mycoplasma, Gram-positive and Gram-negative bacteria (17,22,23). Additionally, fluoroquinolone (0.5 to 25 µg/mL), combination of fluoroquinolone/macrolide (25 µg/mL), and pleuromutilin (10 µg/mL)/tetracycline (5 µg/mL) are anti-mycoplasma antibiotics that have been shown to be effective in eliminating mycoplasmas from contaminated cell lines (10,16). Fluoroquinolone is a nucleic acid synthesis inhibitor with bactericidal activity, while both pleuromutilin and tetracycline are protein synthesis inhibitors with bacteriostatic activity. It is important to note that these anti-mycoplasma antibiotics are not recommended for prophylactic purposes or are routinely used in cell cultures.

1. Use and Effect of Antibiotic Supplements in Mammalian Cell Cultures

As far as bacterial contamination is concerned, the antibiotic-supplemented culture media has become a key

approach. Indeed, antibiotics have caused undesirable side effects in cultured cells differently depending on the cell types. For example, gentamicin exerted a significant cytostatic effect on rabbit keratocytes only at a concentration of 3,000 µg/mL (24). On the other hand, in human osteoblast-like cells, gentamicin engendered a dose-dependent cytostatic effect at concentrations of 100 µg/mL and above (25). Gentamicin, on the other hand, induced cytotoxic effects on human embryonic stem cells (hESCs) during directed differentiation towards hepatic and neural fate at a concentration of 10 µg/mL, but did not affect undifferentiated hESCs (26). Induction of apoptotic cell death by gentamicin in different types of renal cell lines and rat embryonic fibroblasts has been shown to be dose- and time-dependent (27). Here, the advantages and disadvantages of the use of antibiotic supplements in mammalian cell cultures are summarized as follows.

1.1. Advantages

In primary culture, the use of Pen-Strep-supplemented phosphate buffer saline (PBS) to rinse the cells during initial isolation and Pen-Strep-supplemented culture media has been shown to be effective in preventing bacterial contamination (28). Equally important, mycoplasma-contaminated cells can be treated with antibiotic classes such as tetracyclines, macrolides, fluoroquinolones, and pleuromutilins. These anti-mycoplasma regimens have been shown to be effective in eliminating mycoplasma from contaminated cells, 96% of which were permanently mycoplasma-free (10). In either case, antibiotic supplements may be needed when working with precious cells and limited cell resources, either in culture media or alternatively in PBS for cell washing.

1.2. Disadvantages

Despite the efficacy of antibiotics in the elimination and prevention of bacterial contamination in mammalian cell cultures, it has indeed been shown to alter the biological features of cells at cellular and molecular levels (26,29-31). Uphoff et al. (10) reported that around 3 to 11% of cell culture losses were due to anti-mycoplasma antibiotics-induced cytotoxicity. On the other hand, the universal prophylactic approach, such as Pen-Strep, is generally thought to cause cytotoxic, cytostatic, and other undesirable effects on mammalian cells at higher concentrations than recommended. As a matter of fact, Varghese et al. (26) showed that Pen-Strep (100 U/mL-100 µg/mL) did not affect the viability of undifferentiated hESCs after 2- and 5-day post-treatment, but induced apoptotic cell death without significant reduction in cell viability on day 10 of neural differentiation. Standard 1% Pen-Strep-supplemented culture medium has also been demonstrated to induce changes in HepG2 human liver cancer cells at molecular level (31). Then again, Bertram (32) found that Pen with a concentration of 100 U/mL suppressed 3-methylcholanthrene (MCA)-induced malignant transformation of mouse embryo cells (C3H/10T1/2). The inhibitory effect of Pen on MCA-induced malignant transformation in C3H/10T1/2 cells has also been discovered to be dose-dependent. On the other hand, a study discovered that Pen (150 U/mL) did not inhibit muscle development in primary culture of chick myoblasts (33). Table 1 summarizes the reported side effects of the antibiotic supplements on mammalian cells identified in this literature review.

Accordingly, the use of antibiotic supplements in mammalian cell cultures requires careful consideration as the drawbacks are greater than the benefits. It is important to point out that antibiotics exhibit concentration-dependent effects and the response of different mammalian cells to different antibiotic supplements may vary. In the light of pharmacodynamic interactions, the presence of antibiotic supplements in culture media could potentially interact with any type of test agent (32,34). The resulting interaction may increase or decrease the effect of a particular agent and ultimately lead to improper scientific results. With this in mind, studies that focus on cytotoxicity or anticancer screening, as well as any mammalian cell-based assay, are better not to use antibiotic-supplemented culture media.

2. Prophylactic Practice in Mammalian Cell Cultures

From the mid-19th century to the present, the use of Pen-Strep- or gentamicin-supplemented culture media or a combination of both to prevent bacterial contamination remains widespread. Kuhlmann (23) stated that the use of antibiotic-supplemented culture media was unsuitable because antibiotics interfered with cultured cells, yielding incomparable culture conditions and unreliable findings. On the other hand, regular use of antibiotics is not recommended as it may delay detection and mask low levels of bacterial contamination (5,15). Furthermore, the use of antibiotic-supplemented culture media for unnecessarily prolonged periods could contribute to an increase in antibiotic-resistant bacteria, which may result in unmanageable bacterial contamination in mammalian cell culture systems (10,15). One group found that the general prophylactic use of Pen-Strep was insensitive to prevent and eliminate mycoplasmal contamination. Gram-negative, such as *Klebsiella* species, *Providencia* species, and *Pseudomonas aeruginosa* as well as one out of five strains of the Gram-positive *Staphylococcus aureus* have indeed been shown to be resistant to Pen-Strep (21). Additionally, Kastrop et al. (20) discovered that 91.4% of the bacterial strains were either Pen- or Strep-resistant or both, and most of which were *Escherichia coli*.

From now on, the use of prophylactic antibiotics should be limited and discouraged for long-term routine use. Antibiotic supplements certainly do not provide an optimal preventive effect without aseptic techniques and a biological safety cabinet while performing cell culture work. By all means, bacterial-

Table 1. Side effects of antibiotic supplements on mammalian cells

Antibiotic (s) (Concentration)	Cells/Cell line	Significance	Reference
Fluoroquinolones (3, 30, 300 and 3,000 µg/mL)	Rabbit keratocytes	Antiproliferative	Seitz et al. (24)
Gentamicin (100, 300 and 700 µg/mL)	Human osteoblast-like cells	Antiproliferative; decrease ALP activity	Isefuku et al. (25)
Gentamicin (10-200 µg/mL) with or without Pen-Strep (100 U/mL-100 µg/mL)	hESCs (post hepatic and neural differentiation)	Antiproliferative; induce apoptosis; decrease the gene expression of neural stem cell markers	Varghese et al. (26)
Gentamicin (2 mM)	Rat embryonic fibroblasts; LLC-PK1; MDCK	Induce apoptosis	El Mouedden et al. (27)
Pen-Strep (50, 100 and 200 U/µg/mL); gentamicin (10, 25 and 50 µg/mL)	hiPSC-CMs	Induce electrophysiological changes; decrease the gene expression of sodium and potassium ion channels	Hyun et al. (29)
Ciprofloxacin (10 µg/mL); ampicillin (20 µg/mL); kanamycin (25 µg/mL)	MCF10A, PAEC, HMEC, CACO-2 and NHDF	Induce oxidative stress and mitochondrial damage	Kalghatgi et al. (30)
Pen-Strep (1% v/v)	HepG2	Induce global changes in the gene expression and chromatin landscape	Ryu et al. (31)
Gentamicin (50 and 100 µg/mL)	C3H/10T1/2	Antiproliferative	Bertram (32)
Strep (50 and 100 µg/mL)	Chick embryo muscle cells	Delay myogenesis	Moss et al. (33)
Gentamicin (0.1 mM)	MDCK-C11	Antiproliferative; induce morphological and ultrastructural changes, and increase in intracellular calcium level	Coutinho et al. (35)
Gentamicin (50 and 200 µg/mL)	hMSCs	Inhibit osteoblastic cell differentiation	Kagiwada et al. (36)
Pen-Strep (100 U/mL-100 µg/mL)	Human adipose-derived MSCs	Antiproliferative; increase the gene expression of MSCs, adipose tissue, and osteoblastic markers	Skubis et al. (37)
Pen; gentamicin; ciprofloxacin (100 µg/mL)	Human osteoblasts	Antiproliferative; decrease ALP activity	Rathbone et al. (38)
Gentamicin (10 mM)	LLC-PK1	Induce apoptosis	Choi et al. (39)
Gentamicin (100 µg/mL); Pen-Strep (100 U/mL-100 µg/mL)	Murine ESCs	Antiproliferative; reduce cell differentiation efficiency	Cohen et al. (40)
Gentamicin (100 and 500 µg/mL)	Human embryonic lung fibroblasts	Antiproliferative	Litwin (41)
Gentamicin (1,000 µg/mL)	Human keratinocytes	Antiproliferative	Cooper et al. (42)
Pen (5 mM); Strep (5 mM); gentamicin (3 mM)	Rat hepatocytes	Inhibit protein synthesis and protein degradation	Schwarze and Seglen (43)
Pen-Strep (1,000 µg/mL-33 µg/mL)	Rat adipocytes	Induce changes in heparin-releasable lipoprotein lipase activity	Goldstein and Johnson (44)
Pen (100-300 U/mL); gentamicin (6.5-50 µg/mL); Strep (50 µg/mL)	Mice brain cells	Inhibit sulfatide synthesis	Amonn et al. (45)
Gentamicin (1 mM)	LLC-PK1	Antiproliferative; decrease intracellular cyclic adenosine monophosphate level; increase the number and size of lysosomes, and the activity of N-acetyl-β-D-glucosaminidase, aminopeptidase, and ALP	Hori et al. (46)

LLC-PK1: Pig kidney epithelial cells, MDCK: Madin-Darby canine kidney epithelial cells, hiPSC-CMs: Human induced pluripotent stem cell-derived cardiomyocytes, MCF10A: Human mammary epithelial cells, PAEC: Primary human aortic endothelial cells, HMEC: Primary human mammary epithelial cells, CACO-2: Human intestinal epithelial cells, NHDF: Normal human diploid skin fibroblasts, HepG2: Human liver cancer cells, C3H/10T1/2: Mouse embryo cells, hMSCs: Human mesenchymal stem cells, ESCs: Embryonic stem cells, ALP: Alkaline phosphatase, Pen-Strep: Penicillin-streptomycin

free mammalian cell cultures can be achieved without relying on antibiotic supplements, but by following standard aseptic techniques along with a clean and well-maintained cell culture environment and equipment. In any scenario, the potential for bacterial contamination cannot be completely eliminated. Consistent practice of good aseptic techniques and sterilization of all consumables and reagents warrant the use of antibiotic-free culture media. It is important to note that bacterial contamination can occur at any stage of cell cultures and must therefore be visually and routinely assessed for the evidence of contamination.

In addition, it is suggested that the newly purchased mammalian cell line be thawed and maintained in antibiotic-free culture media in order to be able to rule out possible contamination due to Gram-negative and Gram-positive bacteria, yeast as well as mould. Then again, due to the high prevalence of mycoplasmal contaminations in mammalian cell lines, it is necessary to authenticate that the cells are free of them. Mycoplasmas, however, are difficult to detect by visual observations and are mostly identified by molecular-based assays (6,9,12). Mycoplasma-contaminated cell cultures are often occult, but are known to cause changes in cellular and molecular signatures of cells (12-14).

Conclusion

The primary role of antibiotic supplements is to eliminate the bacteria from contaminated mammalian cells. However, for many years, the vast majority of mammalian cell-based studies have been using culture media supplemented with antibiotics on the basis of preventing bacterial contamination. In fact, this paradigm needs to be halted because antibiotics are biologically and pharmacologically active. In addition to the emergence of antibiotic-resistant bacteria, antibiotics could have multilevel effects on eukaryotic cells and may react with any agent or substance in culture media. In this sense, antibiotic-free culture media are recommended to ensure the reliability and reproducibility of mammalian cell culture systems-derived scientific findings.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.N.H., F.A., Design: S.N.H., F.A., Data Collection or Processing: S.N.H., F.A., Analysis or Interpretation: S.N.H., F.A., Literature Search: S.N.H., Writing: S.N.H., F.A.

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Determination of the anxiety and the needs of family members of critical care patients in emergency departments

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ABSTRACT

Aims: It is very important to find ways to meet the needs of patients' family members and to control their anxiety. This study aims to identify the needs and anxiety levels of family members of critically-ill adult patients in emergency departments (ED).

Methods: This descriptive study was conducted in the adult ED of a training and research hospital in Turkey. In order to collect data, we conducted face-to-face interviews with family members of critically-ill patients. The "Critical Care Family Needs Inventory-Emergency Department" (CCFNI-ED) and the "Spielberger State Trait Anxiety Inventory-State Scale" (STAI-S) were also used to identify the needs and the anxiety levels of the family members.

Results: The average age of the participants was 40.81±13.32 years. Of the participants (n=172), 61.6% (n=106) were female. CCFNI-ED results showed that eight of the ten needs expressed by family members were related to communication. Overall anxiety level of the family members was 49.67%. Additionally, a statistically significant correlation was found between being female and STAI-S scores (t=2.41, p=0.01). 18.6% of family members expressed that their needs were unmet, while 29.1% of the participants stated that their needs were met.

Conclusions: This study found no significant correlations between the scores obtained from STAI-S and CCFNI-ED. However, a statistically significant correlation was found between being female and STAI-S scores of relatives. Health professionals should take the higher anxiety levels of female family members into consideration, and they should pay attention to the needs of patients' relatives in order to manage their anxiety.

Introduction

Emergency departments (ED) are the environments that require skilled professionals to take care of critical patients (1,2). Patients and their family members face various problems in the EDs, both in Turkey and over the world. Essential elements of holistic patient care include considering family members as a part of critical care and engaging in attempts to protect and maintain the functions of patients and their families (3). Furthermore, identifying the needs of critically ill patients' family members will help ED professionals focus on and meet the urgent needs of the families. Understanding the feelings of patients' families and identifying their needs may improve health care and communication. In addition, identifying the needs of family members may increase families' confidence in health professionals and prevent negative and even aggressive behaviors (4,5).

EDs are traumatic environments that may create anxiety for patients and their families. The health problems of a family member influence the entire family. Patients' families may consider admittance to the ED as a crisis (1). Moreover, family members who wait for long hours in EDs face uncertainty, which in turn creates stress and anxiety (6). Evaluating the needs of patients and their families and attempting to meet their needs will not only reduce anxiety and stress of family members but also improve patient satisfaction and quality of healthcare (7,8).

Frequently, emergency professionals must turn their attention to saving the patient's life and decreasing the physical effects of trauma (6). Consequently, communication with the patient's family members, identification of their needs, and attempts to decrease their anxiety may fade into the background. Health professionals' attitudes, long waiting times to receive treatment, and remaining uninformed about diagnosis and treatment are among the main problems that patients and family members complain about in EDs (9). These problems may result in conflicts between health professionals and family members. Therefore, it is very important to identify family members' needs, to attempt to meet stated needs, and to control their anxiety (10). However, the number of studies on identifying the anxiety and needs of patients' family members is limited. This study aims to contribute to the literature by identifying the anxiety and the importance order of the needs of family members of critically-care adult patients in EDs.

Methods

Design

This study was conducted in the ED of a training and research hospital in Turkey between May 2016 and November 2017. This ED experiences more than 100,000 visits per year and is composed of two units: the triage area and general care. The clinical status of the outpatients is first evaluated by health professionals in the triage unit using the Emergency Severity Index, and the patients are directed to the appropriate physicians from the triage unit. The triage unit has four emergency treatment rooms, one blood sample collection room, one medical dressing room, one electrocardiogram room, and one orthopedic casting room. One emergency medicine specialist and two practicing physicians work in the ED. The general care unit of the ED has three trauma and resuscitation rooms and 10 monitored-observation rooms, which are allocated to critically-ill patients. Three emergency physicians provide health care services in the general care unit.

Participants and Procedure

This descriptive study was conducted with 172 family members of critically-ill patients, all of whom had accompanied patients to the ED. Family members were informed both verbally and in writing about that participation in the research was voluntary, they could withdraw from the study whenever they wanted, and their decision to withdraw from the study would have no impact upon the healthcare received by their patient relative. After their consent was obtained, family members were interviewed in a room in the ED at a time suitable for the relatives. Data collection lasted about 8-10 minutes for each participant. Given the fact that families' perceived needs could change over time, interviews took place between the first 30 minutes and the first 24 hours after the patient was admitted to ED (4). Family members over the age of 18 years, who accompanied the patient to the ED, were present in the ED for more than 30 minutes, and voluntarily agreed to participate, were included in the study.

Data Collection

We used the "Data Collection Form", "Critical Care Family Needs Inventory-Emergency Department" (CCFNI-ED), and "Spielberger State Trait Anxiety Inventory-State Scale" (STAI-S) for our data collection.

Data Collection Form: Data collection form was prepared by the researchers based on relevant literature and included questions on sociodemographic characteristics of patients and family members (age, gender, profession, educational status, marital status, etc.), relationship with the patient, hour of arrival at the ED, and length of stay in the ED.

CCFNI-ED: The CCFNI was developed by Redley and Beanland (2004) (3) and consists of 40 statements on family needs. Participants rate the importance of the 40 items using a four-point Likert type scale. The scale has four subscales: communication with family members, family member participation in ED care, organizational comfort, and family member support process. Reliability and validity of the Turkish version of the CCFNI-ED were tested by Sucu Dag et al. (11), who found that the Cronbach's alpha coefficient of the Turkish version of the CCFNI-ED was 0.91. We calculated a Cronbach's alpha coefficient of 0.90 for this study.

STAI-S: This scale was developed by Spielberger et al. (12) in order to determine a transitory emotional state at a certain time and under certain conditions; it has 20 items. Participants rate their emotional state using a four-point Likert type scale. Reliability and validity of the Turkish version of the STAI were calculated by Oner and Le Compte (13). Cronbach's alpha coefficient for our study is 0.64.

Ethical Consideration

We obtained permission from the Scientific Research and Publication Ethics Board of the university at which the research was conducted (April 5, 2016; no: 50687469-1491-286-16/1648-931). Participants were informed about the scope of the study and the confidentiality of their personal information, and their verbal and written consent was obtained.

Statistical Analysis

We used Statistical Package for the Social Sciences version 21 statistical software for data and statistical analysis. In terms of descriptive analysis, we used number and percentage for numerical data, and average ± standard deviation for measurable data. The chi-square, one-way ANOVA, and Spearman correlation tests were used for comparative statistical analysis; $p<0.05$ indicated a statistically significant difference.

Results

The average age of the family members coming to the ED with their critically ill patients was 40.81±13.32 years. 61.6% of the participants were female (n=106), 41.9% were high school graduates (n=72), 72.7% were married (n=125), and 55.2% were employed (n=95). In addition, 96.5% of the participants had health insurance (n=166), 28.5% of the participants had one or more children (n=49), 80.8% arrived at the ED with their critically-ill patients (n=139), and 52.3% expressed that their needs were met well in the ED (n=90) (Table 1).

Table 2 shows STAI-S and CCFNI-ED scores of the participants. The average STAI-S score of participants was 49.67±0.67, while the average CCFNI-ED score was 3.55±0.43.

In Table 3, there are sub-dimensions and mean scores of the CCFNI-ED scale. 1st sub-dimension of CCFNI-ED is "Communication with family members". The average score obtained for the "Communication with family members" sub-dimension of the participants is 3.62±0.43. The item "To know about the expected outcome" yielded the highest average score in this subscale (3.98±0.13) whereas the item "To have a staff member with you while visiting your relative" received the lowest score (3.25±1.00).

The second sub-dimension of CCFNI-ED is "family member participation in ED care". The score of "Family member participation in ED care" subscale of the CCFNI-ED was 3.43±0.57. The item "to see your relative as soon as possible" yielded the highest average score in this subscale (3.65±0.75), whereas the item "to be told about religious services" received the lowest score (3.23±1.02).

The 3rd sub-dimension of CCFNI-ED is "Organizational comforts". The average score obtained for the "organizational comforts" subscale was 3.60±0.53. The item with the highest average score in this subscale was "to be treated as individual" (3.70±0.70), whereas the item "to have questions answered honestly" received the lowest score (3.54±0.84).

The fourth sub-dimension of CCFNI-ED, which is the last dimension, is "Family member support processes". The average score of the "family member support processes" subscale was 3.56±0.51. The item "to have a person to care for the family" received the highest score (3.68±0.67), whereas the item "to find out the condition of your relative before being asked to sign papers" received the lowest score (3.42±0.91) (Table 3).

We found no statistically significant correlations between the descriptive characteristics of the participants and CCFNI-ED scores (p>0.05) (Table 4). Although we found a statistically significant correlation between gender and STAI-S scores (females got high scores in STAI-S (t=2.41, p=0.01), no statistically significant correlation was found between the other descriptive characteristics of the participants and STAI-S scores.

Discussion

This study analyzed the anxiety levels and needs of family members of critically-ill adult patients in the ED. In our study, 80.8% of the participants arrived at the ED with their critically ill relatives. Sucu et al.'s (7) study on the family members of 353 critical-care patients found that 82.2% (n=321) of the participants had accompanied their patients. Similarly, another study conducted by Sucu Dag et al. (11) on the relatives of 400 critical-care patients found that 80.1% (n=322) of the

Table 1. Demographic and descriptive statistics for participants (n=172)

Age (mean ± SD) years	40.81±13.32	
Gender	**n**	**%**
Female	106	61.6
Male	66	38.4
Educational level		
Elementary	22	12.8
Secondary	23	13.4
High school	72	41.9
University and above	55	32.0
Marital status		
Married	125	72.7
Single	47	27.3
Employment status		
Employed	95	55.2
Unemployed	77	44.8
Proximity status		
Partner	30	17.4
Child	49	28.5
Mother-father	46	26.7
Brother	17	9.9
Other relatives	16	9.3
Friends	14	8.1
Time for relatives to come to the ED		
With patient	139	80.8
After the patient	33	19.2
Health assurance of the patient		
Yes	166	96.5
None	6	3.5
Meeting the needs		
None	5	2.9
Moderate	27	15.7
Well	90	52.3
Completely	50	29.1

ED: Emergency departments, SD: Standard deviation

participants arrived at the ED with their critically-ill relatives. Yildirim and Ozlu (14) found that nearly all patients (91.6%) were accompanied by their relatives to the hospital. It will be better for health care professionals if family members accompany their critically-ill relatives, in order to receive information about the patient and their illnesses.

The analysis of the relationships between the family members and the patients showed that 28.7% of the participants were children of the patients, 26.7% were parents of the patients, and 17.4% were spouses of the patients. Hsiao et al. (8) found that critically-ill patients were mostly accompanied by their children and others, whereas Sucu et al. (2009) (7) found that family members that accompanied critically-ill patients to the EDs were mostly spouses. In our study, accompanying spouses ranked third. Parallel to our findings, the study by Yildirim and Ozlu (14) showed that critically-ill patients were mostly accompanied by their children (14). We can state that, in Turkey, critically-ill patients admitted to the ED are mostly accompanied by their first-degree relative(s).

