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Palliative Surgery in General Surgery Clinics

Genel Cerrahi Kliniklerinde Palyatif Cerrahi

Adem AKÇAKAYA

Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

My dear readers,

In this issue, I will talk about palliative surgery, which is a problem in general surgery clinics and is difficult for both patients and their relatives, as well as physicians.

Palliative surgery is defined as "surgery performed to provide symptom control and improve quality of life in patients in whom there is no curative surgery option". While curative surgery refers to the complete removal of diseased tissues, even microscopically, especially in patients with cancer, the aim of palliative surgery is to eliminate symptoms (1).

In the past, surgery was avoided in elderly patients with poor general condition and low life expectancy. Today's medical advances have made it possible to perform surgeries safely in these patient groups. The view that the treatment came to an end in patients with no life expectancy was reconsidered with the updates in the definition of palliative care, and the view that treatments, interventional methods and palliative surgery applications to increase the quality of life should widely used became widespread.

In palliative surgery, it is aimed to increase the quality of life of the patient with a wide range of interventions including debulking in large tumors, creating ostomy, ablation and stent placement in occlusions. The method to be chosen is closely related to the clinical experience of the surgeon. When making the decision for palliative surgery, many factors such as the histopathological structure of the cancer or mass, its extent, the age of the patient and the estimated survival time, the severity of the symptoms and their effects on the patient, and the preference of the patient and their relatives are evaluated (2).

Although there is a large group of patients who need palliative care, in this article, I will mainly talk about palliative surgery to be applied to patients with cancer. Palliative surgery in patients with cancer is performed to relieve or remove an obstruction in the digestive tract caused by the tumor, to relieve pain by interrupting the transmission of pain signals, to puncture or shunt to correct acid-related symptoms, to prevent weakened bone fractures or to detect fractures (1). In addition, interventions for perforations, obstructions, passage problems, fistulas and bleedings are also within this scope. Palliative surgery is also applied in enteral nutrition and pain control. The devoted work of an experienced surgeon, oncologist, radiologist, interventional radiologist, anesthesiologist, intensive care doctor, gastroenterologist, neurologist, infectious diseases specialist, clinical dietitian, nurse, anesthesia technician and health personnel in the palliative surgery team is important. The right decision and successful result can be achieved by the team's harmonious and cooperative work (3).

Clinical, laboratory, imaging, endoscopy and laparoscopy findings are evaluated in detail before palliative surgery. If there is a tumor that can be removed in the local control of the disease, it is removed, feeding tubes are placed, ostomy is created. Endoscopy is used or interventional radiologist is consulted to stop bleeding. In pain control, interventions such as removal of the mass causing pressure and pain, sympathectomy and injection into the nerves can be performed. The surgical procedure usually includes resection, reconstruction, functional repair, drainage or biopsy. Although different rates were reported, it was reported in a study that 12.5% of all surgical interventions were palliative surgeries (4). In a study conducted in a cancer center, 40% of all surgical

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consultations were made for palliative surgical evaluation, and 43% of palliative patients underwent surgery and 17% of them underwent other procedures (5). In another study, it was reported that while palliative surgeries constituted 13% of all surgeries, they constituted 21% of all cancer surgeries (6). When palliative surgery was performed in the general surgery clinic, the mortality rate was found to be 24.5%. The average hospital stay was 12.4 days (0-99 days). The 30-day mortality rate was found to be 12.2% (3).

No surgical intervention is risk-free. Due to the high morbidity and mortality rates, the risk is even higher in palliative surgery. The most difficult stage in palliative surgery is the decision of surgery or intervention. While making this decision, the surgeon's dilemma is frequently experienced by the patient and their relatives. When patients are told about the complications and risks of surgery, 15.7% found the intervention risky (6). Surgical intervention for palliation is inevitable and often requires urgent intervention when the patient develops life-threatening bleeding, perforation, intestinal or biliary tract obstruction. Even for palliative purposes, surgical methods such as organ resection, amputation, bypass, ostomy creation, and drainage may be mandatory (3).

Palliative surgery indications in general surgery in end-stage patients include malignant intestinal obstruction, acute abdomen, bowel perforation, debridement, abscess drainage, gastric outlet obstruction, wound/fistula-related discharge, biliary tract obstruction, malignant acid, and tumor-related bleeding. I would like to briefly mention some of them.

Malignant Bowel Obstructions and Ileus

Intestinal obstruction due to malignancy and ileus are the most common indications in palliative surgery. Intestinal obstructions are most common in ovarian and colorectal cancers, but may also occur with other abdominal and non-abdominal malignancies. Intestinal obstruction due to malignancy may be due to tumor, treatment, adhesions or benign causes such as internal hernia. The fastest, safest and most effective procedure should be preferred in removing the blockage. Obstructions that cannot be relieved by conservative treatments such as nasogastric decompression, hydration and discontinuation of oral intake should be considered as evidence of complete obstruction and surgery should be planned. Surgery may not be performed in 6.2% to 50% of patients due to operative risk or surgical contraindications (7).