In terms of time spent in the ED, our study found that 26.2% of the patients stayed for about 1-2 hours. In comparison, Redley and Beanland (3) found that family members of the critically-ill patients spent between 15 minutes and 36 hours (5.5 hours on average).

Al et al.'s (15) study on patients and families in the ED found no statistically significant relationship between relatives' satisfaction with the EDs and education, age, or transfer type of the patient. Similarly, we did not find any statistically significant relationship between these parameters and the order of importance of family members' needs.

We found that the needs of family members were not completely met in the ED. 18.6% of the participants expressed that their needs were unmet, whereas 29.1% stated that their needs were completely met. Satisfaction of patients and their relatives is frequently used as an indicator of quality of healthcare services in EDs. Satisfaction will increase when the needs of family members are met. So, healthcare professionals should be aware of the needs of family members. Botes and Langley's (16) study on family members in an ED found that although the communication subscale of the CCFNI was ranked as highly important, satisfaction with communication was low. Moreover, Bulut (9) found that informing family members increased their satisfaction.

Regarding the subscales of the CCFNI-ED, participants in this study ranked communication needs highest, followed by family member support processes, organizational comfort, and family member participation in ED care. In the study of Sucu et al. (7), the communication subscale ranked the second in importance, whereas family member participation ranked the first. However, family members in Hsiao et al. (8) ranked communication needs highest, followed by family member participation, support, and comfort. Yildirim and Ozlu (14) found that the most important need identified by the family members was communication, whereas the least important need was comfort. Finally, Botes and Langley (16) found that communication ranked the second in importance. Based on these studies, we can suggest that the 'organizational comfort' and 'family member support processes' subscales of the CCFNI-ED are relatively less important for patients' relatives. This indicates that patients' relatives place less importance on their own needs than on the needs of the critically-ill patients.

Item scores related to the needs of the family members in our study were similar to previous findings. All four items that had a score above 3.89 belonged to the 'communication with family members' subscale. Five of the items that had a score above 3.79 were related to the communication need: "to know about the expected outcome" (3.98), "to be given directions regarding what to do at the bedside" (3.91), "to know why things were done for your relative" (3.90), "to be spared distressing details about your relative's illness or injury" (3.90), and "to see what was happening to your relative" (3.81) (Table 2). These findings differ from the findings of Sucu and Sucu Dag et al. (7,11), Yildirim and Ozlu (14), and Hsiao et al. (8) in terms of the order of importance.

Patients' family members go through a unique, intense, and emotional experience in the ED (2). The chaotic structure of EDs often results in difficulties for health professionals,

Table 2. Participants' CCFNI and STAI-S scores

CCFNI sub-dimensions and STAI-S	Mean ± SD	Lower score	Upper score	Scale's ranges
CCFNI				
Communication with family members	3.62±0.43	2.20	4.00	1-4
Family member participation in ED care	3.43±0.57	1.50	4.00	1-4
Organizational comforts	3.60±0.53	1.56	4.00	1-4
Family member support processes	3.56±0.51	1.57	4.00	1-4
CCFNI total	3.55±0.43	1.94	4.00	1-4
STAI-S	49.67±0.67	48.50	51.50	20-80

CCFNI: Critical Care Family Needs Inventory-Emergency Department, STAI-S: Spielberger State Trait Anxiety Inventory-State Scale, ED: Emergency departments, SD: Standard deviation

Table 3. CCFNI-ED scores of the participants

CCFNI-ED Items	Mean	SD	Min	Max
Communication with family members	**3.62**	**0.43**	**2.20**	**4.0**
9. To know why procedures were done for your relative	3.90	0.36	2.00	4.00
10. To be spared distressing details about your relative's illness or injury	3.90	0.36	1.00	4.00
12. To talk to a nurse	3.67	0.70	1.00	4.00
13. To know about the expertise of staff caring for your relative	3.27	0.92	1.00	4.00
14. To know about the expected outcome	3.98	0.13	3.00	4.00
18. To stay out of the way during your relative's care	3.24	0.88	1.00	4.00
20. To have explanations about the treatment area before going in to see your relative for the first time	3.60	0.80	1.00	4.00
21. To have a staff member with you while visiting your relative	3.25	1.00	1.00	4.00
22. To see what was happening to your relative	3.81	0.51	1.00	4.00
24. To be given directions regarding what to do at the bedside	3.91	0.28	3.00	4.00
Family member participation in ED care	**3.43**	**0.57**	**1.50**	**4.00**
4. To have friends and relatives with you while in the emergency department	3.19	0.90	1.00	4.00
19. To see your relative as soon as possible	3.65	0.75	1.00	4.00
23. To be with your relative at any time	3.56	0.74	1.00	4.00
25. To feel helpful to your relative's care	3.63	0.65	1.00	4.00
26. To be included when decisions are made	3.59	0.79	1.00	4.00
27. To have time alone with your relative	3.48	0.81	1.00	4.00
28. To feel accepted by hospital staff	3.53	0.83	1.00	4.00
32. To be encouraged to express emotions	3.36	0.95	1.00	4.00
33. To be reassured as to what normal emotional responses should be	3.44	0.84	1.00	4.00
34. To share emotions with staff	3.09	1.05	1.00	4.00
36. To be told about religious services	3.23	1.02	1.00	4.00
37. To have food and refreshments nearby	3.35	0.89	1.00	4.00
38. To have a telephone in or near the waiting room	3.38	0.82	1.00	4.00
39. To have toilet facilities nearby	3.63	0.68	1.00	4.00
Organizational comforts	**3.60**	**0.53**	**1.56**	**4.00**
11. To talk to a doctor	3.57	0.80	1.00	4.00
15. To have questions answered honestly	3.54	0.84	1.00	4.00
16. To be told about transfer plans while they are being mad	3.61	0.71	1.00	4.00
17. To be assured that the best care possible has been given to your relative	3.60	0.81	1.00	4.00
29. To be treated as an individual	3.70	0.70	1.00	4.00
30. To feel hospital staff care about your relative	3.69	0.72	1.00	4.00
31. To be assured of the comfort of your relative	3.55	0.84	1.00	4.00
35. To feel there is hope	3.56	0.80	1.00	4.00
40. To be able to contact staff at a later date to ask questions	3.59	0.75	1.00	4.00
Family member support processes	**3.56**	**0.51**	**1.57**	**4.00**
1. To have a doctor or nurse meet you on arrival at the hospital	3.57	0.85	1.00	4.00
2. To have a person to care for the family	3.68	0.67	1.00	4.00
3. To find out the condition of your relative before being asked to sign papers	3.42	0.91	1.00	4.00
5. To have a private place to wait	3.45	0.83	1.00	4.00
6. To have explanations given in understandable terms	3.60	0.76	1.00	4.00
7. To be kept updated frequently	3.60	0.80	1.00	4.00
8. To know all the specific facts concerning your relative's progress	3.57	0.65	1.00	4.00
Total	**3.55**	**0.43**	**1.94**	**4.00**

CCFNI-ED: Critical Care Family Needs Inventory-Emergency Department, SD: Standard deviation, Min: Minimum, Max: Maximum

including communication with the patient (17). This may result in ED health professionals being unable to provide important medical information to patients and their families (18). Hsiao et al. (8) found that communication with family members was the most important need not only for family members but also for emergency nurses.

Health professionals should engage in active listening skills when communicating with the patients and their families. Communication in EDs may be verbal or nonverbal, and the communication method depends on the judgment of the emergency professionals. Health professionals working in EDs should maintain effective communication with patients and their families in order to improve the efficiency of healthcare (19). Shorofi et al.'s (20) study on family members found that the most important item of the CCFNI-ED scale was "to have questions answered honestly". In this sense, studies on critically-ill patients show the importance of communication.

EDs are loud and crowded, which may cause anxiety for patients and their families (21,22). However, unexpectedly, our study did not find any statistically significant relationship

Table 4. The descriptive characteristics of the participants and CCFNI-ED and STAI-S scores

Characteristics of participants	CCFNI		STAI-S	
	Mean ± SD	Analysis	Mean ± SD	Analysis
Gender				
Female	3.60±0.36	t=1.79	**49.57±0.63**	t=2.41
Male	3.47±0.51	p=0.07	49.83±0.71	**p=0.01**
Educational level				
Elementary	3.55±0.43		49.61±0.43	
Secondary	3.56±0.48	F=1.14	49.79±0.92	F=0.28
High school	3.56±0.43	p=0.33	49.67±0.63	p=0.83
University and above	3.59±0.38		49.65±0.70	
Marital status				
Married	3.58±0.41	t=0.13	49.70±0.69	t=0.90
Single	3.47±0.54	p=1.51	49.59±0.62	p=0.36
Employment status				
Employed	3.51±0.44	t=1.55	49.67±0.69	t=0.90
Unemployed	3.61±0.41	p=0.42	49.67±0.64	p=0.36
Proximity status				
Partner	3.52±0.47		49.58±0.78	
Child	3.58±0.39		49.59±0.59	
Mother-father	3.60±0.39	F=0.98	49.73±0.79	
Brother	3.60±0.47	p=0.42	49.78±0.59	F=0.57
Other relatives	3.34±0.58		49.84±0.51	p=0.72
Friends	3.51±0.35		49.65±0.59	
Time for relatives to come to the ED				
With patient	3.55±0.45	t=0.44	49.75±0.69	t=1.52
After the patient	3.46±0.22	p=0.65	49.32±0.53	p=0.13
Health assurance of the patient				
Yes	3.56±0.42	t=1.86	49.67±0.68	t=0.29
None	3.23±0.57	p=0.064	49.58±0.61	p=0.76
Meeting the needs				
None	3.66±0.23		49.65±0.67	
Moderate	3.58±0.43	F=0.17	49.31±0.62	F=5.79
Well	3.55±0.40	p=0.94	49.63±0.62	p=0.09
Completely	3.53±0.43		49.97±0.70	

CCFNI: Critical Care Family Needs Inventory-Emergency Department, STAI-S: Spielberger State Trait Anxiety Inventory-State Scale, ED: Emergency departments, SD: Standard deviation

between STAI-S and CCFNI-ED scores. The only statistically significant relationship was between being female and STAI-S scores (t=2.411, p=0.017). Dark et al.'s (2018) (23) study, which analyzed 1,213 ED visits with a discharge diagnosis of anxiety, found that 63.1% of the patients were female, whereas 36.9% were male. For the reason that anxiety disorder is more common among women, we may conclude that female patients and relatives may need special attention from health professionals. Additionally, various studies have assessed the extent to which music may be used to decrease anxiety of patients and their families. For example, a randomized pilot study by Belland et al. (18) found that listening to music reduced anxiety among older adults in the ED. Similarly, Kilic et al. (21) found that music therapy in the ED positively impacted patients' pain levels and anxiety. Based on these studies, we may suggest music therapy in EDs to reduce anxiety of both patients and family members.

Some patients demand to have their family members present in case of a health problem, and the presence of family members may reduce patient anxiety (24). Additionally, providing family-oriented education on communication skills may not only help family members but also reduce anxiety, depression, and stress in patients (14). However, this may not always occur. Batista et al. (2) found that the presence of family members in EDs increased family anxiety and health professional stress levels. The average STAI-S score of the participants in this study reflects a medium anxiety level (mean=49.67).

However, the recent guidelines of the American Heart Association and the European Resuscitation Council state that family members can be present in advanced health situations whenever possible (2). Paavilainen et al. (4) also suggest encouraging family presence in EDs. One advantage of family presence in EDs stems from the fact that family members may provide clinical information about the patient to the health professionals (1). Furthermore, being able to be with the patient helps family members adapt to the unexpected, critical situation. Psychological support to patient families, who experience intensive stress and sorrow, may reduce their anxiety and fears (14). In sum, deciding whether the presence of family members is good or bad is a hard decision; it may vary according to cultural values and perspectives (19).

Health professionals that are responsible for critically-ill patients should provide care that integrates knowledge, skills, experience, and attitudes, all of which are needed to meet the needs of patients and their families (25). Emergency professionals that are aware of patients' and families' needs may be able to meet these needs and thus reduce anxiety; this, in turn, may prevent possible confrontations between health professionals and family members.

Our study had some limitations, such as generalization difficulties because this study was conducted in only one ED. In addition, our working group does not reflect the general situation in the country. The stress levels of the patient relatives may be higher in other hospitals which are not education and research hospitals.

Clinical Implications for Emergency Nursing

Relatives of the patients often feel stressed and worried about the uncertainty of emergency services. These concerns can sometimes come to a dimension that goes back to conflicts with health personnel. It can be difficult for health personnel to manage uncertainty and concern. Health personnel should cooperate with the patient's relative to manage the case effectively and effectively. Otherwise, the situation may become complicated and problems may arise in medical and psychosocial issues. It is important for health personnel to understand the needs and concerns of their relatives. Thus, they can provide them with safe and effective emergency service intervention.

Conclusion

This study found no statistically significant relationship between the STAI-S scores of patients' family members and their CCFNI-ED scores. However, we found a statistically significant relationship between being female and STAI-S scores. The most important need identified by family members was communication, followed by family member support, comfort, and family member participation in ED care. Based on these findings, we suggest that the needs of the family members of critically-ill patients should be identified and met within the context of healthy communication. Emergency professionals should consider the possibility that the anxiety levels of female relatives may be higher, and these professionals should determine and meet the needs of family members in order to control their anxiety.

Ethics

Ethics Committee Approval: We obtained permission from the Scientific Research and Publication Ethics Board of the university at which the research was conducted (April 5, 2016; no: 50687469-1491-286-16/1648-931).

Informed Consent: Participants were informed about the scope of the study and the confidentiality of their personal information, and their verbal and written consent was obtained.

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Authorship Contributions

Surgical and Medical Practices: A.D., Concept: A.D., G.G., Design: A.D., G.G., Data Collection or Processing: A.D., A.K.U., Analysis or Interpretation: E.Ö., Literature Search: A.D., Ö.A., Writing: A.D.

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Complementary and alternative medicine usage in patients with Familial Mediterranean Fever

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ABSTRACT

Aims: Colchicine is mainstay in the treatment of Familial Mediterranean Fever (FMF). In chronic diseases, complementary and alternative medicine (CAM) methods can be chosen as a non-mainstream treatment. We aimed to identify the prevalence and the associated factors for the use of CAM in patients with FMF.

Methods: Data of 165 patients were obtained from patients' medical records and face-to-face interviews. Using any type of CAM methods and patients' having harm and/or benefit were analyzed. The Morisky Green Levine Scale was used to assess the treatment adherence and the Beliefs About Medicines Questionnaire was used to assess the patient's beliefs about medicines.

Results: Fifty-six (33.9%) patients were using CAM. The frequency of patients with the concomitant disease was higher in the CAM user group (35.7%) compared to the CAM non-user group (18.3%) (x^2=6.075, p=0.014). The frequency of patients who had a positive family history for FMF was higher in the CAM user group (78.6%) compared to the CAM non-user group (58.7%) (x^2=6.450, p=0.011). The number of patients who reported benefit from CAM was 42 (75.0%). The median score of concern about colchicine was 3.2 among CAM users, whereas 2.8 among CAM non-users (p=0.035). No relationship was found between the compliance with colchicine treatment and the usage of CAM (p=0.313).

Conclusions: Concomitant diseases in patients, FMF in relatives, and concerns about colchicine may rise the tendency to CAM using. Patients should be well-informed about that CAM methods cannot be an alternative to colchicine.

Introduction

Familial Mediterranean Fever (FMF) is the most common hereditary periodic fever syndrome. It has a high prevalence among Turks, Armenians, Arabs, and Jaws. The prevalence of FMF in Turkey is approximately 0.093% (1). The disease is characterized by recurrent attacks of serositis (peritonitis, pleuritis, pericarditis or arthritis) and fever (2). Frequent FMF attacks lead to the deposition of amyloid in visceral organs. The most important complication of amyloidosis is renal failure. Colchicine reduces the frequency and severity of febrile attacks and the risk of amyloidosis (3,4). Approximately 5-10% of patients may be resistant to colchicine. Biological drugs can be used off-label in the treatment of these patients (5-7).

According to the National Institutes of Health, complementary and alternative medicine (CAM) modalities can be defined as products and practices which are distinct from conventional therapies of the diseases. There are several types of CAM; natural products, manipulative practices, mind-body interventions, and energy therapies. Types of CAM therapies and frequency of use can vary among countries and cultures. Complementary therapy may be used together with conventional therapy; on the other hand, alternative therapy is generally used in place of conventional therapy. Adverse effects, especially those with herbal products, should be considered carefully (8-10).

The frequency of CAM usage among FMF patients is not established yet. The current study aimed to identify the

frequency of CAM using and the factors related to the usage of CAM in patients with FMF.

Methods

Study Design, Sample, and Setting

This cross-sectional descriptive study was conducted in a tertiary rheumatology outpatient clinic between February and August 2019. The study design was approved by the Local Ethical Committee of Gülhane Training and Research Hospital (approval number is 19/46). Written informed consent form was obtained from each participant before any study-related procedure was performed in accordance with the principles of the Helsinki Declaration.

In the current study, 165 patients with FMF were included. The inclusion criteria were; (a) having been diagnosed with FMF according to the Tel-Hashomer criteria (11), (b) being aged 18 years and older, (c) being able to read, write, and speak in Turkish, and (d) being a volunteer to participate in this study. The exclusion criteria were; i) being pregnant, ii) being diagnosed with major psychiatric diseases, iii) having concurrent terminal illness or being unstable clinically, and iv) having cognitive impairment.

Data Collection, Procedure

Demographic and clinical data were obtained from patients' files and face-to-face interviews. Interviews were conducted in outpatient rooms. The interviews took a mean of 20-25 minutes. Firstly, interviewers asked if the patients used CAM. The outcomes of CAM usage were questioned if the answer was positive. The disease severity of patients was evaluated using the International Severity Scoring System for FMF (ISSF) (12). The Morisky Green Levine Scale (MGLS) was used to analyze the adherence of the patients with their treatment (13). This scale consists of 4-item. Each item asks patients whether they exhibit a specific type of non-adherent behavior. For each item, answers 'yes' and 'no' are scored as 1 and 0, respectively. The scores of MGLS range from 0 to 4. In the current study, the patients who scored 0 were accepted as "adherent" whereas those who scored ≥1 were accepted as "non-adherent". The Beliefs About Medicines Questionnaire (BMQ-T), which was validated for Turkish population by Cinar et al. (14,15), was used to assess patient's perceptions and expectations about medications. The BMQ-T has two sections with a total of 18 items; BMQ-T specific and BMQ-T general. BMQ-T specific, which consists of two subgroups (Specific-Necessity and Specific-Concern), is used to assess the patient's beliefs and concerns about one's personal disease and medicine. BMQ-T General also consists of two subgroups, General-Harm and General-Overuse, which are used to assess the patient's general beliefs and perceptions about medicines. Participants indicate the degree of agreement for each statement on a 5-point Likert scale ranging from strongly disagree [1] to strongly agree [5]. An average score for each sub-scale is calculated by dividing the total score for these scales by the number of items in the scale, and a mean score range between 1 and 5 is obtained for each sub-scale. The higher scores of each section indicate a stronger belief in the concept of that section.

Statistical Analysis

Statistical Package for the Social Sciences version 18 was used for statistical analysis. Descriptive statistics were presented as mean ± standard deviation [median (minimum-maximum)] values for measured variables, and frequency and percentage (%) for categorical data. Categorization was done on the basis of CM use. The Spearman correlation coefficient was used to evaluate the association between variables. The Mann-Whitney U test, Pearson chi-square test, Fisher's exact test, and Student's t-test were used to analyze data. Calculated p value less than 0.05 was accepted as statistically significant.

Results

A total of 165 patients [58 (35.2%) female and 107 (64.8%) male] were included in the study. The mean age of the participants was 34.1±12.7 years. The median illness duration was 14.0 years. One hundred and forty-five (87.9%) had peritonitis, 141 (85.5%) had fever, 66 (40%) had febrile myalgia, 61 (37%) had arthritis, 59 (35.8%) had pleuritis, 37 (22.4%) had erysipelas like erythema, 2 (1.2%) had pericarditis, 2 (1.2%) had orchitis during attacks. Twenty-two patients (13.3%) had proteinuria (150 mg/24 hours) and amyloidosis was detected in 7 (4.2%) patients. One hundred and fifty-one (91.5%) patients had *MEFV* gene mutations and the most frequent mutation was M694V (70.3%). Twenty-three percent of the patients had adverse events related to colchicine. The most common adverse events due to colchicine use were gastrointestinal adverse events, and usually diarrhea. Nineteen (11.5%) patients were resistant to colchicine treatment. According to their ISSF scores, 70 (42.4%) patients had mild disease, 82 (49.7%) had moderate disease, and 13 (7.9%) had severe disease. Forty-eight patients had comorbidities and the most common comorbid disease was hypertension in 14 (8.5%) patients. Other common comorbid diseases were 6 (3.6%) asthma, 5 (3.0%) ankylosing spondylitis, 4 (2.4%) Henoch Schönlein purpura, and 4 (2.4%) diabetes mellitus. No statistically significant difference was found between the CAM user group and the CAM non-user group in terms of age, gender, relationship, socioeconomic and employment status, the distance of the patient to the treatment center, dosage of colchicine, adverse events seen with colchicine treatment, characteristics of febrile attacks, the frequency of febrile attacks, severity of illness, presence of amyloidosis, and chronic renal failure (p>0.05). The number of patients with the concomitant disease was 20 (35.7%) in the CAM user group and 20 (18.3%) in the CAM non-user group

(x^2=6.075, p=0.014). Patients with a positive family history for FMF were higher in the CAM user group compared to the CAM non-user group. The frequency of relatives with FMF was 78.6% in the CAM user group, whereas 58.7% in the CAM non-user group (x^2=6.450, p=0.011). The sociodemographic and clinical characteristics of patients and comparisons between CAM user and CAM non-user patients were shown in Table 1.

The number of patients using at least one CAM was 56 (33.9%). Benefit from CAM was reported by 42 (75.0%) patients. The mean duration of using CAM therapies was 7.9±6.4 years. The most frequently chosen types were massage therapy (12.1%), guided imagery (9.7%), relaxation techniques (9.1%), cupping (9.1%), and natural products (9.1%) (Table 2).