Poor prognostic indicators of the patient include ascites, carcinomatosis, palpable intra-abdominal masses, multiple bowel obstructions, previous bowel obstructions, general poor performance, and presence of very advanced disease. Intestinal obstruction is an indication of recurrence in some patients and progression of the disease in some patients. While tumor on the peritoneal surface may cause edema or adhesion, damage to autonomic nerve plexuses as a result of tumor infiltration of the mesentery may cause adhesion, radiation fibrosis, metabolic disorder, sepsis and ileus. Pancreatic carcinomas can cause stomach stasis. In case of complete obstruction, there is no gas and stool discharge. Patients should be hospitalized and nutritional and hydration support should be provided. Medical treatments and minimally invasive interventions are required. Stenting, surgical resection and creation of ostomies for decompression can be applied.

Acute Abdomen

All of the pathologies characterized by sudden onset of abdominal pain, the signs and symptoms of which are concentrated in the abdomen, and develop due to non-traumatic causes are grouped under the heading of "acute abdomen". Acute abdomen is examined under three main headings as surgical pathologies, medical pathologies and extra-abdominal pathologies. Acute abdomen can occur for many reasons such as acute appendicitis, gallstones, small bowel obstruction, ureteral stones, gastritis, peptic ulcer perforation, gastroenteritis, acute pancreatitis, diverticulitis, obstetric and gynecological diseases(1). Gastrointestinal obstruction and perforation, abscess, peritonitis, fistula-related infections and, more rarely, bleeding are seen as life-threatening acute abdominal pathologies in patients with advanced cancer. In these patients, tumor-related acute abdomen may occur, as well as bleeding and intestinal perforations due to anti-angiogenic agents used in the treatment (4). The cause of acute abdomen is very important in planning surgical intervention. For this reason, the cause should be determined first and the surgical decision should be made with multidisciplinary consultations. All possible risks of the acute abdomen and the intervention to be performed should be shared with the patient and their relatives.

Perforation

Biochemical or functional ileus should be considered in the absence of colic abdominal pain with acute abdominal symptoms. Persistent pain may be directly related to the tumor. Intestinal perforation should be considered if there are signs of abdominal distention or peritonitis. While perforation of primary gastrointestinal tumors is common, it is less common in metastatic diseases of the abdominal or pelvic cavity. Perforations occur in the small intestine, colon, and stomach, respectively. The prognosis is worse in metastatic patients. **Typhilitis** (neutropenic enterocolitis), a syndrome involving intestinal inflammation, edema, and thinning of the proximal large bowel wall encountered in patients with neutropenia and receiving chemotherapy and, is a condition with high mortality. Constipation is common in palliative care patients. Intestinal perforation may also develop in stercoral ulcers resulting from this.

The aim of the surgery in end-stage patients is to alleviate the pain caused by intestinal perforation, to eliminate sepsis, and to control the perforated area in order to continue oral nutrition.. Instead of having a curative purpose in emergency intervention,

it should be preferred to perform surgery that will provide the patient's comfort quickly, eliminate life-threatening factors, and require less intervention such as ostomy. Studies indicate that surgical intervention may be preferred in patients with young age and normal albumin levels (8).

Debridement

Debridement is the process of removing necrotic tissue from the area with ulcer to reduce infection and inflammation, provide odor control, and increase patient comfort. Autolytic, mechanical, enzymatic, biological and surgical debridements can be performed. The risk of infection is effective in determining the surgical method to be chosen in these patients.

The immune system is weakened in palliative care patients mostly due to primary disease and nutritional deficiencies. The patient needs supportive treatments to fight the infection. The risk of infection is also a determinant in planned palliative surgical procedures. If possible, minimally invasive methods with the least risk of infection should be preferred. For example, in a study on malignant bowel obstruction surgeries, it was found that surgical site infections were less common in laparoscopic surgeries compared to open surgeries (4% versus 32%) (5).

Pressure sores are one of the most common problems in palliative care, plaguing both patients and healthcare professionals. In addition, extravasation of chemotherapeutic drugs during administration may cause tissue irritation, ulceration, necrosis, nerve damage and, rarely, problems that can progress to extremity loss.

Minimally Invasive Procedures

Surgical interventions should be as simple as possible, risky and major surgeries should be avoided. Because each intervention may cause complications that disrupt the patient's comfort of life. The procedures to be applied should be discussed with the patient and their relatives, and the decision should be made together. The patients and their relatives should know that the interventions are not for prolonging life or curative purposes, they should understand the possible complications, and the procedures they do not approve should not be performed. At this stage, it should be aimed to ensure the comfort of the patient with the simplest possible procedures, and minimally invasive interventions for palliative purposes should be preferred before surgery. In tumors that cannot be removed, endoluminal laser ablation, radiofrequency ablation, and embolization should be performed. Shunts should be applied in acid deposits in the abdomen. Excessive amount of acid formation in the abdomen affects the mobilization of the patient and may also cause abdominal compartment syndrome and inferior vena cava syndrome. In patients in whom medical treatment is insufficient, interventional procedures may be required. In the treatment, a sequence should be followed systematically, and if unsuccessful, the next stage should be tried. The least invasive method possible should be chosen to solve the problems of the patients. For malignant intestinal obstruction, endoscopic procedures may be preferred, especially in those with low life expectancy. The success of metallic stents is higher than the success of latex and silicone drains. Because the risk of migration, perforation and occlusion is lower in metallic stents. Duodenum and colon may be suitable for stenting, but jejunum and ileum are not suitable for stenting (3). Patients should be informed that endoscopic procedures may need to be repeated (5). The primary physician of the patient should strive to improve the quality of life as much as he or she values vital parameters.

In order to ensure a peaceful and beautiful death when it is inevitable, multidisciplinary teamwork should be done and communication with the patient and their relatives should be maintained at every step (3).

The morbidity in palliative surgery ranges from 25% to 40%. When it comes to symptom control, 80-90% of patients achieve good symptom relief. It has been reported that symptom reduction is achieved at a high rate in patients with breast cancer and sarcoma, and at a moderate rate in patients with hepatobiliary cancer (9). Since the patient may lose the ability to make decisions for a while after palliative surgery, it is important to clarify the desired outcome from the patient's point of view before the surgery, the treatments that patients want to endure to achieve these results, and the results that they will find unacceptable after surgery, such as being on a long-term ventilator (10). The decision to continue palliative care and at which stage to perform palliative surgery should be made with a multidisciplinary approach and consensus, including the relatives of the patient. Rather than the priorities of the physician, the expectations and priorities of the patients and their relatives should be determined and a road map should be drawn accordingly.

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Original Article

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Revisiting Myocutaneous Flaps as a Reliable Option for Reconstruction of the Oromandibular Region: An Algorithmic Approach

Güvenilir Bir Seçenek Olarak Miyokütan Fleplerin Oromandibuler Bölge Rekonstrüksiyonu için Yeniden Değerlendirilmesi: Algoritmik Yaklaşım

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ABSTRACT

Objective: Reconstruction of extensive, composite oromandibular defects using osteocutaneous free flaps has become the gold standard procedure over the past two decades, although such reconstruction is associated with severe morbidity in certain patients. In such patients, soft-tissue flaps may be a better option, being associated with less donor-site morbidity but acceptable functional results.

Methods: Seventeen patients were followed up for at least two years. Patients with mid-anterior segmental mandibular and posterior mandibular defects, who underwent reconstruction using boneless, pedicled or free myocutaneous flaps were evaluated in terms of flap failure and overall morbidity.

Results: Five of 7 patients in the pedicled flap group and six of 10 in the free flap group had comorbid diseases that were both severe and more numerous in the pedicled flap group. Four of 17 patients lacked a significant clinical sign affecting the surgical choice. In seven patients, primary reconstructions using pedicled or free flaps were performed. In 10 cases, the reconstructions were salvage procedures. Tumor recurrence or osteoradionecrosis developed in six of the 17 cases. The complication rates were 5/7 in the pedicled flap group and 3/10 in the free flap group.

ÖZ

Amaç: Osteokutanöz serbest flepler kullanılarak kapsamlı, kompozit oromandibuler defektlerin rekonstrüksiyonu son yirmi yılda altın standart prosedür haline gelmiştir, ancak bu rekonstrüksiyon bazı hastalarda ciddi morbidite ile ilişkilidir. Bu gibi hastalarda, yumuşak doku flepleri daha az donör bölge morbiditesi ve kabul edilebilir fonksiyonel sonuçlar ile daha iyi bir seçenek olabilir.

Yöntemler: On yedi hasta en az iki yıl takip edildi. Kemiksiz, pediküllü veya serbest miyokütan flep kullanılarak rekonstrüksiyon yapılan orta-ön segmenter mandibuler ve posterior mandibuler defekti olan hastalar flep sağkalımı ve genel morbidite açısından değerlendirildi.