Table 1. Comparison of sociodemographic and clinical characteristics of patients according to complementary and alternative medicine using (n=165)

Characteristics	Overall (n=165)	Patients using CAM (n=56)	Patients not using CAM (n=109)	Statistics	p
Gender, n (%)					
Male	107 (64.8)	34 (60.7)	73 (67.0)	0.636	0.425[b]
Female	58 (35.2)	22 (39.3)	36 (33.0)		
Age (years)*	29.0 (24.0-43.0)	29.0 (23.3-43.5)	30.0 (24.5-43.0)	-0.360	0.719[a]
Disease duration (years)*	14.0 (9.0-22.0)	14.0 (9.0-22.8)	15.0 (9.5-22.0)	-0.200	0.842[a]
Age of diagnosis (years)*	23.0 (14.0-31.0)	23.5 (16.3-30.8)	22.0 (12.0-31.0)	-0.709	0.478[a]
Delay of diagnosis (years)*	3.0 (1.0-9.0)	4.5 (1.0-11.8)	2.0 [0.5-(8.0)]	-1.646	1.000[a]
Age of symptom onset (years)*	15.0 (8.0-24.0)	15.0 (7.0-23.8)	15.0 (8.0-24.0)	-0.589	0.556[a]
Dose of colchicine, (mg/day)*	1.5 (1.0-1.5)	1.5 (1.0-1.5)	1.5 (1.0-1.5)	-0.492	0.622[a]
Mean ± SD	1.36±0.43	1.37±0.39	1.35±0.45		
Educational status (n, %)					
Primary/secondary school	35 (21.2)	16 (28.6)	19 (17.4)	2.767	0.251[b]
High school	27 (16.4)	8 (14.3)	19 (17.4)		
University and over	103 (62.4)	32 (57.1)	71 (65.2)		
Marital status (n, %)					
Married	80 (48.5)	27 (48.2)	53 (48.6)	0.002	0.960[b]
Single/widowed/divorced	85 (51.5)	29 (51.8)	56 (51.4)		
Working status (n, %)					
Employed	103 (62.4)	34 (60.7)	69 (63.3)	0.106	0.745[b]
Unemployed	62 (37.6)	22 (39.3)	40 (36.7)		
Living place					
The village/town	23 (13.9)	6 (10.7)	17 (15.6)	0.735	0.391[b]
City	142 (86.1)	50 (89.3)	92 (84.4)		
Access to the treatment center					
Easy	135 (81.8)	45 (80.4)	90 (82.6)	0.122	0.727[b]
Difficult	30 (18.2)	11 (19.6)	19 (17.4)		
Socioeconomic status					
Less than income	31 (18.8)	11 (19.6)	20 (18.3)	0.353	0.838[b]
Equal to income	116 (70.3)	40 (71.4)	76 (69.7)		
More than income	18 (10.9)	5 (9.0)	13 (12.0)		
Experiencing colchicine related adverse events (n, %)					
Yes	38 (23.0)	17 (30.4)	21 (19.3)	2.567	0.109[b]
No	127 (77.0)	39 (69.6)	88 (80.7)		
Amyloidosis					
Yes	7 (4.2)	3 (5.4)	4 (3.7)	0.259	0.611[b]
No	158 (95.8)	53 (94.6)	105 (96.3)		
Resistant to colchicine					
Yes	19 (11.5)	8 (14.3)	11 (10.1)	0.639	0.424[b]
No	146 (88.5)	48 (85.7)	98 (89.9)		

Table 1. Continued

Characteristics	Overall (n=165)	Patients using CAM (n=56)	Patients not using CAM (n=109)	Statistics	p
History of FMF in relatives					
Yes	108 (65.5)	44 (78.6)	64 (58.7)	6.450	**0.011[b]**
No	57 (34.5)	12 (21.4)	45 (41.3)		
Presence of MEFV mutations					
Yes	151 (91.5)	54 (96.4)	97 (89.0)	2.636	0.104[b]
No	14 (8.5)	2 (3.6)	12 (11.0)		
Comorbidities					
Yes	40.0 (24.2)	20 (35.7)	20 (18.3)	6.075	**0.014[b]**
No	125 (75.8)	36 (64.3)	89 (81.7)		
Disease severity according to ISSF					
Mild	70 (42.4)	17 (30.4)	53 (48.6)	5.099	0.078[b]
Moderate	82 (49.7)	34 (60.7)	48 (44.0)		
Severe	13 (7.9)	5 (8.9)	8 (7.4)		

Data represented either as the mean ± SD, median (25^{th}-75^{th} percentile) or as the frequency.
*Variables as median (25^{th}-75^{th} percentile)
[a]Mann-Whitney U test, [b]Pearson chi-square test.
SD: Standard deviation, CAM: Complementary and alternative medicine, FMF: Familial Mediterranean Fever, ISSF: International Severity Scoring System for FMF

Table 2. Prevalence of complementary and alternative medicine modality types used among patients

Type of CAM therapy	Total n (%)*
Massage therapy	20 (12.1)
Guided imagery	16 (9.7)
Relaxation techniques	15 (9.1)
Cupping	15 (9.1)
Natural products	15 (9.1)
Ginger and curcuma	2 (1.2)
Camomile and balm	2 (1.2)
Sage tea and various types of tea	2 (1.2)
Black seed oil	2 (1.2)
Cherry stem	1 (0.6)
Sycamore leaf	1 (0.6)
Avocado leaf	1 (0.6)
Milk thistle	1 (0.6)
Ringel blume	1 (0.6)
Mint and lemon	1 (0.6)
Centaury	1 (0.6)
Breathe therapy	10 (6.1)
Art therapy	6 (3.6)
Hydrotherapy	2 (1.2)
Yoga	2 (1.2)
Meditation	2 (1.2)
Electric stimulation therapy	2 (1.2)

*The number of patients stating that they have used CAM modalities. Patients marked more than one method.
CAM: Complementary and alternative medicine

According to the BMQ-T specific, the patients who were CAM users, had a higher rate of concern about colchicine. The median score of BMQ-T specific concerns was 3.2 among patients who were using CAM and 2.8 among patients who were not using CAM (p=0.035) (Table 3). No significant correlation was found between adherence to colchicine treatment and using CAM regarding MGLS scores (p=0.313).

Discussion

According to our knowledge, this is the first study evaluating the use of CAM therapies among patients with FMF. Approximately one-third of patients were using at least one type of CAM therapies. The World Health Organization defines CAM therapies as a broad range of health services that are not part of the country's traditional practices and behaviors and are not integrated into the dominant health system (16,17).

There are several reasons that can motivate patients to use CAM methods, such as failure or inadequate response to conventional treatments, reliability, and assumed positive experiences.

The gold standard for treating FMF is colchicine due to its known effect on decreasing the severity and frequency of FMF attacks and the risk of development of amyloidosis (3). Because of the early-onset and chronic course of the disease, patients may seek an alternative treatment method.

In the current study, 56 (33.9%) patients were using at least one type of CAM therapies. There are several studies in the literature observing the prevalence of using CAM therapies among patients with rheumatic diseases. The prevalence of CAM users differs from 22% to 95% in the literature (18-21). Among patients with fibromyalgia, the prevalence may increase by up to 98% (22). There are few studies from Turkey, which evaluate CAM usage among patients with rheumatic disease. The frequency of CAM using is 76.0% among patients with arthritis, 46.9% among patients with rheumatoid arthritis (RA),

Table 3. Comparison of beliefs about medicines and treatment adherence according to complementary and alternative medicine using

Variable	Overall (n=165)	Patients using CAM (n=56)	Patients not using CAM (n=109)	Statistics	p
BMQ-T-Specific Necessity[c]	4.0 (3.4-4.6)	4.0 (3.6-4.6)	4.0 (3.3-4.6)	-0.410[a]	0.682
BMQ-T-Specific Concerns[c]	2.8 (2.4-3.6)	3.2 (2.6-3.8)	2.8 (2.4-3.6)	-2.110[a]	**0.035**
BMQ-T-General Overuse[c]	2.5 (2.3-3.3)	2.5 (2.3-3.3)	2.5 (2.0-3.1)	-0.675[a]	0.500
BMQ-T-General Harm[c]	2.3 (2.0-3.0)	2.4 (2.0-3.0)	2.3 (2.0-3.0)	-0.858[a]	0.391
Morisky Green Levine Scale Adherence[d]	37 (22.4)	10 (27.0)	27 (73.0)	0.016[b]	0.313
Non-adherence[d]	128 (77.6)	46 (35.9)	82 (64.1)		

[a]Mann-Whitney U test, [b]Pearson chi-square test.
[c]Variables were given as median (25^{th}-75^{th} percentile).
[d]Variables were given as n (%).
CAM: Complementary and alternative medicine, BMQ-T: Beliefs about Medicines Questionnaire Turkish translation

and 36.6% in ankylosing spondylitis among Turkish patients (23-25).

Massage therapy was the most popular CAM modality in our study. Although natural products and herbs are a part of traditional culture in Turkey, the patients rarely mentioned the use of herbal remedies. This may be related to the concern of possible interaction between herbal remedies and colchicine. On the other hand, certain CAM therapies such as Ayurveda, Tai Chi, and Reiki, which are well known and widely used in Far East countries, are not widely known and used in Turkey.

According to the study results, the rate of CAM usage is higher among FMF patients with a positive family history. This may be related to advices or learned behaviors from close relatives. Also, the current study indicated that having a concomitant disease was associated with the increased use of CAM. CAM therapies were widely used for preventing chronic pain. Therefore, providing pain control in patients with multiple diseases may be related to increased use of CAM therapies. On the other hand, patients may wish to decrease the number of drugs they use for comorbid diseases. Chronic concomitant diseases of the patients may lead to a decrease in the compliance of the patients with drugs and increase the usage of CAM modalities.

In a previous study conducted among patients with rheumatic diseases, a significant association was found between using CAM therapies and being female, young and having poor health status (18). Another study showed that higher education and employment were associated with higher rates of CAM use (26). However, our study found no significant association between the use of CAM and age, gender, educational or social status.

Lahiri et al. (27) showed that CAM therapies might lead to a delay in the treatment of early RA patients. Physicians should be careful with inadequate or delayed colchicine treatment for FMF patients who were using CAM.

The current study had some limitations. First, the history of CAM use was not evaluated. Secondly, because of the cross-sectional design of the study, longitudinal data could not be shown. Some of the patients may be reluctant to declare the use of CAM. Besides, the guiltiness regarding utilizing CAM therapies may lead patients to hide this from physicians. These situations may be related to the lower incidence of CAM users.

Conclusion

In conclusion, tendency of CAM using may raise as a result of the concerns about colchicine. Patients should be informed about the safety of the colchicine treatment. Also, the sufficient information should be given to the patients about that types of CAM cannot be an alternative to colchicine. Studies with larger samples should be designed to identify the use of CAM therapies and to confirm the effect of CAM therapies on the disease course in patients with FMF.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee of Gülhane Training and Research Hospital (19/46).

Informed Consent: Written informed consent form was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ç., E.T., S.Y., M.Ç., Concept: S.Ç., E.T., F.İ.Ç., S.Y., M.Ç., Design: S.Ç., E.T., F.İ.Ç., S.Y., M.Ç., Data Collection or Processing: S.Ç., E.T., F.İ.Ç., S.Y., M.Ç., Analysis or Interpretation: S.Ç., E.T., F.İ.Ç., S.Y., M.Ç., Literature Search: S.Ç., E.T., F.İ.Ç., S.Y., M.Ç., Writing: S.Ç., E.T.

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Factors associated with overweight and obesity in students of 5-14 age group in Mersin

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ABSTRACT

Aims: Obesity is a health problem caused by excessive fat deposition in the body, which spreads rapidly, threatening the age group of children as well as adults. When it occurs in childhood, it probably continues in adulthood. This study aims to determine the factors related to overweight and obesity in primary and secondary school children in Mersin.

Methods: This cross-sectional study was carried out with the children aged between five and 14 years in primary and secondary schools in Mersin, following the school health activities done by Mersin Public Health Directorate. Minimum sample size was calculated as 1.735 and questionnaires were sent to 2.000 people considering the variables of the class and school location. The independent variables of the study were sociodemographic characteristics, feeding habits, time allocated for physical and other activities, children's body mass index (BMI) categories according to the parents' declarations and parents' BMI categories according to their declarations. And, the dependent variable was the children's BMI values calculated by our measurements. The data of 1.980 students were analyzed.

Results: The mean age of the study group was 9.28±2.53 (minimum-maximum: 5-14) years, and 50.9% of them were male. It was found that 14.6% of the group were obese and 21.5% were overweight. While 38.3% of boys were in the overweight or obese category, this rate was 33.8% for girls ($p>0.05$). The prevalence of overweight or obesity was significantly higher in secondary school students than in primary school students ($p<0.05$).

Conclusions: The factors affecting childhood obesity identified in the studies conducted in Turkey have also become apparent in the current research we did on the school children aged 5-14 years in Mersin.

Introduction

Obesity, which is an increasing public health problem, has become an important health threat in children as well as adults. It occurs as a result of an excessive storage of fat in the body and brings with physical and mental problems (1). According to the reports of World Health Organization (WHO) in 2016, the number of overweight or obese children under the age of five years is more than 41 millions, and the number of children between the ages of five and 19 years is more than 340 millions (2). According to the results of the United States National Nutrition and Health Survey in 2015-2016, the prevalence of obesity was reported to be 42.8% in middle-aged adults, 13.9% in children aged 2-5 years, 18.4% in children aged 6-11 years and 20.6% in adolescents aged between 12 and 19 years (3). The prevalence of obesity, which is described as a disease of our age, is increasing day by day in children and adolescents in our country as well as in the world. While the obesity rate was 15.2% in children over 15 years of age in 2008 in Turkey, it rose to 19.9% in 2014 (4). The Project Research of Monitoring

School-Age Children's Growth in Turkey (TOÇBİ) conducted in 2009 revealed that the overweight rate was 14.3% and obesity rate was 6.5% in the children between six and nine years of age (5).

The prevalence of obesity in boys and girls aged 6-9 years in Europe has been found to range between 5% and 43% according to the WHO's study of the European Childhood Obesity Surveillance Initiative (COSI) (1). The results of COSI-Turkey 2013 (TUR) revealed that the percentage of lightweight was 14.2% and the rate of obesity was 8.3% in the children aged 7-8 years and that 23.3% of boys and 21.6% of girls were overweight and obese (6). According to COSI-TUR 2016 data, overweight and obesity rates were determined to be 14.6% and 9.9%, respectively, in the second-grade children (7).

Childhood obesity is frequently carried to later ages and forms the basis for many diseases (8). An obese child is highly likely to become overweight or obese in adulthood (9). In other words, overweight and obesity seen in childhood continue in adulthood and constitute the basis for many diseases such as cardiovascular diseases, hypertension, diabetes and respiratory problems (10). It, at the same time, causes a decrease in life expectancy at birth and adversely affects the quality of life. Lipid metabolism disorders, steatohepatitis, and type-2 diabetes, which are known to be associated with obesity, have recently become common in children and adolescents (8). In addition to these diseases, failures in education, skeletal system problems, cardiovascular diseases, and mental problems including lack of self-worth are also important problems faced by an obese child (11).

Such factors as family's obesity, socioeconomic status, education level, and family type play a role in the increase of childhood obesity prevalence. Besides, it is also noted that there is a strong relationship between obesity and the duration of a child's breastfeeding, nutritional characteristics, physical activity and television/computer use (12). Thus, the underlying factors need to be evaluated to understand the primary prevention of obesity. Although childhood obesity is an important and rapidly increasing public health problem, the measures implemented to prevent it remain inadequate today (13).

Considering all these conditions makes it important to define the incidence and risk factors of obesity among school-age children, to plan and implement the attempts to increase healthy nutrition and physical activity. Accordingly, this study aims to determine the factors related to overweight and obesity in primary and secondary school children in Mersin.

Methods

This cross-sectional study was carried out in the children aged between five and 14 years in primary and secondary schools in Mersin, following the school health activities done by Mersin Public Health Directorate. The ethics committee approval was obtained from Non-Interventional Clinical Research Ethics Committee of Hacettepe University with the number 16969557-1126 dated July 26, 2017. The studies were carried out within the framework of the school health services cooperation protocol signed in May 2016 between the Ministry of Health and the Ministry of National Education of Turkey.

Before the research, the work conducted by Mersin Public Health Directorate was as follows; following the receipt of the institutional approval from the Public Health Agency of Turkey for the field study as a part of the school health studies, the parents and students were informed about the study and their consent forms were obtained. After this formal procedure, the height and weight of 205.605 children out of 247.156 children (except those who were absent and migrated to another city, and younger than 66 months and older than 14 years) studying at primary (including kindergarten) and secondary schools in the city center and districts of Mersin in 2017-2018 academic year were measured. Their body mass index (BMI) values were calculated and classified according to the criteria (*Z*-score) accepted by the WHO (14). As a result of this classification, it was found out that the prevalence of overweight or obesity was 34.5% among children aged 66 months and over in primary (including kindergarten) and secondary schools in Mersin. The same brand and model equipment with good calibration and accurate and reliable measurement was used in the anthropometric measurements. At the time of the measurement, each student's shoes, jacket, or other heavy clothing were removed and his/her pockets were emptied.

After the study conducted by Mersin Public Health Directorate, to determine the factors related to overweight and obesity, the sample size was calculated as 347 out of 205.605 people with an error rate of 5%, confidence interval of 95% and overweight or obesity frequency of 34.5% in the Epi Info program. The minimum sample size was set as 1,388 (347x2x2) to represent gender (male-female) and education levels (primary and secondary). Taking the non-response rate (25%) into consideration, the minimum sample size was calculated as 1,735, and questionnaires were sent to 2,000 people considering the variables of the class and school location.

During the sampling process, the students' lists were sorted according to their BMIs, classes, genders, and a number from 1 to 102 was selected. Starting from this number, every 102nd person was taken as sample.

The independent variables of the study were sociodemographic characteristics, feeding habits, time allocated for physical and other activities, children's BMI categories according to the parents' declarations and parents' BMI categories according to their declarations. And the dependent variable was the children's BMI values calculated by our measurements.

The height and weight values of the parents were evaluated according to their declarations and categorized as weak (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (>30.0) in reference to the BMI values obtained (15).

Following the approval of the ethics committee, a questionnaire and informed consent form were sent to the children's parents.

Statistical Analysis

The data obtained from 1.980 students who accepted to participate in the study and answered the questionnaire were analyzed with the Statistical Package for the Social Sciences-25 package program. While descriptive variables were expressed as mean, standard deviation, number, and percentage, chi-square analysis was performed to compare categorical variables. The statistical significance in this study was considered to be $p<0.05$.

Results

The mean age of the 1.980 children included in the study was 9.28±2.53 (minimum-maximum: 5-14) years. After the BMI values were classified, it was found that 14.6% (n=289) of the students were obese, 21.5% (n=426) were overweight, 62.3% (n=1233) were normal weight, 1.4% (n=27) were weak, and 0.3% (n=5) were very weak.

Males constituted 50.9% (n=1.007) of the current study group and 57.5% (n=1.139) of the participants were living in the central district. Those studying at secondary school formed 50.8% (n=1.006) of the whole group. While 38.3% (n=386) of boys were in the overweight or obese category, it was 33.8% (n=329) for girls. Whereas there was no significant difference among the BMI categories according to gender (p=0.108), it was found that the frequency of overweight or obesity was significantly higher in the age group of 13-14 years compared to the other groups (p<0.001). Similarly, the prevalence of overweight or obesity was significantly higher in secondary school students than in primary school students (p=0.002) (Table 1).

Of the residents in the central district, 62.9% (n=717) were of normal weight, 35.5% (n=404) were overweight or obese, and 1.6% (n=18) were weak or very weak while 61.4% (n=516) of those living in the periphery were normal weight, 37.0% (n=311) were overweight or obese, and 1.7% (n=14) were weak or very weak. As a result, there was no statistically meaningful difference among BMI categories according to residence type ($x^2=0.524$, p=0.769).

The children walking or cycling to or from school constituted 55.3% (n=1.094) of the group, but those commuting by a motor vehicle were 36.6% (n=724). According to the evaluation of the access type to school, there was no statistically significant difference among the BMI categories of those walking or cycling, using a motor vehicle and both ($x^2=2.840$, p=0.585).

It was noted that 27.7% (n=548) of the group did not devote any time to weekly sports and physical activity including weekends. As for the time spent in front of TV and computers, 18.6% (n=369) and 42.3% (n=837) spent more than two hours on TV and computers on weekdays and on weekends, respectively. The frequency of overweight or obesity (30.7%) was significantly lower in those devoting more than 4 hours to sports and physical activities including the weekend when compared to the other groups ($x^2=20,346$, p<0.001). It was also found that the frequency of overweight or obesity decreased as the time spent on TV-computers per day during the week or at the weekend decreased (Table 2).

BMI categories were found to differ according to the frequency of having breakfast weekly. While 95.7% (n=22) of those who had breakfast every day of the week were in the normal weight category, the frequency of normal weight was 51.1% (n=46) and the frequency of overweight or obesity was 45.6% (n=41) in those never having breakfast ($x^2=44.313$, p<0.001).

Table 1. Distribution of body mass index categories by gender, age groups, and school categories

		Weak and very weak		Normal weight		Overweight or obese		χ^2	p
		n	%	n	%	n	%		
Gender	Male (50.9%)	15	1.5	606	60.2	386	38.3	4,444	0.108
	Female (49.1%)	17	1.7	627	64.4	329	33.8		
Age group	5-6 years (18.3%)	2	0.6	255	70.4	105	29.0	34,872	<0.001
	7-8 years (23.2%)	5	1.1	290	63.0	165	35.9		
	9-10 years (21.8%)	12	2.8	267	61.8	153	35.4		
	11-12 years (23.3%)	8	1.7	290	62.9	163	35.4		
	13-14 years (13.4%)	5	1.9	131	49.4	129	48.7		
School category	Primary school (49.2%)	10	1.0	641	65.8	323	33.2	12,592	0.002
	Secondary school (50.8%)	22	2.2	592	58.8	392	39.0		

The percentages in parentheses indicate the distribution of the related parameter within the group.

The group's BMI categories varied according to vegetable, whole milk, and yogurt-tzatziki-ayran consumption, as well. While 32.3% (n=113) of those consuming vegetables every day of the week were found to be overweight or obese, it was 34.8% (n=200) in those who consumed vegetables frequently (4-6 days a week), 39.1% (n=313) in those rarely (1-3 days) consuming, 35.6% (n=58) in those consuming less than one a week, and 33.7% (n=31) in those who never consumed. This difference in the groups was statistically significant (x^2=20.438, p=0.009). As for the consumption of whole milk, the frequency of overweight or obesity was 30.5% (n=99) in the students who consumed it every day of the week, 36.2% (n=123) in those consuming frequently (4-9 days), 32.5 (n=160) in those consuming rarely (1-3 days), and 41.6% (n=107) in those consuming less than once a week. And it was found that 40.0% (n=226) of the students who did not consume whole milk were in the overweight or obese category (x^2=17.332, p=0.027). While the prevalence of overweight or obesity was 32.2% (n=19) in those who did not consume any yogurt, tzatziki, and ayran, it was 34.3% (n=23) in those who consumed less than once a week, 36.7% (n=130) in those rarely (1-3 days) consuming, 40.5% (n=265) in those who consumed frequently (4-6 days), and 32.9% (n=278) in those who consumed every day (x^2=17.544, p=0.025).

The BMI categories of the participants were not found to be statistically different according to their consumption of fresh fruit, ready-made 100% fruit juice, freshly squeezed fruit juice, carbonated drinks (cola etc.), dietary drinks other than milk, low or semi-skimmed milk, cheese, pudding and other instant dairy products, salty snacks such as meat, fish, chips, sugar bar, chocolate dessert, biscuits, cakes, pastry, cookies, pizza, pita, lahmacun and French fries (p>0.05).

There was no statistically significant difference among BMI categories according to the total number of children in the family, either (x^2=10.825, p=0.212). According to the answers of the families about how they regarded their children's weight, the BMI categories were statistically significantly different. The children of 93.2% (n=221) of those who thought their child were overweight, the children of 92.6% (n=25) were obese, the children of 34.7% (n=450) of those who thought their child were normal weight, the children of 2.8% (n=11) were underweight and 25.8% (n=8) of those who did not express any opinion were overweight or obese (x^2=611.534, p<0.001) (Table 3).

Children's BMI categories were significantly different according to maternal education level, job, and BMI category. The highest prevalence of overweight or obesity was found in the children of college/university graduate mothers with 43.9% (n=115) (x^2=27.311, p<0.001). According to the evaluation of the mother's employment (job) status, the prevalence of being overweight or obese was 80.0% (n=4) in the children whose mothers were retired, and 34.6% (n=546) in those whose mothers were housewives/unemployed (x^2=16.934, p=0.031). When the BMI categories of the children were compared according to the mother's BMI category, 46.8% (n=177) of the children whose mothers were obese were overweight or obese, and this value was found to be significantly higher than the non-obese mothers (x^2=44.748, p<0.001) (Table 3).

BMI categories of the children did not show a significant difference regarding fathers' job status while they differed according to fathers' educational levels and BMI categories. The incidence of overweight or obesity was found to be 42.2% (n=19) in the children whose fathers were illiterate (x^2=15.599, p=0.048). And 49.2% (n=203) of the children whose fathers were obese were found to be overweight or obese (x^2=63.152, p<0.001) (Table 3).

Table 2. Distribution of body mass index categories according to the time set aside for the TV-computer and physical activity by the students (n=1.980)

		Weak and very weak		Normal weight		Overweight or obese		χ^2	p
		n	%	n	%	n	%		
Allocated time for sports-physical activity, including weekend (per week)	0 (27.7%)	16	2.9	322	68.8	210	38.3	20,346	<0.001
	1-4 hours (42.6%)	11	1.3	508	60.3	324	38.4		
	>4 hours (29.7%)	5	0.8	403	68.4	181	30.7		
Time spent on TV-computer on weekdays (per day)	0 (23.4%)	10	2.2	307	66.3	146	31.3	9,717	0.045
	1-2 hours (58.0%)	18	1.6	714	62.2	416	36.2		
	>2 hours (18.6%)	4	1.1	212	57.5	153	41.5		
Time spent on TV-computer at the weekend (per day)	0 (16.7%)	11	3.3	213	64.4	107	32.3	14,941	0.005
	1-2 hours (41.0%)	15	1.8	515	63.4	282	34.7		
	>2 hours (42.3%)	6	0.7	505	60.3	326	38.9		

The percentages in parentheses indicate the distribution of the related parameter within the group.

Table 3. Body mass index categories according to the total number of children in the family, parents' thoughts about the child's weight, parents' weight and economic status

		Weak or very weak		Normal		Overweight or obese		χ^2	p
		n	%	n	%	n	%		
Total number of children	1 (9.2%)	3	1.6	102	56.0	77	42.3	10,825	0.212
	2 (38.6%)	10	1.3	479	62.7	275	36.0		
	3 (30.6)	7	1.2	390	64.5	208	34.4		
	4 (10.8%)	5	2.3	126	58.9	83	38.8		
	5 and over (10.9%)	7	3.3	136	63.3	72	33.5		
Do you think your child's weight?	Underweight (19.6%)	25	6.4	352	90.7	11	2.8	611,534	<0.001
	Normal weight (65.5%)	7	0.5	840	64.8	450	34.7		
	Overweight (12.0%)	0	0.0	16	6.8	221	93.2		
	Fat (1.4%)	0	0.0	2	7.4	25	92.6		
	Don't know/not specified (1.6%)	0	0.0	23	74.2	8	25.8		
Mother's education (n=1.954)*	Not vote (11.0%)	6	2.8	130	60.5	79	36.7	27,311	0.001
	Literate (5.4%)	5	4.8	58	55.2	42	40.0		
	Primary school (43.4%)	13	1.5	523	61.6	313	36.9		
	Secondary/high school (26.8%)	4	0.8	360	68.8	159	30.4		
	College/university (13.4%)	4	1.5	143	54.6	115	43.9		
Mother's job (n=1.954) *	Housewife/unemployed (80.9%)	26	1.6	1.008	63.8	546	34.6	16,934	0.031
	Worker (7.3%)	4	2.8	76	53.1	63	44.1		
	Officer (6.4%)	0	0.0	71	56.3	55	43.7		
	Self-employed (5.1%)	2	2.0	58	58.0	40	40.0		
	Retired (0.3%)	0	0.0	1	20.0	4	80.0		
Mother's BMI category (n=1.954)*	Very poor or poor (1.5%)	1	3.3	23	76.7	6	20.0	44,748	<0.001
	Normal (39.9%)	17	2.2	537	68.8	226	29.0		
	Overweight (39.2%)	12	1.6	455	59.4	299	39.0		
	Obese (19.3%)	2	0.5	199	52.6	177	46.8		
Father's education (n=1.938)**	Not voted (2.3%)	1	2.2	25	55.6	19	42.2	15,599	0.048
	Literate (4.2%)	4	4.9	46	56.8	31	38.3		
	Primary school (41.4%)	18	2.2	505	63.0	279	34.8		
	Secondary/high school (34.3%)	4	0.6	430	64.7	231	34.7		
	College/university (17.8%)	5	1.4	205	59.4	135	39.1		
Your father's job (n=1.938)**	Unemployed (6.0%)	5	4.3	61	52.6	50	43.1	12,288	0.139
	Worker (42.8%)	14	1.7	538	64.9	277	33.4		
	Officer (9.6%)	2	1.1	117	62.9	67	36.0		
	Self-employment (38.6%)	10	1.3	461	61.5	278	37.1		
	Retired (3.0%)	1	1.7	34	58.6	23	39.7		
Father's BMI category (n=1.938)**	Very poor or poor (0.5%)	0	0.0	8	88.9	1	11.1	63,152	<0.001
	Normal (28.2%)	13	2.4	396	72.5	137	25.1		
	Overweight (50.1%)	15	1.5	601	62.0	354	36.5		
	Obese (21.3%)	4	1.0	206	49.9	203	49.2		
Monthly household income	Minimum wage (1.404) and below (53.4%)	21	2.0	659	62.3	377	35.7	5,885	0.436
	1.405-3.000 (29.4%)	7	1.2	362	62.2	213	36.6		
	3.001-5.000 (10.7%)	3	1.4	139	65.9	69	32.7		
	5.001 and above (6.6%)	1	0.8	73	56.2	56	43.1		

Table 3. Continued

		Weak or very weak		Normal		Overweight or obese		χ^2	p
		n	%	n	%	n	%		
Financial situation assessment	One month passes easily (22.4%)	6	1.4	273	61.6	164	37.0	6,369	0.383
	One month passes without much difficulty (27.7%)	5	0.9	356	65.0	187	34.1		
	Difficult to end a month (33.0%)	13	2.0	407	62.2	234	35.8		
	Cannot make the end of the month (16.9%)	8	2.4	197	58.8	130	38.8		

The percentages in parentheses indicate the distribution of the related parameter within the group.
*Twenty-six children with no information about their mothers were excluded from the evaluation.
**Forty-two children with no information about their fathers were excluded from the evaluation.
BMI: Body mass index

According to monthly household income and financial status assessment, there was no significant difference among the children's BMI categories (p>0.05) (Table 3).

Discussion

Childhood obesity affects an individual's whole life. Also, it is an important health problem in terms of causing many chronic diseases. The rapid increase in obesity requires urgent measures, firstly, to stop and then reduce the upward trend. While there were 32 million overweight and obese children in the 0-5 age group in the world in 1990, it increased up to 41 millions in 2016. During this period, the number of overweight or obese children in the age group of 0-5 years in Africa increased from four millions to nine millions. The rate of increase in overweight and obesity in developing countries is more than 30%, and a significant majority of overweight and obese children live in these countries (11,15). The prevalence of overweight and obesity among children and adolescents (5-19 years) has dramatically increased from 4% to 18% between the years 1975 and 2016. The increase is similar among both boys and girls. In 2016, 18% of girls and 19% of boys were overweight. While the prevalence of obesity in children and adolescents was less than 1% in 1975, it increased to approximately 7% in 2016 (16).

In the present study, the prevalence of overweight was found to be 21.5% and obesity was 14.6% in children aged 5-14 years. When compared to our study, the prevalence of obesity was high in the studies performed by different researchers in the same age group in Ankara, Erzurum, and Konya (17-19). However, in the studies conducted in Izmir and Ankara, it was found to be lower (20,21). The different results among the studies may be due to differences in the effects of socioeconomic, climatic and cultural characteristics of the study areas on nutritional status and physical activity, as well as differences in sample size and diagnostic methods used.

In our study, the prevalence of overweight or obesity was highest in the age group of 13-14 years with 48.7%. Similarly, it was higher in the older age group in middle school students than in primary school students. In a study conducted in the age group of 6-15 years in Mugla, the prevalence of obesity was found to be significantly higher in children aged 10 years compared to children in other age groups (22). However, in another study conducted on primary school students in Izmir, the age group with the highest frequency of obesity was determined to be 12 years of age (23). This may be associated with the relationship between obesity and puberty. The increase in the tendency to spend more time outside the home and consuming fast food for socialization in this age group may be among the reasons as well.

Although there was a higher incidence of overweight or obesity in men in our study, this difference was not statistically significant. In a study conducted in Izmir, obesity was found to be more common in all age groups of men (20). Likewise, the frequency of obesity was found to be significantly higher in boys than in girls in a research conducted in Duzce (24).

In our study, no significant difference was found among BMI values regarding the type of school access. The ways of going to school in primary school students at two different socioeconomic levels were examined in a study conducted in Istanbul. A significant difference was found among BMI values with regard to the types of access to school (25).

One of the most important factors affecting obesity is the lack of desired physical activity. Urban and apartment life, narrow playgrounds in the streets as a result of modern life and the increase in the time spent on TV and computers due to technological developments decrease the physical activity and create a still lifestyle in children (26,27).

Preschoolers and school-age children should be approached differently in terms of performing physical activity. Preschoolers need to play games for two hours a day in a physically active way while one hour of physical activity to perspire is enough for school-age children (28). In our study group, the incidence of obesity was less in those who had more than four hours per week for physical activity including weekends. Nonetheless, no significant difference was found among BMI categories

according to the method of school access (walking or cycling, motor vehicle). The prevalence of obesity was found to be high among the students who did not play games requiring movement (14.3%) and those who did not perform regular sports (9.7%) in a study conducted in Erzincan (29). In a study conducted in Elazig, the frequency of obesity was found to be higher in those who went to school by a vehicle than those who went on foot, but the difference was not significant (30). As a result, children should be encouraged to do more physical activities by explaining the importance of it by their families and teachers, and safe sports areas should be established in schools and other living spaces as far as physical settings are concerned.

In our study group, it was found that the frequency of overweight or obesity increased as the time spent on computers and TV increased. With the development of technology, the time spent on devices such as computers, television, and mobile phones increases. The rise in the duration of the TV watching in children increases the frequency of obesity, as well. It is known that children need to be physically active and to have adequate sleep. They are not recommended to watch TV for more than two hours (31,32). In a study conducted in Corum, a positive correlation was found between the students' BMI categories and the time spent in front of computers and television, which is also in harmony with the present study. As the time spent in front of computers and television increases, so do BMI values (33). In a study conducted in Elazig, obesity was found to be more frequent in those who spent four hours or more in front of the television than those who spent 1-3 hours (30).

In the current study, no significant difference was found among the BMI categories according to socioeconomic levels. However, in the study conducted by Pirinççi et al. (34) in the province of Elazig, an increase in obesity was found in parallel with the income level. Still in another study conducted in Elazig, it was found that there was no difference in the prevalence of obesity according to income levels (30). This difference is thought to be due to the fact that the data on the economic situation are based on the verbal declaration of the families.

When the frequency of having breakfast, which is one of the important dietary habits, and BMI values were evaluated in our study, the frequency of being overweight or obese was found to be statistically lower in those who had daily breakfast. The prevalence of obesity was reported to be higher in those who did not eat regularly and did not have breakfast on a regular basis in the provinces of Ankara, which is also consistent with our study findings (21). Moreover, in a study conducted in Erzurum, the frequency of obesity was found to be significantly higher in children who did not eat breakfast, which is compatible with our study as well (18). It is known that skipping the breakfast leads to susceptibility to obesity. This is attributed to the fact that the feeling of hunger is more dominant during the day in those who do not have breakfast, thereby necessitating eating more or resulting in a diet with higher energy content (35). Therefore, families, teachers, and children should be informed about the importance of the habit of having breakfast every day. Nutritional hours suitable for breakfast should be established until the end of primary education at schools, and children should be encouraged to have breakfast during these hours.

Even if the frequency of overweight or obesity in our study was lower in those who consumed fresh fruit every day, it was not statistically significant. In a study conducted in Erzincan, however, the prevalence of obesity among those consuming fruits and vegetables during snacks was 2.9%, which seems to be lower than in other groups (29). Another study conducted in Greece in 2012 revealed that the prevalence of obesity was 7.3% and the frequency of overweight was 23.9% with a significant relationship found between skipping breakfast, not consuming fruit and vegetables and the prevalence of obesity (36).

Not only was the frequency of obesity in the students who consumed whole milk, yogurt, tzatziki and ayran every day found to be lower in the present study but also the overweight or obesity prevalence was determined to be lower in them. Similarly, a study conducted abroad showed that the risk of low obesity was associated with the consumption of whole milk (37). As a result, whole milk consumption in children is reported to be associated with low BMI values (38).

In this study, there was no significant difference among BMI categories regarding the consumption of fizzy drinks (cola, etc.), salty snacks such as chips, candy bars, and chocolate dessert. But in a study conducted in Ankara, it was found that the prevalence of obesity was higher in students who consumed sugary fizzy drinks more (21).

The frequency of obesity was found to be high in children with high family income levels in this research, but it was not statistically significant. The obesity rate was found to be significantly higher in children with high family income levels according to a study conducted in Erzurum (18).

In our study, the frequency of obesity was found to be significantly higher in mothers with high school and university education. And the highest prevalence of obesity was seen in the children of retired mothers. Although there was no significant difference among the BMI categories according to the father's job status, the frequency of overweight or obese was found to be significantly higher in the fathers who were illiterate and graduated from college/university. A study conducted in Ankara revealed that the frequency of obesity was higher in the children of highly educated mothers, although not statistically significant. No significant relationship was found between the mother's occupation and obesity in the same study (21). In a research conducted in Izmir, obesity was found to be related to the educational level of the parents (20).

In our study, the incidence of being overweight or obese was higher in the children whose mother or father was in the obese category than other groups. In the Australian National Nutrition Survey, the relationship between 1.581 overweight or obese children aged 7-15 years and parental BMI was examined and the incidence of obesity was found to be higher in children with overweight or obese mothers (39). In a study conducted in Mugla, a positive and significant relationship was found between BMI values of mothers and children. Similarly, a significant positive correlation was found between BMI values of fathers and children, too (22). In a study comparing patients who visited the clinic for obesity but did not have any problems related to obesity, it was determined that the presence of an obese person in the family affected the incidence of obesity in the study group (40).

Since the weight and height of the parents are taken according to their own statements, data that do not reflect current or accurate information can be found.

Conclusion

The factors affecting childhood obesity identified in the studies conducted in Turkey have also become apparent in the current research we did on the school children aged 5-14 years in Mersin province. This study is expected to support further studies, to be conducted both regionally and nationally, for the early recognition of childhood obesity and the timely implementation of the necessary interventions.

Ethics

Ethics Committee Approval: The ethics committee approval was obtained from Non-Interventional Clinical Research Ethics Committee of Hacettepe University with the number 16969557-1126 dated July 26, 2017.

Informed Consent: Parents' approval was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D., S.Ü., Concept: S.D., H.Ş., S.Ü., Design: S.D., H.Ş., M.K., S.Ü., Data Collection or Processing: S.D., M.K., S.Ü., Z.K., Analysis or Interpretation: S.D., H.Ş., M.K., G.K., Literature Search: S.D., H.Ş., Z.K., G.K., Writing: S.D., H.Ş., Z.K., S.Ü.

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Comparison of vitamin D profile between patients with inflammatory and non-inflammatory rheumatic diseases

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ABSTRACT

Aims: The aim of this study was to compare serum vitamin D levels in patients with inflammatory rheumatic diseases and non-inflammatory musculoskeletal disorders presenting with pain.

Methods: Patients were divided into three groups. Group 1 consisted of patients with inflammatory rheumatic diseases; group 2, non-inflammatory musculoskeletal disorders; and group 3, healthy controls. The plasma levels of 25(OH)D <10 ng/mL were accepted as vitamin D insufficiency. Correlation between pain intensity (visual analog scale), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, disease activity score 28 (DAS28)-CRP for rheumatoid arthritis patients, Bath Ankylosing Spondylitis Disease Activity Index for ankylosing spondylitis patients, and 25(OH)D levels were analyzed.

Results: Eighty-one patients with inflammatory rheumatic diseases (group 1, mean age=47.8±12.2 years), 26 patients with non-inflammatory musculoskeletal disorders (group 2, mean age=46.6±4.5 years), and 36 healthy controls (group 3, mean age=45.2±9.2 years) were included. There was a significant difference among the groups regarding 25(OH)D levels (group 1=16.4±11.3 ng/mL, group 2=13.9±6.4 ng/mL, group 3=20.4±8.2 ng/mL) (p=0.031). 25(OH)D levels in patients with non-inflammatory musculoskeletal diseases were lower than the healthy controls (p=0.003). No significant difference was seen between two patient groups (p=0.334). There was a weak-to-moderate negative correlation between pain intensity, ESR, CRP, DAS28-CRP and 25(OH)D levels (r=-0.302, p=0.002; r=-0.259, p=0.020; r=-0.259, p=0.020; r=-0.374, p=0.022 respectively).

Conclusions: The results of this study are important in terms of routine monitoring and replacement of vitamin D in case of deficiency in chronic inflammatory and non-inflammatory rheumatic diseases presenting with pain.

Introduction

Vitamin D is synthesized in the skin in the presence of sunlight and then metabolized into an active metabolic form in the liver, kidney and peripheral immune/inflammatory cells. Active metabolite of vitamin D [1,25$(OH)_2$D] is important for bone metabolism and function of neuromuscular system. The deficiency of this hormone is mainly associated with osteoporosis in adults and rickets in pediatric population. Also, the deficiency of this hormone is observed to be associated with different forms of non-inflammatory chronic pain conditions (1-4). One of the types of non-inflammatory chronic pain is persistent nonspecific musculoskeletal pain, such as non-inflammatory unexplained arthralgia or myalgia, which is seen frequently in rheumatology clinics. In this type of chronic pain conditions, reaching a precise diagnosis and decision on an effective treatment can be quite challenging for the clinician.

Vitamin D is also known to have a role in the regulation of immune system. Active metabolite of vitamin D appears to have an immunosuppressive effect and to play a role in the autoimmune diseases (5). It is not so evident that the deficiency of vitamin D has causality for rheumatic diseases, whereas the prevalence is claimed to be high (6-8). Several surveys indicated that patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), scleroderma, polymyositis, dermatomyositis and systemic lupus

erythematosus had lower levels of 25(OH)D than the healthy population (6,7). Also, there are a number of studies in which vitamin D was reported to be related to the disease activity in patients with inflammatory rheumatologic diseases (9-11). Among these, two of the mostly studied rheumatologic diseases are RA and AS. The initiation and progression of these diseases have been thought to be associated with the plasma values of vitamin D (12).

To the best of our knowledge, no comparative analysis of serum vitamin D exists between inflammatory and non-inflammatory musculoskeletal diseases. The primary aim of this study was to investigate plasma vitamin D levels among patients with inflammatory rheumatic diseases and those with non-inflammatory musculoskeletal disorders who presented with pain, and to compare vitamin D levels with healthy controls. The secondary aim was to determine the relationship between disease activity of inflammatory rheumatologic diseases and vitamin D levels.

Methods

Subjects

This retrospective case-control study was conducted between the dates of December 2015 and March 2016. Patients with inflammatory and non-inflammatory rheumatic diseases along with the healthy controls, who were referred to the physical medicine and rehabilitation outpatient clinic, were retrospectively screened up to the date of January 2009.

Group 1 consisted of patients with inflammatory rheumatic diseases including RA and AS. The diagnoses of RA and AS were based upon the 2010 ACR/EULAR criteria and 1984 modified New York criteria, respectively.

Group 2 included the patients with non-inflammatory musculoskeletal disorders, such as unexplained myalgia, bone pain and arthralgia without tenderness, erythema, limitation of motion or swelling persisting for more than three months, which could not be attributed to any precise disease based on clinical, radiographic and laboratory examinations.

Group 3 was comprised of healthy controls.

Patients with fibromyalgia, osteoarthritis, chronic kidney and/or liver disease, malignancy, inflammatory rheumatic diseases other than RA and AS, malabsorption syndromes, pregnancy, and individuals who were on corticosteroid regimen or vitamin D supplementation were excluded from the study.

Measurements

All descriptive, clinical and laboratory data were recruited from the hospital database. Pain levels which were measured with visual analog scale (VAS); tender and swollen joint counts (SJC); disease activity, which was recorded as disease activity score 28 (DAS28)-C-reactive protein (CRP) score for RA and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score for AS, were obtained from patients' medical records.

The baseline 25(OH)D levels prior to any vitamin D supplementation, which were measured with the high performance liquid chromatography technique using chromo system kit, were noted. The plasma levels of 25(OH)D >30 ng/mL were considered as optimal vitamin D status, whereas levels <10 ng/mL were accepted as vitamin D insufficiency (13). Concurrent erythrocyte sedimentation rate (ESR) and CRP levels of the patients with inflammatory rheumatic diseases were also documented.

Statistical Analysis

Data evaluation was conducted with Statistical Package for the Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics was performed to calculate mean and standard deviation, median and range values. Normality of the variables was checked by the Kolmogorov-Smirnov Test. Two group comparisons and multiple group comparisons were performed via the Mann-Whitney U and Kruskal-Wallis tests, respectively. Values are given as mean (±standard deviation). The Spearman correlation analysis was used in order to evaluate the associations between variables. The correlation coefficient (r) value of 0-0.24 was considered as "no correlation", 0.25-0.49 as "weak", 0.5-0.74 as "moderate", and 0.75-1 as "strong"correlation. $P<0.05$ was considered as statistically significant.

Ethical approval of the study was obtained from the Cukurova University Faculty of Medicine Local Ethics Committee (protocol number: 2014/34).

Results

Eighty-one patients with inflammatory rheumatic diseases (group 1, mean age=47.8±12.2 years), 26 patients with non-inflammatory musculoskeletal disorders (group 2, mean age=46.6±4.5 years) and 36 healthy controls (group 3, mean age=45.2±9.2 years) were included in the study. The demographic, clinical and laboratory results of the patients are summarized in Table 1.

The mean 25(OH)D levels were measured as 16.4±11.3 ng/mL in group 1 (15.51±12.15 ng/mL in RA patients, 40.63±9.29 in AS patients), 13.9±6.4 ng/mL in group 2, and 20.4±8.2 ng/mL in group 3. According to one-way ANOVA test, 25(OH)D levels significantly differed among three groups (p=0.031). In post-hoc analysis, the level of vitamin D in the non-inflammatory musculoskeletal disease group was statistically significantly lower than in the healthy control group (p=0.003), whereas there was no statistically significant difference between the inflammatory disease group and other groups (group 1-2, p=0.334; group 1-3, p=0.087). The percentages of vitamin D

Table 1. Demographic, clinical and laboratory characteristics of the groups

Rheumatoid arthritis		Group 1		Group 2	Group 3	p#
		Ankylosing spondylitis	Non-inflammatory musculoskeletal pain	Healthy control		
Age (years) (mean ± SD)		54.78±10.46	40.63±9.29	46.58±4.53	45.23±9.223	0.473
Gender [female (%)]		39 (95.1%)	22 (55%)	19 (73.1%)	18 (51.4%)	0.034*
Vitamin D levels (mean ± SD) (ng/mL)		15.51±12.15	17.31±10.39	13.869±6.439	20.41±8.22	0.031*
Sedimentation rate (mean ± SD) (mm/h)		32.00 (20.00-45.50)	24.50 (11.00-36.50)	-	-	
CRP (mean ± SD) (mg/dL)		0.80 (0.30-1.93)	0.73 (0.37-1.76)	-	-	
RF (mean ± SD) (IU/mL)		22.40 (20.00-55.60)	20.75 (20.00-21.50)	-	-	
DAS28-CRP		3.16±1.59	-	-	-	
BASDAI score		-	3.69 (2.70-5.82)	-	-	
PTH levels (mean ± SD) (pg/mL)		51.22±34.26	47.49±32.40	60.28±32.40	-	
Calcium levels (mean ± SD) (mg/dL)		9.28±0.43	9.24±0.51	8.90±0.53	-	
ALP [median (25-75)] (U/L)		64.0 (55.0-85.0)	67.0 (56.0-88.5)	69.0 (58.0-91.5)	-	
SJC n, [median (25-75)]		0.0 (0.0-2.5)	-	-	-	
TJC n, [median (25-75)]		1.5 (0.0-6.5)	-	-	-	
VAS n, [median (25-75)]		5.00 (2.00-7.00)	4.00 (3.00-6.75)	4.00 (3.00-5.25)	-	
Medication	NSAID n, %	3 (7.3%)	12 (30%)	-	-	
	B.DMARD n, %	3 (7.3%)	10 (25%)	-	-	
	S.DMARD n, %	35 (85.4%)	18 (45%)	-	-	

*P<0.05 is considered statistically significant.
#P values represent for the comparisons between 3 groups (group 1, group 2 , group 3).
SD: Standard deviation, CRP: C-reactive protein, RF: Rheumatoid factor, DAS28-CRP: Disease activity score for rheumatoid arthritis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, PTH: Parathyroid hormone levels, ALP: Alkaline phosphatase, SJC: Swollen joint count, TJC: Tender joint count, VAS: Visual analog scale, NSAID: Non-steroidal anti-inflammatory drugs, B.DMARD: Biological disease modifying anti-rheumatic drugs, S.DMARD: Synthetic disease modifying anti-rheumatic drugs

insufficiency [25(OH)D <10 ng/mL] in group 1 (RA/AS), 2 and 3 were 29.7% (39%/25%), 23.1% and 8.6%, respectively.

VAS values were found to be similar in RA, AS, and non-specific musculoskeletal pain patients (p=0.720). Vitamin D levels had no difference between female (17.01±11.15 ng/mL) and male (17.74±7.03 ng/mL) patients (p=0.862).

We found weak-to-moderate negative correlation between VAS, SJC, ESR, CRP, DAS28-CRP and 25(OH)D levels (r=-0.302, p=0.002; r=-0.389, p=0.045; r=-0.259, p=0.020; r=-0.259, p=0.020; r=-0.374, p=0.022; respectively). No correlation was found between vitamin D levels and BASDAI scores (p=0.913) (Table 2).

Table 2. Correlation analysis between pain, inflammation markers, disease activity indexes and 25(OH)D levels

25(OH)D levels	r	p
Visual analog scale (pain)	-0.302	0.002*
Swollen joint count	-0.389	0.045*
Erythrocyte sedimentation rate	-0.259	0.020*
CRP	-0.259	0.020*
Disease Activity Score 28-CRP	-0.374	0.022*
Bath Ankylosing Spondylitis Disease Activity Index	-0.214	0.913

*p<0.05 is considered as statistically significant.
CRP: C-reactive protein

Discussion

The findings of the study revealed that i) patients with non-inflammatory musculoskeletal conditions had significantly lower vitamin D levels when compared to the patients with the inflammatory diseases and the healthy controls, ii) vitamin D had a weak correlation with inflammatory markers and disease activity parameters in patients with inflammatory rheumatic diseases and also with pain intensity in all groups.

Both genetic and environmental factors play a role in the pathophysiology of rheumatic diseases. As an environmental compound, the deficiency of vitamin D appears to be associated with the initiation and progression of the disease in patients

with both RA and AS. A study conducted in the Asian region demonstrated that 65% of the RA patients had vitamin D levels below 30 ng/mL (14). Sahebari et al. (15) showed low levels of vitamin D even among the early-diagnosed RA patients. Furthermore, Merlino et al. (16) suggested that vitamin D supply to RA patients had an impact on lowering the incidence of RA. Similar to RA patients, studies conducted on AS patients have shown that low serum vitamin D profile is a common finding in also AS population. Zhao et al. (17), in their systemic review, addressed several cross-sectional studies, which revealed that AS was related to low vitamin D concentrations. Also, a recent meta-analysis has showed that the activation of AS is inversely correlated with 25(OH)D levels and higher serum vitamin D concentrations might decrease the risk of AS (18).

Our results are consistent with the general opinion that low vitamin D levels are commonly seen in inflammatory rheumatic diseases even if it has no statistical significance when compared to the healthy controls. Additionally, the results also indicated that vitamin D level was also significantly lower in patients with non-inflammatory musculoskeletal conditions. We additionally found that vitamin D levels were weakly correlated to inflammatory markers, disease activity in rheumatic conditions and pain intensity in all groups. These findings raise a number of questions: Is the vitamin D deficiency in inflammatory rheumatic diseases independent from inflammation? Is there a common mechanism that explains the decrement of vitamin D in inflammatory and non-inflammatory rheumatic conditions?

There are several observational studies suggesting an association between vitamin D levels and inflammatory markers (19,20). However, these studies are mostly on specific patient groups; thus, it cannot be generated to all population. According to a review written by da Silva and Rudkowska (20), studies investigating the association of vitamin D with inflammatory markers have conflicting results. According to a meta-analysis in RA patients, serum vitamin D level was found to be significantly low in patients with RA, vitamin D deficiency was prevalent in RA patients compared to controls, and the vitamin D level correlated inversely with RA activity (21). However, a recent study showed opposite results in which they found similar levels of 25(OH)D levels in the RA patients with age- and gender-matched healthy controls, and no association with joint damage and disease activity (22). Similarly, the studies in AS are not completely in agreement about a possible relation between poor vitamin disease activity parameters and serum vitamin D levels (23). In our study, we found a weak correlation of vitamin D with disease activity in RA, whereas no correlation was found with disease activity of AS patients. One should remember that pain is the common component of disease activity indexes and affects patients' global health. Therefore, it can raise the question whether the relation might be caused by this component rather than the inflammation itself.

There is little evidence in the literature regarding the relationship between vitamin D deficiency and non-inflammatory musculoskeletal conditions (24-26). Again, pain-being the common ground of all these conditions emerges as a variable, which might explain the relation of vitamin D with both non-inflammatory and inflammatory musculoskeletal diseases. Verifying this theory, a study conducted on patients with non-specific musculoskeletal pain showed that vitamin D deficiency was as high as 95.4% and pain responded to vitamin D supplementation in majority of the vitamin D deficient patients (27). According to a review published in 2015, vitamin D was believed to have beneficial effect over placebo in chronic pain (28). In the study of Kumar et al. (29), in which they investigated the vitamin D levels in non-inflammatory musculoskeletal complaints, they found low vitamin D level was frequently the sole cause of polyarthralgia, myalgia, bone pain and chronic widespread pain in patients. In their study, they also observed 75% low vitamin D levels in healthy population. Similar results were reached in the study of Plotnikoff and Quigley (4), where they showed severe hypovitaminosis D in patients with non-specific musculoskeletal pain. In our study, we observed vitamin D deficiency in both inflammatory and non-inflammatory painful rheumatic conditions, but significantly lower vitamin D levels in non-inflammatory musculoskeletal conditions referring to rheumatology clinics with chronic pain. All these studies including the present study confirm the impact of vitamin D on the pathophysiology of pain. Vitamin D can modulate neuronal excitability, play a role in astrocyte detoxification, limit macrophage colony stimulating factor, and decrease macrophage induced inflammation; thus, has a potential of inhibiting pain formation (24,28).

The strong points of the present study are; i) comparing the vitamin D levels in both inflammatory and non-inflammatory musculoskeletal conditions with healthy controls, ii) being able to record the baseline 25(OH)D levels prior to any vitamin D supplementation therapy, and ii) having enough sample size to allow between group comparisons. However, several limitations exist, as well. As a result of its retrospective design, confounders of vitamin D deficiency (such as, daily exposure to sunlight, physical activity level etc.) could not be obtained from the database. There was a gender difference between the groups; albeit, the vitamin D levels were similar between female and male patients.

Conclusion

In conclusion, low vitamin D level is common in both inflammatory and non-inflammatory rheumatic diseases. Thus, routine monitoring and optimization of vitamin D might be beneficial in all patients presenting with pain. Future prospective trials taking all confounders of vitamin D into account are needed in order to confirm the results of this study.

Ethics

Ethics Committee Approval: Ethical approval of the study was obtained from Cukurova University Faculty of Medicine Ethics Committee (protocol number: 2014/34).

Informed Consent: Retrospective case-control study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.C., İ.C.B., S.B., T.S., Concept: N.C., İ.C.B., S.B., T.S., Design: N.C., İ.C.B., S.B., T.S., Data Collection or Processing: N.C., İ.C.B., S.B., T.S., Analysis or Interpretation: N.C., İ.C.B., S.B., T.S., Literature Search: N.C., İ.C.B., S.B., T.S., Writing: N.C., İ.C.B., S.B., T.S.

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Autonomy, depression and affecting factors in the elderly people

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ABSTRACT

Aims: This study aimed to investigate the relationship between autonomy and depression in individuals older than 65 years and to evaluate the factors affecting these variables.

Methods: This study was conducted at the geriatric outpatient clinic of Gülhane Training and Research Hospital. The sample of the study consisted of 101 patients over 65 years of age, the ability to evaluate the truth was not impaired, there was no diagnosis of mental illness, and they accepted to participate in the study. The data were collected by using the "Descriptive Information Form", "The Functional Autonomy Measurement System-SMAF" and "Geriatric Depression Scale".

Results: The autonomy assessment scale total score average of the participants was -9.63±-9.17. The mean total score of geriatric depression was 11.15±7.25. There was a negative correlation between geriatric depression scale mean scores and autonomy assessment scale mean scores of elderly individuals and this relationship was statistically significant.

Conclusions: It was found that individuals over 65 years of age were at risk of losing their functional independence and that they had possible depression. Decreased functional independence increases with age and elevates the risk of depression in elderly individuals.

Introduction

The population aged 65 years and over is increasing all over the World (1). In Turkey, the elderly population was 5 million 891 thousand 694 people in 2013 and increased by 17% in the last five years and became 6 million 895 thousand 385 people in 2017. While the ratio of the elderly population in the total population was 7.7% in 2013, it increased to 8.5% in 2017 (2). High life expectancy and economic burdens may pose a problem for the health system that best serves elderly adults with chronic diseases and high risk of hospitalization (3). Prolongation of the life span and physical, sensory and mental regressions that occur together bring physiological, psychological, and social problems in the elderly (4,5). Physical and mental illnesses associated with the aging process may limit autonomic independence. Losses such as retirement or death of the spouse may also change the role performance. With the decrease in the effectiveness of the older person's life over time, social interaction is affected, and social isolation can be seen (6,7). In a study examining the quality of life of elderly individuals living at home, it was stated that as the participants' functional independence levels decreased, their quality of life also decreased (8). In another study conducted with the elderly living in the nursing home, it was determined that more than half of the elderly living in the nursing home had depression, and depression and quality of life were significantly correlated with each other (9).

With the increase in the elderly population, more people are at risk of being diagnosed with depression in the future. This situation may cause emotional pain in many individuals over 65 years and their relatives and it also may affect the quality of life negatively. However, early diagnosis and treatment may help to cope with geriatric depression and its consequences (10). In a meta-analysis by Huang et al. (11) (2010), stroke, hearing loss, decreased visual function, heart disease, and chronic lung disease were reported to be factors associated with depression in old age. The presence of chronic physical diseases in elderly individuals and the expectation that their functional independence will be low in elderly individuals may prevent the diagnosis of depression. Therefore, comprehensive physical assessment of these people is particularly important in geriatric depression, in terms of both revealing the main organic causes and identifying potential inflammation factors (12). Geriatric depression is a multifactorial disorder due to the combination of factors (genetic, biological, psychosocial) that cause various degrees of disorder (13). Depression, which causes a significant decrease in the quality of life in the elderly, is a serious condition that may lead to an increased risk of early death (14).

It is known that the physical activity capacity of the individual decreases as the age progresses and muscle atrophy and muscle weakness occur. Regular physical activity is an important requirement for older individuals to maintain overall health (15). In a randomized controlled study examining the effects of the walking program applied to the elderly, it was stated that the walking program positively affected the quality of life and sleep (16). Maintaining the functional independence of elderly individuals at an optimal level is among the goals of health promotion and maintenance (17). The purpose of the nursing approach provided to elderly individuals is to preserve their quality of life and to ensure that they live a supported life with independence as much as possible (18). In this study, we aimed to investigate the relationship between autonomy and depression in individuals older than 65 years and to evaluate the factors affecting these variables.

Methods

Ethical approval was obtained from the Institutional Review Board (University of Health Sciences Turkey, Gülhane Non-Interventional Ethical Committee, no: 2018-38, date: 06.02.2018). The participants were informed about the research and their consent was obtained. This study was conducted between March and May 2018 at the geriatric outpatient clinic of Gülhane Training and Research Hospital. The sample of the study consisted of 101 subjects over 65 years of age who were mentally intact and had the ability to evaluate the truth. The data were collected by using the “Descriptive Information Form”, “(The Functional Autonomy Measurement System-SMAF)” and “Geriatric Depression Scale”. Participants were reached after the examination at the outpatient clinic and data collection forms were applied face to face by the researchers.

1. Descriptive Information Form: This form includes data on gender, age, marital status, educational status, having a child, with whom the participants live, being a source of income and having a chronic illness.

2. The Functional Autonomy Measurement System-SMAF: This form evaluates the 29 functions of an individual in the age group of 65 years and above related to activities of daily living, movement, communication, mental functions and instrumental daily living activities. The total inability score of the scale is obtained by adding all function scores. If the total score is less than - 5, the elderly individual is at risk of losing functional independence (5).

3. Geriatric Depression Scale: The validity and reliability study of the scale was conducted by Ertan et al. (19) in 1997. The self-report scale consists of 30 questions and can be answered as “yes” or “no”. In the scale, questions 3, 4, 5, 6, 8, 10, 11, 12, 13, 14, 16, 17, 18, 20, 22, 23, 24, 25, 26 and 28 contain the opposite explanation. In the scoring of the scale, 1 point is given for each response in favor of depression and 0 point is given for the other response, and as a result, total score is accepted as depression score. Scoring of the scale is as follows; 0-10 points were scored as “no depression”, 11-13 points were scored as “possible depression”, and 14 points and above were scored as “definite depression”. The scores that can be obtained from the scale are minimum: 1 and maximum: 30 (19).

Statistical Analysis

Statistical package for Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 package program was used to evaluate the data. Mean ± standard deviation, number and percentage representation were used for descriptive statistics. Differences between groups were analyzed with the Mann-Whitney U test and Kruskal-Wallis test (for two or more comparisons). The Pearson correlation analysis was used to examine the relationship between the parameters.

Results

Percent of 61.4 the participants were female, 47.5% were primary school graduates, 47.5% were 71-80 years old, 72.3% were married, and all had children. Percent of 61.4 lived with their spouse, 79.2% had a source of income, and 88.1% had a chronic disease. Diseases of patients with chronic disease included diabetes mellitus, hypertension, heart disease, chronic obstructive pulmonary disease, rheumatic diseases, osteoporosis, thyroid, and asthma (Table 1). There was a negative correlation between the mean geriatric depression scale scores and the mean autonomy assessment scale scores of elderly individuals and this relationship was statistically significant (r=-0.388, p=0.001).

The autonomy assessment scale total score average of the participants was -9.63±-9.17. There was no statistically

significant difference between the mean scores of autonomy assessment scale according to gender, income source status, and having a chronic disease. A statistically significant difference was found between the autonomy assessment scale total score averages of the participants according to their educational background (p<0.05). Paired analyses were conducted to determine which groups were the source of this difference. Accordingly, the mean score of illiterate participants (-15.43±11.40) was lower than that of high school graduates and university graduates (-4.62±4.67; -7.73±7.03), while the mean score of literate participants (-15.43±11.40) was lower than those of primary school graduates -9.67±9.58).

A statistically significant difference was found between the autonomy assessment scale total score means of the participants according to marital status (p<0.05). In order to determine in which groups this difference was caused, dual analyses were performed. According to this, the mean score of the autonomy assessment scale (-8.90±6.98) was lower than that of the divorced (-1.16±7.63) and higher than the widow (-12.80±13.53). In addition, the mean score of autonomy assessment scale (-1.16±7.63) of the divorced was higher than that of the widow (-12.80±13.53). A statistically significant difference was found between the participants' autonomy evaluation scale total score average according to those who lived with the participants (p<0.05). Paired analyses were conducted to determine which groups originated from this difference. According to this, it was seen that the mean scale scores of the participants who preferred the other (-2.00±2.00) were higher than those of their spouses, spouses and children and those living with their children (-8.56±6.91; -12.66±6.81; -16.50±15.95). On the other hand, it was found that those living alone (-6.25±5.86) were higher than those living with their spouse and children (-12.66±6.81). A statistically significant difference was found between the mean scores of the autonomy assessment scale of the participants by age (p<0.05). In the dual analyses conducted in order to determine which groups displayed this difference, it was seen that the mean score of autonomy assessment scale (-7.09±8.01) of the age group of 61-70 years was lower than that of the age group of 81-90 years (-12.14±8.69) (Table 2).

Table 1. Introductory information of participants

Introductory information		n	%
Gender	Female	62	61.4
	Male	39	38.6
Education	Not literate	11	10.9
	Literate	15	14.9
	Primary school	48	47.5
	High school	12	11.9
	University	15	14.9
Marital status	Married	73	72.3
	Divorced	3	3
	Widow	25	24.8
Having a child	Yes	101	100
Who does he/ she live with?	Alone	12	11.9
	With partner	62	61.4
	With partner and children	9	8.9
	With children	15	14.9
	Other	3	3
Income source status	Yes	80	79.2
	No	21	20.8
Age	51-60	2	2
	61-70	26	25.7
	71-80	48	47.5
	81-90	25	24.8
Chronic illness	Yes	89	88.1
	No	12	11.9
Total		101	100

The mean total score of geriatric depression was 11.15±7.25. There was no statistically significant difference between the mean scores of geriatric depression according to marital status, chronic disease status, the age range of participants, and those with whom they lived (p>0.05). The mean score of geriatric depression scores of female participants (13.35±7.56) was higher than that of men (7.66±5.10) (p≤0.005). The mean geriatric depression scale scores (9.95±6.69) were found to be lower than in those without income (15.76±7.60) (p<0.05). A statistically significant difference was found between the mean scores of the geriatric depression scale of the participants according to their educational status (p<0.05). In the dual analyses conducted to determine from which groups this difference arose from, the total scale mean scores of the illiterate (12.27±6.60) were lower than those of the literate (17.93±7.62) and higher than those of primary school, high school and university graduates (10.56±6.85; 10.33±5.78; 6.13; ±4.80). On the other hand, the mean scores of geriatric depression scale (17.93±7.62) of the literate participants were higher than those of primary school, high school and university graduates (10.56±6.85; 10.33±5.78; 6.13±4.80) (Table 3).

Discussion

The mean score of the geriatric depression scale of the individuals over 65 years of age, who participated in the study, was 11.15±7.25. This mean score indicates the presence of possible depression. İnel Manav et al. (20) (2018) evaluated the cognitive function level, depression, and quality of life of older people living in a nursing home. In the study, it was stated that the mean score of the geriatric depression scale was 14.92±4.29. Similarly, the mean geriatric depression scale score of the elderly who participated in a study (2008) in which the risk of pain and depression was examined in the elderly in the nursing home

was found to be 14.47±5.89 (21). 11-13 points from the geriatric depression scale are interpreted as “possible depression” and 14 and above points are interpreted as “definitive depression (19). These findings are similar to our results. One of the common psychiatric disorders seen in the elderly population is depressive disorders (22). However, considering depressive symptoms as a part of the nature of old age may be a factor preventing health professionals from being consulted.

In the study, the mean score of geriatric depression scores of female participants was found to be higher than that of men. In the study conducted by Çınar and Kartal (23) with elderly individuals, it was stated that the mean score of Beck Depression Scale that women received was higher than that of men. Kockler and Gender (24) (2002) evaluated the effect of gender differences on the occurrence of depressive symptoms in elderly individuals; women experienced more depressive symptoms than men. These findings are similar to our results and show that women are more likely to experience depression. This may be related to the roles that society attributes to women. In our society, women have responsibilities such as making food, cleaning, child/grandchild care etc. On the other hand, despite the deterioration in the health status of women due to the rootstock aspect, they can strive to fulfill these roles. The combination of these burdens and growing health problems is thought to increase the risk of depression in women.

In our study, it was found that the mean scores of geriatric depression of individuals with low educational level were higher than in those with a high educational level. On the other hand, it was seen that the mean autonomy rating scale scores of the elderly individuals with low educational level were lower than in those with high educational level. According to the results of the research, a negative correlation was found between the autonomy assessment scale scores of elderly individuals and geriatric depression scale scores. Akyol et al. (25) (2010) evaluated the quality of life and depressive symptom level in the geriatric population and stated that individuals with low educational level had higher depression

Table 2. Autonomy assessment scale score averages according to the introductory information of the participants

Introductory information		Mean ± SD	Statistical analysis*
Gender	Female	-9.82±10.34	Z=-0.658 p=0.511
	Male	-9.34±6.81	
Education	Not literate	-9.63±6.96	**χ^2=10.683 p=0.030**
	Literate	-15.43±11.40	
	Primary school	-9.67±9.58	
	High school	-4.62±4.67	
	University	-7.73±7.03	
Marital status	Married	-8.90±6.98	Z=5.945 p=0.015
	Divorced	-1.16±7.63	
	Widow	-12.80±13.53	
Who does he/she live with?	Alone	-6.25±5.86	**χ^2=11.138 p=0.025**
	With partner	-8.56±6.91	
	With partner and children	-12.66±6.81	
	With children	-16.50±15.95	
	Other	-2.00±2.00	
Income source status	Yes	-9.70±9.47	Z=-0.216 p=0.829
	No	-9.40±8.10	
Age	51-60	-3.25±3.88	**Z=8.430 p=0.038**
	61-70	-7.09±8.01	
	71-80	-9.97±9.81	
	81-90	-12.14±8.69	
Chronic illness	Yes	-9.67±8.04	Z=-1.476 p=0.140
	No	-9.33±15.69	
Total		-9.63±-9.17	

*Z: Mann-Whitney U test, χ^2: Kruskal-Wallis test, SD: Standard deviation

Table 3. Geriatric depression scale score averages according to the introductory information of the participants

Introductory information		Mean ± SD	Statistical analysis*
Gender	Female	13.35±7.56	**Z=-3.574 p=0.001**
	Male	7.66±5.10	
Education	Not literate	12.27±6.60	**χ^2=19.706 p=0.001**
	Literate	17.93±7.62	
	Primary school	10.56±6.85	
	High school	10.33±5.78	
	University	6.13±4.80	
Marital status	Marital	10.46±7.37	Z=1.382 p=0.240
	Divorced	6.00±6.08	
	Widow	13.80±6.37	
Who does he/she live with?	Alone	12.91±5.50	χ^2=7.373 p=0.117
	With partner	9.88±7.57	
	With partner and children	13.55±4.97	
	With children	12.93±7.91	
	Other	14.33±6.10	
Income source status	Yes	9.95±6.69	**Z=-3.030 t=0.002**
	No	15.76±7.60	
Age	51-60 years	6.00±4.24	Z=1.323 p=0.724
	61-70 years	11.07±6.84	
	71-80 years	11.50±7.76	
	81-90 years	10.96±6.99	
Chronic illness	Yes	10.97±7.30	Z=-0.802 p=0.423
	No	12.50±7.02	
Total		11.15±7.25	

*Z: Mann-Whitney U test, χ^2: Kruskal-Wallis test, SD: Standard deviation

levels. In a study in Sanliurfa (2016) examining the prevalence of depression and the factors affecting it in the elderly, it was stated that the risk of developing depression was higher in the elderly with a low educational level (26). It is thought that access to information more easily for the elderly with high education level helps them to be more successful in the process of finding solutions to their health problems and thus to be more successful in coping with the stressors they face. As a result, the rate of depression may be lower in individuals with a high educational level. Again, considering the importance of healthy aging of individuals with higher education level, it is thought that they will contribute to increasing the autonomy of lifestyles considering components such as healthy eating and regular exercise.

In our study, it was seen that the mean geriatric depression scale scores of the elderly individuals with a source of income were lower than the non-geriatric depression scale scores. Arslantaş and Ergin (27) (2011) examined loneliness, depression, need for social support and the factors affecting them in individuals aged 50-65 years in Aydın in their study. According to the results of the study, it was found that the presence of depressive symptoms in participants was twice as high in those who did not work in an income-generating job. It is thought that having an income, working in a professional group and maintaining productivity will decrease the incidence of depression in elderly individuals. On the other hand, the lack of a source of income is seen as an obstacle for the individual to reach the necessary means for protection, maintenance and treatment when necessary.

Maintaining mental and physical well-being of elderly individuals is important for healthy aging (28). Difficulties in daily living activities in the elderly may result in the presence of depression and poor quality of life (22). In our study, it was seen that the autonomy scores of elderly individuals decreased with increasing age. It shows that the aging process makes it difficult for the individual to perform daily life activities and functional independence decreases.

It was seen that the autonomy assessment scale scores of married individuals were higher than those of the widows and lower than those of the divorced individuals. When the autonomy scores of the participants with whom they live were examined, the scores of the participants who preferred the other (elderly care homes etc.) were higher than those of their spouses, spouses and children, and those living with their children; it was observed that those living alone were higher than those living with their spouses and children. In addition, Bozkurt and Yılmaz (29) (2016) conducted a study with individuals over 65 years of age and found that autonomy scores of married participants were higher than those of the divorced and widows. Altay et al. (4) (2016) did not find a statistically significant difference between the autonomy of married and unmarried participants in their studies evaluating health perception, quality of life and health-related quality of life of older people aged 60 years and older. Marriage can be seen as an atmosphere where responsibilities and burdens are shared for family members who share the same house, and it can be seen as an environment that increases the responsibilities of women, especially in our society. It is thought that family environment, where domestic violence and conflicts are intense and positive sharing is insufficient, may adversely affect the physical and mental health of the individual. Therefore, it can be thought that the elimination of negative family environment factors of divorced individuals before divorce may have contributed to increase their autonomy levels. For the widows, it is thought that the loss of life and the spouses in which the burdens are shared causes the autonomy to decrease due to the burdens and responsibilities of the loss. It is also thought that the differences in the autonomy scores of the elderly individuals according to their marital status and with whom they live may be due to the differences in the number of participants per group (Table 1).

The fact that the research is single-centered is one of the limitations of the research. Research results can only be generalized to this sample group.

Conclusion

It was found that individuals over 65 years of age were at risk of losing their functional independence and that they had possible depression. Depression is one of the most frequently observed mental health problems in elderly individuals. Decreased functional independence increases with age and increases the risk of depression in elderly individuals. On the other hand, it is thought that the individual's ability to continue daily activities independently will have a positive effect on mental health. In this respect, it is recommended to increase the initiatives to increase the functional independence level of elderly individuals, to evaluate the functional levels of elderly individuals at regular intervals, to conduct researches that will create awareness about this aspect of care given at home or in hospital and to increase in-service training.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Review Board (University of Health Sciences Turkey, Gülhane Non-Interventional Ethical Committee, no: 2018-38, date: 06.02.2018).

Informed Consent: The participants were informed about the research and their consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.S., Ü.S., Design: G.S., Ü.S., Data Collection or Processing: Ü.S., Analysis or Interpretation: G.S., M.İ.N., E.Ö.,

Literature Search: G.S., M.İ.N., E.Ö., Writing: G.S., Ü.S., M.İ.N., E.Ö.

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Retrospective analysis of patients with relapsed/refractory medulloblastoma after autologous stem cell transplantation

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ABSTRACT

Aims: Medulloblastoma is very rare and accounts for only 1% of intracranial tumors in adults. There are limited treatment options for adult medulloblastoma patients who have relapsed or refractory disease. We aimed to show real-life data on health outcomes in adult patients with recurrent or refractory medulloblastoma patients who received autologous hematopoietic stem cell transplantation (AHSCT).

Methods: We analyzed the data of 15 patients who underwent AHSCT after ifosfamide, carboplatin, and etoposide (ICE) as high-dose chemotherapy (HDCT) regimen for relapsed or refractory medulloblastoma from 2010 to 2020. Overall response rate (ORR), overall survival (OS) and progression-free survival (PFS) of the patients were evaluated.

Results: Fifteen patients were observed in this study. The mean age of the study group was 27.9±8.1 years and 53.3% of the patients were female (n=8). ORR was 100%. The median OS and PFS were 24 months [95% confidence interval (CI): 11.4-36.5] and 13 months (95% CI: 10.2-15.8), respectively. One-year OS and PFS rates were 77% and 55.2%, respectively. Five-year OS rate was 82.5%.

Conclusions: AHSCT with ICE as HDCT regimen is a safe and effective treatment option for relapsed or refractory adult medulloblastoma patients with an acceptable ORR, OS and PFS time.

Introduction

Medulloblastoma is the most common central nervous system embryonal tumor of childhood, constituting 25% of all intracranial neoplasms (1). In contrast, adult medulloblastoma is very rare and accounts for only 1% of intracranial tumors (2). Current conventional management of adult medulloblastoma involves maximum safe resection followed by craniospinal radiation with or without concurrent adjuvant chemotherapy depending on the clinical risk classification (3). Clinical risk stratification included age, the extent of resection, metastatic status, and tumor biology (4). Metastatic patients might undergo chemotherapy. Besides, autologous hematopoietic stem cell transplantation (AHSCT) should be selected (5). In the literature, a limited number of patients underwent high-dose chemotherapy (HDCT) and AHSCT due to relapsed or refractory medulloblastoma even after surgical debulking and radiotherapy (6,7). According to the literature, data about AHSCT in adult medulloblastoma patients appear to be small case series. Similar treatment methods are used in Turkey. The only center which use AHSCT in solid organ tumor in Turkey is the Gülhane Training and Research Hospital Medical Oncology Department. The other oncology departments in Turkey are sending their

medulloblastoma patients to our center for treating with AHSCT. Therefore, the results reflect the data of Turkey.

We aimed to demonstrate the real-life data about relapsed or refractory medulloblastoma patients who received HDCT and AHSCT and to increase the awareness of this rare treatment choice.

Methods

Study Design and Patients

The study was carried out by investigating the patients with relapsed and refractory adult medulloblastoma, who had received HDCT and AHSCT in University of Health Sciences Turkey, Gülhane Training and Research Hospital between January 2010 and March 2020 in diagnosis, follow-up, treatment, complications outcomes. The study is a single-center, retrospective study.

A retrospective case control study was carried out with 15 cases that were previously diagnosed and treated or currently on a treatment for medulloblastoma, and they were evaluated in terms of demographic characteristics, cancer specific features including histology, stage of the cancer, previous or ongoing treatment and previous surgery or radiotherapy.

The patients received ifosfamide at a total dose of 12 gr/m^2 divided six days on days -8 to -3, carboplatin at a total dosage of 1,200 mg/m^2 divided six days on days -8 to -3 and etoposide at a total dosage 1,200 mg/m^2 divided six days on days -8 to -3 ifosfamide, carboplatin, and etoposide (ICE) as HDCT (8). After chemotherapy, the patients rested on days -2 and -1. Autologous stem cells were reinfused on day 0. We infused at least 3 million ($3x10^6$) CD34+ stem cells. After infusions, all patients were followed in our Stem Cell Infusion Center. All patient rooms were single, isolated with a special ventilation system. During the stem cell transplant process, patients' relatives were forbidden to visit and bring food from outside for protecting them from infections.

The primary endpoint of this study was to assess the progression-free survival (PFS) and overall survival (OS) periods. Secondary endpoints were to identify prognostic clinical factors for disease progression after AHSCT, and to define the safety and the toxicity profile of the HDCT and AHSCT.

The ethics committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital approved the study with 2020-112 ethical committee number on March 10, 2020. All procedures were performed in accordance with the Helsinki Declaration of 1975, which was revised in 2008, and all procedures were convenient to the ethical standards of the responsible committee on human experimentation (institutional and national).

Data Collection

Medical records of the patients, who were admitted to the Department of Medical Oncology at the University of Health Sciences Turkey, Gülhane Training and Research Hospital and eventually diagnosed with medulloblastoma, were investigated whether they previously or currently had received AHSCT. Medical records of suitable cases were enrolled in a SPSS data-sheet by the registered staff of Department of Oncology at the University of Health Sciences Turkey.

Statistical Analysis

Patients' demographics, clinical and biochemical features, and clinical and radiologic outcomes were recorded on an SPSS v.17 (SPSS Inc., Chicago, IL USA) data sheet considering the patients' confidentiality. Data were accessible only by the authorized institutional staff and caregivers. The Student's t-test was utilized for evaluating normal distribution of data. Demographic indices provided the mean values with the standard deviation or the median values as appropriate. Frequencies were noted in numbers with percentiles. Survival analysis was conducted utilizing the Kaplan-Meier tables and survival plots provided.

Results

Patient and Disease Characteristics

We determined that 50 patients were followed up with the diagnosis of medulloblastoma between January 2010 and March 2020. Fifteen of the patients (30%) received HDCT and AHSCT. The mean age of the study group was 27.9±8.1 years and 53.3% of the patients were female (n=8). All patients were stage 4 at the time of diagnosis. Tumor histology revealed classic type medulloblastoma in 12 (80%) patients and three (20%) patients showed desmoplastic/nodular type medulloblastoma at diagnosis. Large anaplastic type and extensive nodular types were not observed. Bone was the most seen metastatic site [4 (26.7%)] among the patients included in the study. Lymphoid nodes and lungs were the other most common metastatic sites, respectively. Three patients (20%) of them had more than two metastatic sites. Numbers of lines before AHSCT treatment were more than three in all cases. Six (40%) of the patients were treated with AHSCT as the third line therapy. Nine (60%) of them were treated with AHSCT as the fourth line therapy (Table 1). Eleven patients had complete response (73.3%), two patients had partial response (13.3%) and two patients had stabile disease (13.3%). Progression was not observed at the first controls. Overall response rate (ORR) was 100%. Later in long term follow-up period, we detected progression. All cases received radiotherapy as the first line therapy after surgery. They underwent different combination therapies for the second, third and fourth lines (Table 1).

Treatment Administration and Survival Outcome

All cases underwent AHSCT following various degrees of salvage chemotherapy both before and after surgery due to relapsed or refractory disease. As HDCT, all patients received ICE regimen. The mean and median follow-up times

following AHSCT were 15.1±18.4 months and seven months, respectively. The median OS and PFS were as follows; 24 months [95% confidence interval (CI): 11.4-36.5] and 13 months (95% CI: 10.2-15.8), respectively (Figure 1, 2, Table 2). OS and PFS at the 12th month were 77% and 55.2%, respectively. Five-year OS was 82.5%.

Toxicity of AHSCT

The numbers of side effects related to AHSCT are demonstrated in Table 3. Leukopenia, anemia, thrombocytopenia, neurotoxicity, febrile neutropenia, diarrhea and vomiting/nausea were found 100%, 100%, 100%, 46.6%, 100%, 66.6%, and 100%, respectively. Majority of the patients received erythrocyte, thrombocyte transfusions and granulocyte colony stimulating factors several times after 12 or 16 days following the AHSCT. Eleven patients (73.3%) had grade 4 thrombocytopenia. No bleeding was observed in any patients. Grade 2 and 3 febrile neutropenia were observed among all patients. A broad-spectrum antibacterial therapy was administered in all patients, including 3rd generation

Table 1. The demographic and disease-related characteristics of the patients

Features	n (%)	Mean ± SD	Median
Age (years)	15 (100)	27.9±8.1	27 (18-43)
Gender			
Male	7 (46.7)		
Female	8 (53.3)		
Histopathology			
Classic type	12 (80)		
Desmoplastic/nodular type	3 (20)		
Large/anaplastic type	0 (0)		
Extensive nodular type	0 (0)		
Stage at the time of diagnosis			
4	15 (100)		
Site of metastases			
No metastases	0 (0)		
Liver	2 (13.3)		
Lymph node	3 (20)		
Lung	3 (20)		
Bone	4 (26.7)		
More than 1 sites	3 (20)		
The response of the patients after AHSCT			
Stable response	2 (13.3)		
Partial response	2 (13.3)		
Complete response	11 (73.4)		
Progressive disease	0 (0)		
The treatments lines patients received before AHSCT			

Treatments	First line: n (%)	Second line: n (%)	Third line: n (%)	Fourth line: n (%)
Radiotherapy	15 (100)	1 (6.7)		
Vincristine+Procarbazine+Mustard		3 (20)		
Cisplatin+Etoposide+Cyclophosphamide		8 (53.3)	1 (6.7)	
Cisplatin+Lomustine+Vincristine		1 (6.7)		
Ifosfamide+Carboplatin+Etoposide		2 (13.3)	5 (33.3)	
HDCT (ICE) + AHSCT			6 (40)	9 (60)

AHSCT: Autologous hematopoietic stem cell transplantation, HDCT: High dose chemotherapy, ICE: Ifosfamide, Carboplatin, Etoposide, SD: Standard deviation

cephalosporins, teicoplanin, anti-pseudomonal azlo-ureido penicillin, carbapenems, linezolid and macrolides for empirical purpose. Blood and urine cultures were taken. No bacteria or fungal infections were seen. There was no life-threatening toxicity. One patient had reversible grade 3 renal toxicity. No death was observed relating to the treatment. There was no death in the first 100 days. Six (40%) patients died due to the disease progression at the follow-up period.

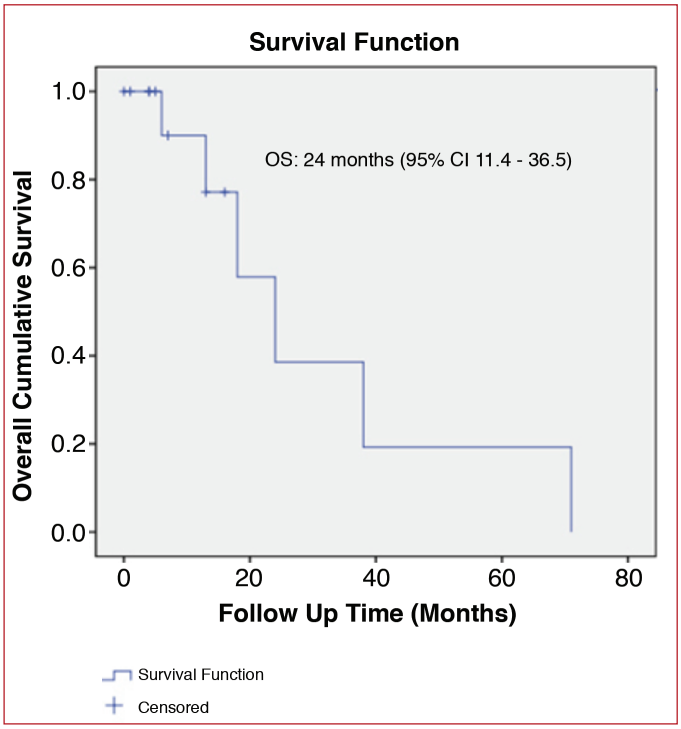

Figure 1. Overall survival of patients underwent autologous hematopoietic stem cell transplantation treatment (Kaplan-Meier curve)
OS: Overall survival, CI: Confidence interval

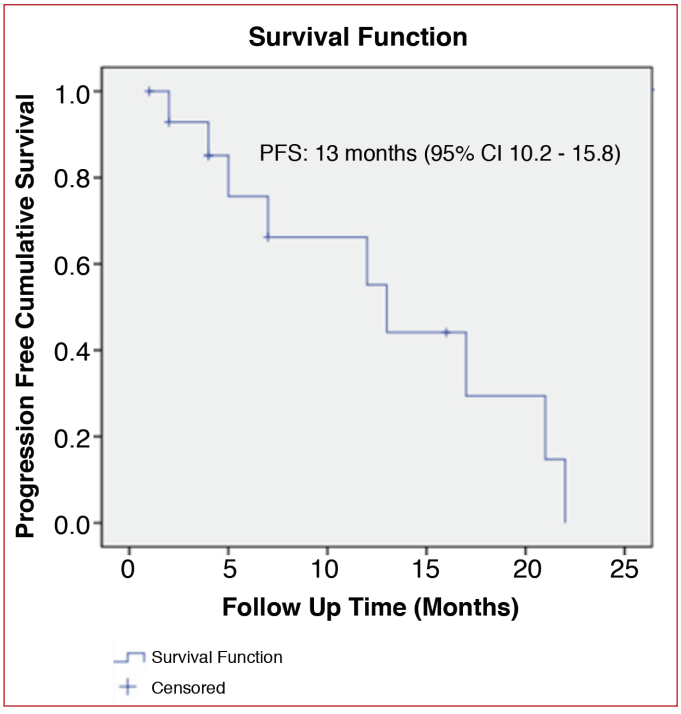

Figure 2. Progression free survival of patients underwent autologous hematopoietic stem cell transplantation treatment (Kaplan-Meier curve)
PFS: Progression-free survival, CI: Confidence interval

Discussion

Medulloblastoma treatment is based on clinical risk stratification (3). Current therapy combines surgery, chemotherapy, radiotherapy, and HDCT with AHSCT (9). In this study, we analyzed the efficacy and safety of HDCT with ICE regimen and AHSCT treatment in patients with relapsed or refractory adult medulloblastoma, who underwent at least three lines of therapy before. All patients underwent surgery. Before AHSCT, all patients had radiotherapy as the first-line therapy. As a second-line therapy, they received combination chemotherapies such as Vincristine plus Procarbazine plus Mustard, Cisplatin plus Etoposide plus Cyclophosphamide, Cisplatin plus Lomustine plus Vincristine or Ifosfamide plus Carboplatin plus Etoposide (10,11). Medulloblastoma is a high risk for most of our patients that received AHSCT as the third-line therapy. According to the packer staging criteria, which included age, the extent of resection, metastatic status, and tumor biology, all patients in our study were high-risk and additionally as far as we know, medulloblastomas are chemosensitive tumors (12,13). There were several retrospective studies about AHSCT in medulloblastoma (6,7). Most of them consisted of pediatric patients. Various HDCT regimens were applied before AHSCT. Moreover, all patients were stage four at diagnosis. All the patients received ICE regimen as HDCT in our study.

Histologically, medulloblastoma is an embryonal neuroepithelial tumor originating from the cerebellum and dorsal brain stem. Classic, desmoplastic/nodular, large cell/anaplastic, and extensive nodularity are the subgroups of medulloblastoma. The most common histologic variant is classic medulloblastoma in both children and adults (70-80%), and the least common is

Table 2. Overall survival and progression free survival of patients underwent autologous hematopoietic stem cell transplantation treatment

	n (%)	Median	Mean ± SD
OS		24 months (95% CI: 11.4-36.5)	
PFS		13 months (95% CI: 10.2-15.8)	
12 months OS	**77**		
12 months PFS	**55.2**		
5 years OS	**82.5**		
The duration of follow-up time		7 (3-71)	15.1±18.4

OS: Overall survival, PFS: Progression free survival, AHSCT: Autologous hematopoietic stem cell transplantation, SD: Standard deviation, CI: Confidence interval

medulloblastoma with extensive nodularity (3%) (14,15). We observed classic type medulloblastoma in 12 (80%) patients and desmoplastic/nodular type medulloblastoma in three (20%) patients at diagnosis.

The five-year survival rate for both children and adult medulloblastoma is intermediate and about 70%. SHH subtype predicts poor prognosis. SHH, WNT, and group 4 are detected 60%, 15%, and 25% of adult patients, respectively (16). Five-year survival rate is 80% in adults who have WNT subtype. In our study SHH, WNT and group 4 were detected as 80% (n=12), 6.7% (n=1) and 13.3% (n=2), respectively and 5-year survival was 82.5%. This was similar to the literature.

Table 3. Toxicities during autologous hematopoietic stem cell transplantation treatment

	n (%)
Leukopenia	
Grade 4	15 (100)
Anemia	
No	0 (0)
Grade 1	1 (6.7)
Grade 2	10 (66.7)
Grade 3	4 (26.6)
Thrombocytopenia	
No	0 (0)
Grade 1	0 (0)
Grade 2	1 (6.7)
Grade 3	3 (20)
Grade 4	11 (73.3)
Neurotoxicity	
No	8 (53.3)
Grade 1	3 (20)
Grade 2	4 (26.7)
Febrile neutropenia	
No	0 (0)
Grade 1	0 (0)
Grade 2	14 (93.3)
Grade 3	1 (6.7)
Vomiting/nausea	
No	0 (0)
Grade 1	1 (6.7)
Grade 2	2 (13.3)
Grade 3	9 (60)
Grade 4	3 (20)
Diarrhea	
No	5 (33.3)
Grade 1	2 (13.3)
Grade 2	7 (46.7)
Grade 3	1 (6.7)
The final status of the patients	
Exitus	6 (40)
Alive	9 (60)

AHSCT: Autologous hematopoietic stem cell transplantation

Some studies showed ORRs in the range of 83-100% (5-7). Okada et al. (8) observed ORR in 83% patients who underwent ICE regimen as HDCT. Zia et al. (6) observed ORR in 100% of patients who underwent carboplatin, etoposide, and cyclophosphamide. Both of these studies had six children patients. We observed ORR as 100% in 15 patients. Later progression developed in eight patients. Six of them died in the follow-up (40%, n=6). Nine patients are still alive. Six of the alive patients have complete remission. Three patients are still receiving treatment.

Zia et al. (6) showed an average of 13.5 months of PFS and an average of 21.5 months of OS after AHSCT. Additionally, Zia et al. (6) reported the median 26.8 months of OS for the medulloblastoma patients receiving AHSCT (6). In our study, we observed OS and PFS at the 12th month as 77% and 55.2%, respectively. The OS rate for five years was 82.5%. These results were similar to previous literature.

Okada et al. (8) reported that the rate of grade 4 neutropenia and thrombocytopenia were observed to be 100%. The toxicities were recovered within 26 days. Safety analysis of this report showed the feasibility of the ICE regimen as HDCT and AHSCT in patients with heavily pretreated medulloblastoma. In our study, all toxicities were observed.

Although this study had a small sample size of medulloblastoma patients with further line AHSCT and long follow-up, there are some limitations to report. It was a retrospective study, and the patient population was relatively heterogeneous. The patient sample size was small. Medulloblastoma patients in this study underwent AHSCT for metastatic medulloblastoma at an experienced high-volume referral center. We believe that these patients need multidisciplinary expertise and hence should be treated at centers of stem cell transplantation with excellence. The strengths of the study include AHSCT in further lines and relatively more patients in a rare disease. The results cannot be applied to other countries with different cancer epidemiology and practice.

Conclusion

In conclusion, AHSCT with ICE regimen remains one of the best determined systemic treatment options for progressive adult medulloblastoma patients. Also, the treatment was associated with good efficacy and tolerability.

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Ethics

Ethics Committee Approval: The ethics committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital approved the study with 2020-112 ethical committee number on March 10, 2020.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.S., B.B.B., Design: E.S., B.B.B., Data Collection or Processing: R.A., İ.E., Analysis or Interpretation: B.Y., M.B.A., G.S.Y.K., Literature Search: E.S., N.K., H.K., S.O., Writing: E.S., B.B.B.

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The association of serum beta-2-microglobulin with autoantibody production and disease activity in patients with primary Sjögren's syndrome

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Keywords: Primary Sjögren's syndrome, beta-2-microglobulin, ESSDAI, ESSPRI, biomarkers

ABSTRACT

Aims: The aim of the this study is to evaluate beta-2-microglobulin (B2M) levels in patients with primary Sjögren's syndrome (pSS) and to investigate their correlation with serum biomarkers and disease activity indexes commonly used in daily clinical practice.

Methods: Eighty-one patients with pSS were included in this retrospective and cross-sectional study. Demographic data, clinical characteristics, B2M, immunoglobulin (Ig) A, IgG, IgM, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum complement (C) 3 and C4 levels, anti-nuclear antibody, rheumatoid factor (RF), anti-SSA and anti-SSB antibodies were obtained from the medical records. Disease activity was evaluated by the European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) and EULAR SS Patients Reported Index (ESSPRI).

Results: Serum B2M level was significantly higher in patients with anti-SSA and anti-SSB antibody (median: 2.64 mg/dL, minimum: 2.02 mg/dL, maximum: 10.10 mg/dL) than in only anti-SSA positive patients (median: 2.31 mg/dL, minimum: 1.33 mg/dL, maximum: 4.26 mg/dL, p=0.010) and both antibody negative patients (median: 1.80 mg/dL, minimum: 1.20 mg/dL, maximum: 2.65 mg/dL, p<0.001). Also, patients with anti-SSA antibody have significantly higher serum B2M levels than anti-SSA and anti-SSB antibodies negative patients (p=0.009). Serum B2M level was significantly correlated with ESSDAI (r=0.482, p=0.001), serum IgG level (r=0.374, p=0.001), IgA level (r=0.341, p=0.002), RF levels (r=0.412, p=0.021) and ESR (r=0.239, p:0.031). There was no correlation between ESSPRI, IgM, CRP and serum B2M levels. ESSDAI was not correlated with C3 (r=0.044, p=0.697), C4 (r=-0.053, p=0.640), ESR (r=0.111, p=0.326), CRP (r=0.111, p=0.324) and IgG (r=0.154, p=0.169).

Conclusions: Although serum B2M levels were higher in autoantibody positive patients, it has a weak correlation with clinical disease activity.

Introduction

Sjögrens's syndrome (SS) is a chronic disease at the junction of systemic autoimmune disorders and lymphoproliferative conditions (1). SS is characterized by a chronic lymphocytic infiltration of exocrine glands, predominantly the salivary and lacrimal glands (2). The clinical spectrum of SS extends from dryness of the mucosal surfaces such as mouth and eyes to severe life-threatening condition such as vasculitis and lymphoma (3). Due to the systemic nature of the disease, almost every organ can be affected (4). Early detection of high-risk patients will reduce mortality and morbidity (5). Biomarkers offering an early diagnosis, predicting the disease outcome and therapy response are still a need that has not been met.

Beta-2-microglobulin (B2M) is a low-molecular weight protein with sequence homology to immunoglobulins (Ig) and expressed on the surface of all nucleated cell. B2M is non-covalently linked to the alpha chain of major histocompatibility complex-class 1 and plays a role in the antigen presentation to cytotoxic (CD8+)

T lymphocytes (6). Also, B2M complexes with a cluster of differentiation 1 (CD1), MR1, human leukocyte antigen (HLA)-E, HLA-F, HLA-G, neonatal Fc receptor (FcRn) and human hemochromatosis protein (HFE)/HLA-H, which are related to mucosal immunity, tumor surveillance, maternofetal immune tolerance, iron metabolism, homeostasis of immunoglobulin (Ig) and albumin (7). During normal cell turn over, it is released into the body fluids and presents as a soluble form at a constant rate. Serum level of B2M has been established as a prognostic marker in solid organ malignancies, hematologic disorders, and various autoimmune diseases such as Crohn's disease, SS, systemic lupus erythematosus and rheumatoid arthritis (8-10).

Serum B2M is an independent predictor of the primary SS (pSS) development in subject with sicca symptoms (11). It has also been associated with extraglandular systemic involvement of pSS overall, organ specific manifestation of pSS and lymphoma development (12-19). However, to date, studies which evaluate the relationship between B2M and disease activity in patients with pSS are limited (20-22).

The aim of this study is to evaluate B2M levels in patients with pSS and to investigate their correlation with serum biomarkers and disease activity indexes commonly used in daily clinical practice to evaluate disease status.

Methods

This study was planned as a retrospective and cross-sectional study. Medical records of pSS patients who applied to our outpatient clinic between July 2016 and July 2017 were retrospectively scanned from the electronic database of our tertiary hospital. In our rheumatology department, standard clinical and laboratory investigation are made at each visit to assess the disease activity and organ involvement of patients with pSS. After taking accurate medical history and carefully performing physical examination, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), B2M, IgA, IgG, IgM, serum complement (C) 3 and C4 levels are routinely evaluated as the predictors of disease activity. Disease activity is assessed with European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) and EULAR SS Patients Reported Index (ESSPRI). In the present study, clinical and laboratory values of the most recent visit were evaluated. Patients with impaired renal function, concomitant autoimmune disease, known solid organ malignancies, or lymphoproliferative disorders were excluded, as these conditions are associated with increased serum B2M levels. Consequently, a total of 81 pSS patients who fulfilled 2002 American European Consensus Group criteria for diagnosing pSS were enrolled (23). The study was approved by the Committee on Human Research Ethics at Zekai Tahir Burak Women's Health Training and Research Hospital (dated: 28.02.1017, decision number: 39/2017).

Demographic data, clinical characteristics and laboratory results, including anti-nuclear antibody (ANA), rheumatoid factor (RF), anti-SSA and anti-SSB antibodies, ESR, CRP, serum levels of B2M, IgA, IgG, IgM, C3 and C were obtained from electronic medical records.

In our hospital, serum concentrations of IgA, IgG, and IgM, as well as serum levels of C3 and C4, were measured by laser nephelometry. Normal values were 79 to 152 mg/dL for C3 and 16 to 38 g/L for C4. ANA were detected by indirect immunofluorescence HEp-2 cells. Anti-SSA and anti-SSB antibody levels were determined by commercial enzyme linked immunosorbent assay. The serum B2M level was determined using nephelometry. According to the recommendations of manufacturer, a serum B2M value of 1.8 mg/dL or more was considered to be increased.

The ESSPRI is a patient-administered questionnaire which evaluates symptoms including pain, fatigue and dryness. Each individual symptom is evaluated with an eleven-point numerical scale. The scale is composed of 0 (no symptoms) to 10 (severe symptoms) scores. The final ESSPRI score is calculated by taking the average scores of these domains. Total ESSPRI score ranges from 0 to 10. The ESSPRI scores of <5 define low disease activity and scores of ≥5 define high disease activity (24,25).

The ESSDAI is a physician-based index for the assessment of the disease activity in patients with pSS. This index includes 12 domains as follows: constitutional, lymphadenopathy, glandular, articular, cutaneous, respiratory, renal, muscular, peripheral nervous system, central nervous system, hematological and biological. Each domain is scored from 0 to 3 or 4 according to activity levels. Total ESSDAI score is calculated by taking the sum scores of these domains score with a maximum severity score of 123. ESSDAI score <5 is defined as low disease activity, 5 ≤ESSDAI score ≤13 is defined as moderate disease activity, and ESSDAI score ≥14 is defined as high disease activity (25,26).

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 16.0 program for Windows. The variables were investigated using visual and analytical methods to determine whether they were normally distributed. Continuous values were expressed as mean ± standard deviation and categorical variables as number and percentage. Among serum Ig, C3, C4 and B2M levels were not normally distributed and the Kruskal-Wallis test was conducted to compare these parameters among the antibody status. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Spearman's correlation coefficient was used to evaluate the linear relationship between the predictive variables. A value of $p<0.05$ was considered to be statistically significant.

Results

Clinical and immunologic features of patients are presented in Table 1. C3 and C4 levels were decreased in 4 (4.9%) and 7 (8.6%) patients, respectively. Patients with anti-SSA antibody or both anti-SSA and anti-SSB antibody had statistically significant higher serum B2M levels, IgG and IgA than those without autoantibodies (Table 2). The serum B2M level had a weak correlation with ESSDAI (r=0.482, p=0.001), serum IgG level (r=0.374, p=0.001), serum IgA level (r=0.341, p=0.002), serum RF levels (r=0.412, p=0.021) and ESR (r=0.239, p=0.031). Serum B2M levels were not correlated with ESSPRI (r=0.089, p=0.429), IgM (r=0.009, p=0.934), CRP (r=-0.105, p=0.352).

According to the ESSPRI score, 47 (58%) patients had low disease activity. Although patients with high disease activity tended to have higher serum B2M levels, there was no statistically significant difference (2.13±0.69, 2.48±1.62 respectively, p=0.531).

According to the ESSDAI score, 38 (46.9%) of 71 patients had low disease activity, 31 (38.3%) patients had moderate disease activity and 12 (14.8%) patients had high disease activity. The median (minimum-maximum) serum B2M level was 1.83 (1.20-2.59) in patients with low disease activity, 2.46 (1.55-5.41) in those with moderate disease activity, and 2.97 (1.60-10.20) in those with high disease activity. Patients with low disease activity had significantly lower serum B2M levels than patients with moderate disease activity (p<0.001) and high disease activity (p=0.001). Although patients with high disease activity tended to have higher serum B2M levels, there was no statistically significant difference between high and moderate disease activities (p=0.147). Also, ESSDAI score was not correlated with C3 (r=0.044, p=0.697), C4 (r=-0.053, p=0.640), ESR (r=0.111, p=0.326), CRP (r=0.111, p=0.324), and IgG (r=0.154, p=0.169).

Discussion

In this study which investigated the usefulness of serum B2M level in evaluating disease activity of pSS patients, it was found that serum B2M level was positively correlated with ESSDAI, serum IgG level, IgA level, RF level and ESR. In addition, serum B2M level was significantly higher in patients with anti-SSA antibody or both anti-SSA and anti-SSB antibody than in those without autoantibodies. Furthermore, patients with anti-SSA and anti-SSB antibody had significantly higher serum B2M levels than patients with only anti-SSA antibody. In another study, Gottenberg et al. (19) evaluated the association between autoantibody production and serum B2M levels in patients with pSS. Similar to our study, they reported that the serum B2M level was significantly higher in patients with anti-SSA and anti-SSB antibodies than in those with anti-SSA antibody alone or those without anti-SSA and anti-SSB autoantibodies. In addition, they showed that serum B2M level was significantly correlated with serum RF (r=0.33, p=0.001), IgG (r=0.42, p=0.001), and ESR (r=0.39, p=0.001) (19).

During normal cell turn over, B2M is primarily released from immune-related cells including macrophages, active T and B lymphocytes in to most biological fluids (7). Following glomerular filtration, B2M is completely reabsorbed and catabolized in the

Table 1. Clinical and immunological features of patients with primary Sjögren's syndrome

Age, years	51.19±10.83
Male/female	2/79
Rheumatoid factor positive (n) (%)	28 (34.6%)
Serum IgA level (mg/dL)	251.00 (75.30-637.00)
Serum IgG level (mg/dL)	1270.00 (773.00-2970.00)
Serum IgM level (mg/dL)	113.00 (44.50-269.00)
Serum C3 level (mg/dL)	125.00 (52.50-186.00)
Serum C4 level (mg/dL)	23.30 (7.38-46.30)
CRP mg/L	3.66 (1.04-17.30)
ESR (mm/h)	19.00 (2.00-66.00)
Anti-SSA and anti-SSB antibodies negative	40 (49.4%)
Only anti-SSA antibody positive	22 (27.2%)
Anti-SSA and anti-SSB antibodies positive	19 (23.5%)
Serum beta-2-microglobulin (mg/dL)	2.02 (1.20-10.20)
ESSDAI	5.00 (0-26)
ESSPRI	4.00 (0.00-9.33)

Data shown as median (minimum-maximum) where otherwise stated.
Ig: Immunoglobulin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, ESSDAI: EULAR Sjögrens's Syndrome Disease Activity Index, ESSPRI: EULAR Sjögrens's Syndrome Patients Reported Index

Table 2. Serum immunoglobulin (Ig) A, IgG, IgM, C3, C4 and beta 2 microglobulin levels according to the antibody status

	Anti-SSA and anti-SSB antibodies negative (n=40)	Only anti-SSA antibody positive (n=22)	Anti-SSA and anti-SSB antibodies positive (n=19)	p value	p value*	p value**	p value***
IgA (mg/dL)	208.50 75.30-480.00	266.50 128.00-425.00	358.00 185.00-637.00	**<0.001**	**0.010**	**<0.001**	0.030
IgG (mg/dL)	1190.47 773.00-1600	1390.00 835.00-2660	1580.00 994.00-2970	**<0.001**	**0.006**	**<0.001**	0.080
IgM (mg/dL)	121.00 44.90-269.00	113.50 57.10-241.00	111.00 44.50-242.00	0.866	0.680	0.858	0.610
C3 (mg/dL)	122.50 73.70-156.00	122.50 52.50-150.00	131.00 82.00-186.00	0.562	0.763	0.363	0.333
C4 (mg/dL)	24.60 12.10-41.00	21.70 7.38-36.40	22.80 13.30-46.30	0.228	0.086	0.527	0.374
Beta-2-microglobulin (mg/dL)	1.80 1.20-2.65	2.31 1.33-4.26	2.64 2.02-10.20	**<0.001**	**0.009**	**<0.001**	**0.010**

*Difference between patients without anti-SSA and anti-SSB antibodies and patients with only anti-SSA antibody.
**Difference between patients without anti-SSA and anti-SSB antibodies and patients with anti-SSA and anti-SSB antibodies.
***Difference between patients with only anti-SSA antibody and patients with anti-SSA and anti-SSB antibodies.
Mann-Whitney U test was used to compare the differences between the groups.

proximal renal tubules (27). The abnormality of serum or urine B2M level is associated with various hematologic malignancies, autoimmune disease, and renal disorders (7,28,29).

Although the specific function of serum B2M remains unknown in pSS, previous studies reported that B2M level was increased in pSS patients with particular individual clinical manifestations. Hatron et al. (17) reported that B2M was increased in the serum of pSS patients with latent alveolitis. Lahdensuo and Korpela (18) reported that pSS patients with pulmonary hyperinflation had elevated serum B2M levels and disturbed lung function was correlated with high serum B2M levels. Pertovaara et al. (13) showed that high level of serum B2M was one of the best predictors of the development of distal renal tubular acidosis in pSS patients. In addition, a longitudinal cohort study contucted by Pertovaara et al. (14) showed that baseline serum B2M level was a significant predictor of lymphoma development in pSS patients (Odds ratio: 1.9; 95% confidence interval: 1.1 to 3.4; p=0.031).

In our pSS patient, ESSDAI score was correlated significantly with serum B2M levels (r=0.482, p=0.001) but was not correlated with serum levels of IgG (r=0.154, p=0.169) and C4 (r=-0.053, p=0.640), although these parameters are included in the ESSDAI. Like our study, Pertovaara and Korpela (20) reported that serum B2M level was significantly correlated with the ESSDAI score (r=0.383, p=0.001) and not correlated with serum levels of IgG (r=0.014, p=0.906) or C4 (r=-0.105, p=0.359). Authors suggested that this was presumably due to the fact that serum levels of IgG and C4 were given a rather low weight in the calculation of ESSDAI score. In another study conducted by James et al. (30), it was reported that serum B2M level was an independent predictor of ESSDAI scores (30). Unlike our study, in their study, according to the Poisson regression of serum B2M level against the ESDDAI domain, serum B2M level was significantly associated with biological domains of ESSDAI. Also, Gottenberg et al. (21) evaluated the baseline clinical and immunological features of the Assessment of Systemic Signs and Evolution of SS cohort and showed that pSS patients with elevated serum B2M levels had higher ESSDAI scores at enrollment.

In our study, serum B2M level was not correlated with the ESSPRI score, which evaluates patient's dryness, fatigue and pain. Similar to our results, Gottenberg et al. (21) observed that ESSPRI was not correlated with serum B2M levels. This is probably due to the fact that ESSPRI is based on the subjective perception of patients.

Several limitations to the present study warrant attention. The small sample size is a major limitation of our study. Larger sample size may be needed to identify serum biomarkers in systemic autoimmune diseases, which are heterogeneous diseases. The cross-sectional design is another limitation of this study. This study does not provide sufficient results to investigate possible causality and effect relationship. Also, our results do not give information about the changes in serum B2M level with disease duration, disease activity and treatment response. Despite these limitations, our results support the previous findings that serum B2M is a considerable biomarker for assessing disease activity of pSS.

Conclusion

As a conclusion, serum B2M level may be a useful biomarker in evaluating disease activity of pSS. In the future, there is a need of well-designed, prospective, controlled studies with a

larger sample size to validate clinical value of this simple, widely available, and inexpensive blood test as an activity marker in pSS patients.

Ethics

Ethics Committee Approval: The study was approved by the Committee on Human Research Ethics at Zekai Tahir Burak Women's Health Training and Research Hospital (dated: 28.02.1017, decision number: 39/2017).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T., D.B., Z.G., F.G., Concept: D.T., D.B., Z.G., F.G., Design: D.T., D.B., Z.G., F.G., Data Collection or Processing: D.T., D.B., Z.G., F.G., Analysis or Interpretation: D.T., D.B., Z.G., F.G., Literature Search: D.T., D.B., Z.G., F.G., Writing: D.T., D.B., Z.G., F.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Is mitral balloon valvuloplasty really innocent?: A case report of right ventricular rupture

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Keywords: Mitral balloon valvuloplasty, percutaneous, ventricular rupture

ABSTRACT

Percutaneous mitral balloon valvuloplasty (PMBV) is the primary treatment modality in patients with mitral stenosis without contraindications and with appropriate valve anatomy. In the literature, the mortality rate associated with PMBV was reported to be 1%. This process may cause rare and serious complications; such as pericardial effusion, acute mitral regurgitation, cardiac tamponade, and thrombus formation. In this case report, we present a 45-year-old female patient who underwent emergency surgery because of right ventricular rupture during PMBV.

Introduction

Mitral balloon valvuloplasty is a method that has proven to be increasingly widespread and effective as a percutaneous intervention for mitral stenosis (1). Serious complications can occur during percutaneous cardiac catheterization, which may cause mortality and morbidity. Percutaneous mitral valvuloplasty is among the procedures that cause the highest rate of cardiac tamponade (2). In the literature, the frequency of developing cardiac tamponade during mitral balloon valvuloplasty has been found to be between 1% and 9% (3). Pericardiocentesis or emergency surgical intervention may be required due to cardiac tamponade. In this case report, we presented the successful treatment of right ventricular rupture, as an unprecedented complication during percutaneous mitral balloon valvuloplasty (PMBV).

Presentation of Case

A 45-year-female patient presented with symptoms of palpitation and shortness of breath since last twelve months. On her clinical examination, her pulse was 75/min; rhythmic and regular, blood pressure was 120/80 mmHg. There was

an opening snap, 3/8 diastolic murmur and 2/6 holosystolic murmur in cardiac auscultation. Blood tests were normal. Normal sinus rhythm was detected in electrocardiography. In 2D echocardiography, severe mitral stenosis was detected, and the mitral valve area was 1.3 cm^2 with PHT and the valve gradient was 25/12 mmHg. Also, commissural calcification and moderate pulmonary hypertension (65 mm of Hg) were detected. The procedure was performed under sedation and with transesophageal echocardiography. Brockenbrough needle was used for transseptal puncture through the right femoral vein approach. Contrast-enhanced ventriculography was performed due to the development of bradycardia and hypotension during the procedure. The contrast was observed in the extracardiac area (Figure 1). The patient was taken to the operating room urgently. The patient underwent median sternotomy. After opening the pericardium, hemorrhagic fluid was evacuated. The catheter tip which ruptured the right ventricle was seen (Figure 2). A purse stitch was placed around the catheter and the catheter was withdrawn. The rupture was repaired with 4.0 prolene suture. Mitral valve replacement was performed after bleeding control was achieved. We used 25 mm St. Jude Medical mechanical prosthesis (St. Jude Medical, Inc., St. Paul, Minn.) with 4-0 pledget-supported Ti-Cron sutures (Davis & Geck, Inc., Danbury, Conn.). The operation was terminated without complications. The patient was discharged from the hospital on the 7th postoperative day.

Discussion

PMBV is a safe and effective treatment modality in patients with mitral stenosis, morphologically appropriate and symptomatic. The first successful PBMV was made in 1984 by Inoue (4). The Inoue technique can be widely accepted and used more widely for PBMV (5). General complications of PBMV are acute mitral regurgitation (MR), thromboembolism, and cardiac perforation. Perceptional intervention indication areas are expanding with experience. However, patients who are not eligible for percutaneous intervention are guided to surgical valve replacement or are treated medically in high surgical risk situations.

The most important complications of mitral balloon valvuloplasty procedure are death, shock, severe MR, systemic embolism, cardiac tamponade, emergency surgical need, and acute myocardial infarction. Minor complications are vasovagal reaction, prolonged hypotension, and arrhythmias requiring treatment. The incidence of all these complications is approximately 12% (6). Cardiac perforation followed by tamponade develops in approximately 4% of patients and often causes death during the procedure (6). Significant complications have been seen less frequently in recent years with processor experience and carefully administered septostomy.

In invasive cardiology, transthoracic or transesophageal echocardiography is often used to provide safety and control. It is essential for minimizing the complication rate in the procedure to be performed. Professional support is essential in these types of interventions, such as mitral balloon valvuloplasty, which are more sensitive, and complications are more serious. It is useful to follow the intracardiac catheter location, direction and complications such as perforation. It helps pinpoint exact location with real-time scanning (7). One of the most important issues to prevent complications during the procedure is that the

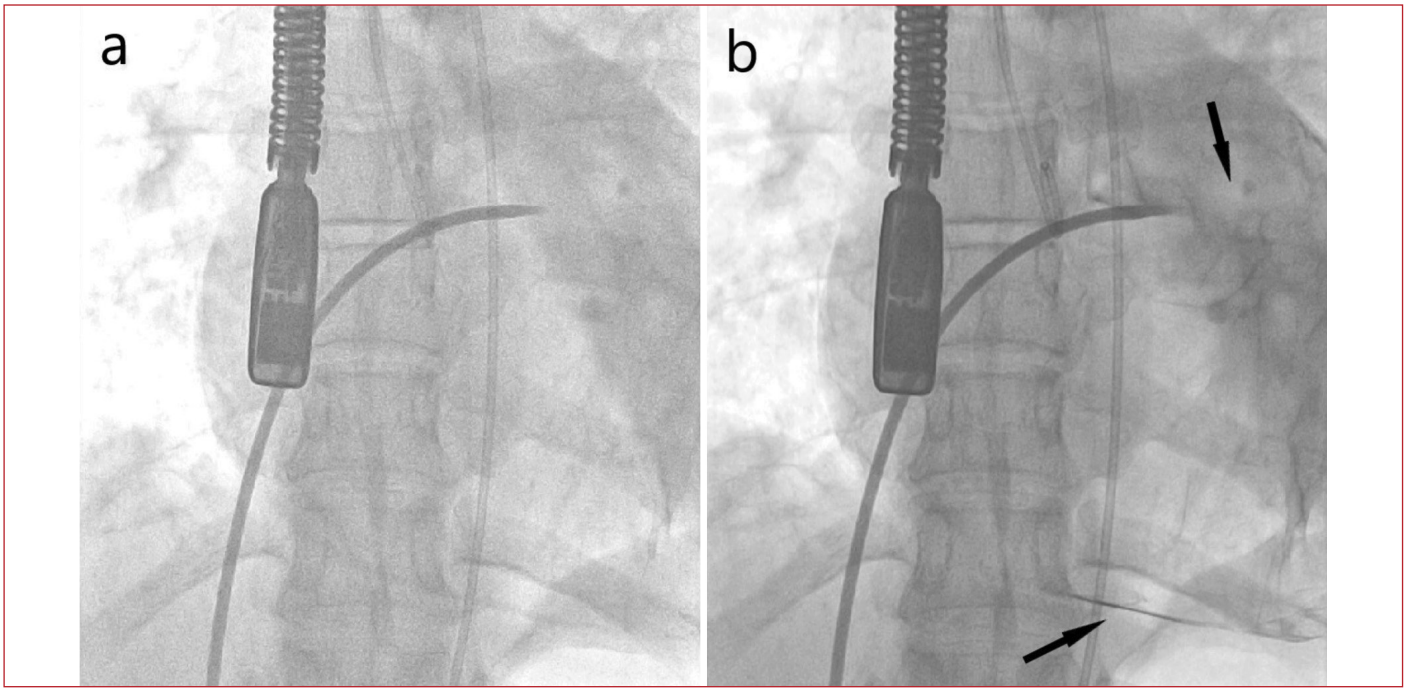

Figure 1. Contrast agent leaks to the extra cardiac area before (a) and after (b) contrast-enhanced ventriculography (arrows)

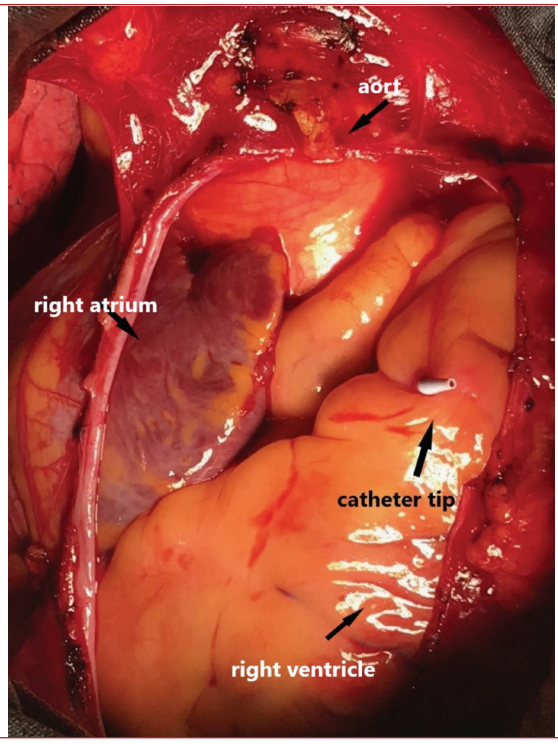

Figure 2. Intraoperative image of the catheter tip causing right ventricular rupture

doctor who performs echocardiography should have sufficient experience.

As shown in our case; mitral balloon valvuloplasty is widely used in patients with mitral stenosis and its never before seen and unexpected complications may occur. The surgical team should always be present against these complications with a high risk of mortality.

Conclusion

As a result of developing technology and minimally invasive methods, transseptal mitral commissurotomy is an effective and still safe method. Due to the low risk of complications after the procedure and its being minimally invasive for the patient, it continues to be preferred today. However, the most important issue to be considered is that the team should have sufficient experience and be able to perform emergency surgical intervention for possible mortal complications.

Ethics

Informed Consent: The patient gave an informed consent to publish the case report without revealing his identity, which was followed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.S., E.D., Concept: H.K., G.A., Design: H.S., Data Collection or Processing: E.D., Analysis or Interpretation: C.G., Literature Search: B.S.Ö., Writing: H.S.

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A rare cause of acute abdomen; paratubal cyst torsion

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ABSTRACT

Paratubal cysts are asymptomatic embryological residues. These cysts are mostly diagnosed in the adolescent and reproductive period. Generally, its dimensions are small, but complications such as rupture, torsion, or hemorrhage may develop. Paratubal cysts are mostly found by chance on ultrasound examination. In this case, we present our 43-year-old patient, who presented with abdominal pain and abdominal distention. In the tomographic examination, it was observed that there was a giant mass in the abdomen, and it was evaluated in our examinations that our patient was anemic. During laparotomy, paratubal cyst was diagnosed and therefore cystectomy and left salpingectomy were performed.

Introduction

Paratubal cysts constitute 10-20% of all adnexial masses and they exist in the broad cord between the ovary and tube. They arise from mesonephric, mesotelial or mesonephric remnants. Even if paratubal cysts have been reported in all female age groups, they are seen mostly in between 20 and 40-year-old women. These cysts have thin walls. Preoperative differential diagnose is very difficult due to the closeness to the ovary. Paratubal cysts are usually small and asymptomatic. However, bigger lesions can reach a size of 20 cm or more and become symptomatic with complications such as torsion, hemorrhage, perforation and neoplasm (1). Most of these cysts are benign; on the other hand, borderline tumors and carcinomas have been reported as well. Smaller lesions can be followed. Bigger lesions, symptomatic lesions and sonographic uncertain findings (septations, papillations, liquid and solid components) are usually investigated surgically. Classic treatment is the enucleation of the cyst from the mesosalpynx without damaging the ovaries and fallopian tubes (2). However, salpyngooopherectomy can rarely be needed in complicated cases (3,4). In this article, we present the management of a patient who had an abnormally large paratubal cyst.

Presentation of Case

Our patient was a 43-year-old female, having 3 gravidities and 3 parities. The main complaint of our patient was abdominal pain which had been lasting for two months. During physical examination, the abdomen was distended and there were general palpational sensitivities.

In the abdominal tomography, a 28x22 cm mass was detected and evaluated as mesenteric cyst, which reached from the epigastric area to the pelvis in abdominal midline superior, to abdominal wall in anterior, to prevertebral area in posterior, to the intestines in lateral areas. And free fluid was seen together with the cyst in inferior. The physical examination and ultrasonographic scan were performed as a result of the consultation of obstetrics and gynecology and no gynecological pathology was evaluated. The patient was evaluated as anemic

in the tests (hemoglobin: 7.74 g/dL, hematocrit: 24.63%). All the other tests including tumor markers were seen in normal limits.

During explorative laparotomy, a purple, about 25-30 cm mass was seen as soon as the abdomen was entered. The mass was seen as left ovarian originated and tortioned. It was detortioned. Then, it was excised with the ovary by fixing its root. Free fluid was seen inside the abdomen and a sample was taken for pathological study. Then, it was aspirated. Inside of the abdomen was washed abundantly with saline. The right ovary and uterus were evaluated as normal. Then a Jacksonpratt drainage was placed in the Douglas cavity. The operation was finished by closing the layers anatomically (Figures 1, 2).

The patient was discharged after pulling the drainage out on the postoperative 5th day. In the pathological study, serohemorrhagic fluid discharge from the cystectomy material was seen. The wall of the cyst was seen as hemorrhagic and brown purple colored. Macrophages full of hemosiderin were seen on the wall of the cyst. When the abdominal fluid was studied pathologically, it was seen as malignancy-negative.

Discussion

Paratubal cyst is a vesicle which is full of liquid and unilaterally growing on the broad ligament between the uterus and ovary. The origin of these tumors can be referred to the ovaries because tubes cannot usually be seen in ultrasonographic examination.

Characteristic ultrasonographic findings such as non-stromal, unilateral cystic mass can help the differential diagnosis of paratubal cyst. Paratubal cysts are assumed that they are originated from the remnants of paramesonephric (mullerian) and mesonephric (wolffian) ducts which exist during urogenital embryologic development.

Paratubal cysts constitute 10% of whole adnexial masses (5). They are not rare, but they are found incidentally because they are usually asymptomatic. Therefore, the real incidence of them is actually unknown. When paratubal cysts are symptomatic, they often appear with unilateral pelvic pain. Symptoms start to appear when the cyst grows extremely, bleeds, and becomes tortioned or ruptured. In our case, the cyst was extremely growing with tortion and hemorrhage.

Paratubal cysts are usually bound to mesosalpynx with a peduncle and tortion can occur around this (6,7). The incidence of paratubal cyst is uncertain but it must be suspected in the patients with acute or intermittent pelvic pain. In most cases, the diagnosis of tortion can be made with only surgical exploration. Malignant neoplasms can sometimes develop in paratubal cysts (8).

The size of paratubal cysts can change between 2 and 20 cm but most of the cases are between 6 and 10 cm (9). Bigger paratubal cysts were reported in the literature (10,11). The size of the cyst was measured as 30 cm and weighted at 4.5 kg in our case.

Treatment options for paratubal cysts can be selected according to the patient's age, parity, existing gynecologic pathologies and neoplastic degeneration. There is no need to intervene or constantly observe for paratubal cysts which have a radius of <10 cm and are seen simple in ultrasound. Surgical treatment of paratubal cyst is simple excision. Giant paratubal cysts are extraordinary masses and they must be treated with laparotomy. Laparoscopic approach is also reliable, but the size of the cyst is a limiting factor.

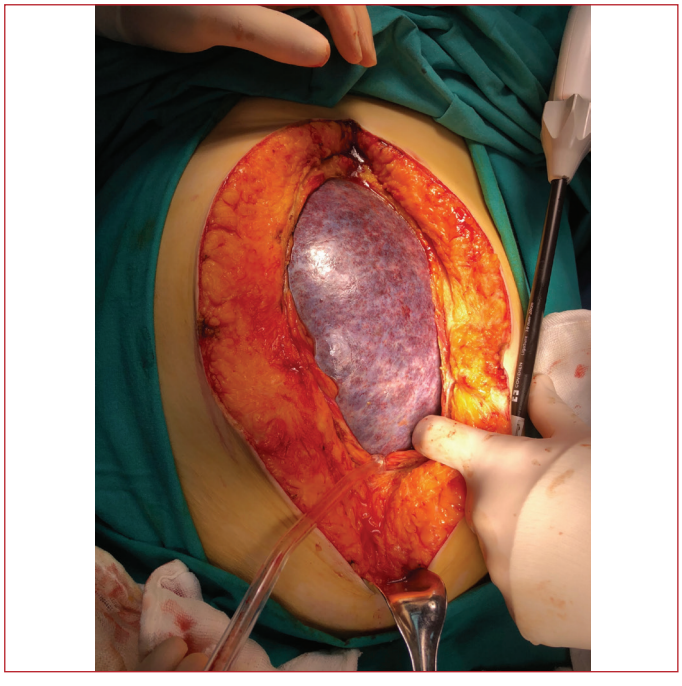

Figure 1. The mass rests against the anterior abdominal wall

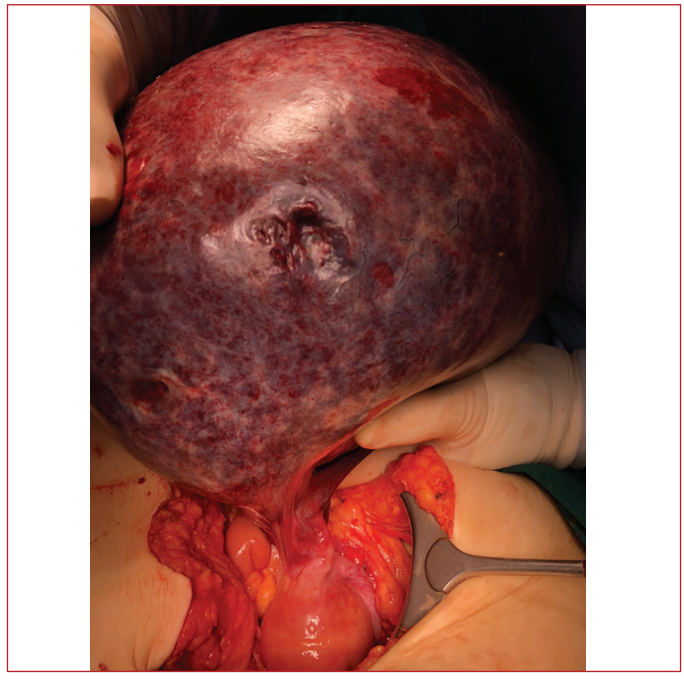

Figure 2. View after mass detortion

Conclusion

Consequently, if there is not any ultrasonographic malignancy criteria in giant cystic masses, paratubal cyst must be considered in differential diagnosis. Cyst excision protecting the ovary is enough in cases without any complications. Salpyngooopherectomy must be performed as well in the tortion cases with circulation disorder and suspicion of malignancy.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.Ş., T.G., Concept: Z.Ş., T.G., Design: Z.Ş., T.G., Data Collection or Processing: Z.Ş., T.G., Analysis or Interpretation: Z.Ş., T.G., Literature Search: Z.Ş., T.G., Writing: Z.Ş., T.G.

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COVID-19 pandemic and dental health care system: An Indian scenario

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Keywords: COVID-19, dentistry, dental professionals

Dear Editor,

In view of the worldwide Coronavirus disease-2019 (COVID-19) pandemic, routine dental procedures have been suspended in most countries in order to avoid virus transmission (1). The major consideration in routine dental practice is the use of aerosol generating procedures using air-rotors, ultrasonic scalers and high pressure 3:1 air syringe. Dentists have a high risk of getting infected from patients and potentially spreading it to their families, other patients and their peers (2). Under these circumstances, it is natural for dentists to develop a fear of being infected by their patients (2). Due to increased contagiousness of SARS-CoV-2, dental healthcare providers have to adopt new protocols to prevent spreading the virus.

On March 17th, 2020, the Dental Council of India (DCI) issued an advisory that clinical procedures involving aerosol generation such as Air rotor/Ultrasonic Scalers to be avoided/minimized for the time being and only emergency procedures to be performed (3). Local health authority protocol was different in various states of India. Total closure and telemedicine were suggested. During the lockdown period, most dentists continued their services such as initial consultation and expert opinion to their patients through teledentistry for free of cost. Emergency dental services were provided at hospital settings.

Indian Dental Association (IDA) also highlighted the need to provide task-specific education and training on preventing transmission of infectious agents, including refresher training for all dental personnel (4). The IDA local branches, different state branches and IDA head office arranged webinars for dentists to familiarize them with infection control measures and practice management post lockdown.

Dental professionals in India faced difficulty in the procurement of personal protection equipment due to its unavailability and cost factor. Due to complete closure of dental clinics, private dental practitioners faced financial issues. In order to follow the pre-operative and post-operative infection control protocols, dentists had to invest extra on practice modifications to combat coronavirus disease.

The Ministry of Health and Family Welfare (MoHFW), Government of India, issued guidelines for Dental Professionals regarding COVID-19 pandemic situation on May 19th, 2020. The guidelines have mentioned that dentists, auxiliaries and dental patients are at high risk of cross-infection due to close contact with the patient's oral cavity, saliva, blood, and respiratory tract secretions. Unified guideline was issued by MoHFW because several guidelines were issued by DCI, IDA and other organizations earlier. Dentists were not sure which guidelines to follow. The dental clinics were advised to remain closed in the containment zone and to continue with teledentistry. In the red zone, emergency dental procedures could be performed. The dental clinics in orange and green zone were allowed

to provide dental consultations and to do only emergency and urgent treatment procedures. All routine and elective dental procedures to be deferred for a later review until new policy/ guidelines were issued (5).

Even though dentistry has been worst hit by COVID-19 pandemic, dental professionals need to stay proactive, composed and provide patients with the best dental care. Most of the dental clinics in India are private establishments and professionals are self-supported. In addition to regular expenditure such as rent of clinic, repayment of loan for clinical establishments, equipment and material cost, lab costs, salary to support staff, utility bills dentists have to invest extra for personal protection equipment and disinfectants to avoid possible spread of COVID-19. This inevitably has to be transferred to patients, which will lead to increase in the cost of treatments. However, dentists find it difficult to raise prices for their low and middle income group of patients. The government advisory recommends only emergency dental treatments in the near future, which will definitely deteriorate financial status of dentists. Considering the overall downfall of economy, general public will also tend to opt for absolutely necessary dental treatments even after the lockdown period. Almost after two months of dilemma, fear and uncertainty, dental professionals have geared up, equipped themselves, and trained themselves to face the new challenge.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.H., Concept: S.H., Design: S.H., Data Collection or Processing: S.H., Analysis or Interpretation: S.H., V.A., Literature Search: S.H., Writing: S.H., V.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Comment on "The effect of maternal obesity on the success of labor induction with a cervical ripening double-balloon catheter and on pain perception during catheter insertion"

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Keywords: Maternal obesity, cervical ripening, balloon catheter

Dear Editor,

We are pleased to read the article "The effect of maternal obesity on the success of labor induction with a cervical ripening double-balloon catheter and on pain perception during catheter insertion" (1) by Kınay et al. (1) in Gülhane Medical Journal. In their study, the authors aimed to determine the impact of maternal body mass index (BMI) on the success of labor induction with a cervical ripening double-balloon catheter and to evaluate pain perception during catheter insertion. They also checked the cesarean delivery rates, normal delivery rates within 24 hours of labor induction, and visual analog scale pain scores during double-balloon catheter insertion between the women with a BMI at or above 30 kg/m^2 and women with a BMI <30 kg/m^2.

This study is important since it evaluates and provides data for the mechanical cervical ripening and pharmacological cervical ripening agents have some drawbacks due to side effects.

It will be nice if the authors have a chance to compare single balloon systems with double balloon systems in their future studies, since single balloon systems may be economically more convenient (2) and more readily available in limited source settings.

Also, it would have been nice to see whether the outcomes of the study would be different if BMI stratifications of normal (BMI: 18.5-24.9), overweight (BMI: 25-29.9), obese (BMI: 30-39.9) and very obese (BMI: over 40) had been used, rather than only non-obese and obese stratification. Of course, this would necessitate a higher number of participants.

As for the pain scores in the study, it has been mentioned by Torensma et al. (3) that some obese patient groups have lower pain thresholds, and some have higher pain thresholds, and Kınay et al.'s (1) study adds valuable data to the current literature.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.N.S., K.E.K., Design: E.N.S., K.E.K., Data Collection or Processing: E.N.S., K.E.K., Analysis or Interpretation: E.N.S., K.E.K., Literature Search: E.N.S., K.E.K., Writing: E.N.S., K.E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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