Bulgular: Pediküllü flep grubunda 7 hastanın beşinde ve serbest flep grubunda 10 hastanın altısında komorbid hastalık bulunmaktaydı. On yedi hastanın dördünde cerrahi yöntemi etkileyen önemli bir klinik bulgu yoktu. Yedi hastada pediküllü veya serbest flep kullanan primer rekonstrüksiyonlar yapıldı. On olguda rekonstrüksiyonlar kurtarma prosedürleriydi. On yedi olgunun altısında tümör nüksü veya osteoradionekroz gelişti. Komplikasyon oranları pediküllü flep grubunda 5/7 ve serbest flep grubunda 3/10 idi.

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Conclusion: Soft tissue flaps are a suitable option that can be used in posterior and/or posterolateral defects in primary reconstruction or secondary salvage procedures.

Keywords: Boneless, myocutaneous flap, musculocutaneous flap, oromandibular, reconstruction

Sonuç: Yumuşak doku flepleri primer rekonstrüksiyon veya sekonder kurtarma prosedürlerinde posterior ve/veya posterolateral defektlerde kullanılabilecek uygun bir seçenektir.

Anahtar Sözcükler: Kemiksiz, miyokütan flep, muskulokütan flep, oromandibuler, rekonstrüksiyon

Introduction

Reconstruction of oromandibular defects using osteocutaneous free flaps has been the gold standard procedure for the past two decades (1). Many modifications of fibular flaps have been described. Today, virtual surgical planning and computer-aided design and manufacture are valuable innovations (2,3). When treating patients with advanced cancer who require postoperative radiotherapy, in whom bony reconstructions have failed, or patients in poor general health with short life expectancies, complex reconstruction procedures such as placement of free, vascularized bony flaps are best avoided. In such patients, techniques that allow rapid recovery, oral competence, and minimal donor-site morbidity are preferred (4). Soft-tissue-only flaps are also useful for patients with large defects secondary to temporomandibular joint (TMJ) resection (5). Some other indications for the use of soft-tissue-only flaps may include the lack of suitable bone donor sites, or prior vanishing bone disease (6-9). There are vascularized bone reconstruction examples in the literature after giant ameloblastoma resections (10). In this study, we also suggest that posterolateral defects with a history of giant ameloblastoma resection can be an indication for soft tissue only flaps.

Although anterior oromandibular defects should be reconstructed with osseous flaps to maintain rigidity; to obviate the development of an Andy Gump deformity; and to prevent airway collapse, facial distortion, and leakage of liquid through the oral commissure; the functional morbidity in patients with composite segmental mandibular defects is attributable to the loss of the soft-tissue lining rather than the bone defect per se. Therefore, reconstruction of such defects using soft-tissue flaps, such as a pedicled latissimus dorsi or free rectus abdominis flap, rather than osteocutaneous flaps, is a form of boneless reconstruction. Such procedures are commonly termed salvage procedures, and are easier, safer, and quicker than bony reconstruction, imposing less stress on the patient. Compared with the placement of bony flaps, these procedures require less surgical time, better obliterate dead space, form a better lining, and prevent orocutaneous fistula formation more reliably. Boneless flaps are also thought to be more resistant to radiotherapy than bony flaps (5,11-16).

The literature does not describe the boneless reconstruction of extensive oromandibular defects using only soft-tissue flaps in any detail. Pedicled latissimus dorsi myocutaneous (LDMC) flaps and trapezius myocutaneous flaps have been placed during salvage procedures in patients requiring head-and-neck reconstructions (6,17). We discuss the advantages of such procedures not only in terms of salvage, but also (in selected cases) as a form of primary reconstruction.

Methods

Seventeen patients with oromandibular defects reconstructed using soft-tissue flaps between 2011 and 2016 have been retrospectively evaluated. Patients with traumatic mandibular defects were excluded. In addition, two patients exhibiting prior osteocutaneous free flap failure were not shown in the free flap group, but rather in the pedicled flap group. Therefore, none of the patients were mentioned in both groups. All defects were attributable to tumor resection or radionecrosis. Both free and pedicled musculocutaneous flaps were used for primary reconstruction or salvage.

Table 1 lists patient demographic features, including age and gender, etiological factors, the locations of the defects, preoperative status, comorbidities, surgical preferences, duration of operations and hospitalization, complications, and secondary surgical procedures.

Defects were located in the posterior mandible in 6 patients (pedicled LDMC flaps were placed in 4 patients and free vertical rectus abdominis myocutaneous [VRAM] flaps in 2); the posterolateral mandible in 6 patients (pedicled LDMC flaps were placed in 3 patients and free VRAM flaps in 3); the anterior segmental mandible in 1 patient (reconstructed using a free VRAM); and the anterolateral mandible in 4 patients (free VRAMs were placed in all patients).

The choice of a soft-tissue rather than a vascularized bone flap was made after a detailed evaluation of all patients. The subcutaneous transfer technique was used when placing all pedicled LDMC flaps (17). All free soft-tissue flaps were VRAM flaps. Patients with segmental defects (i.e., the condyle and part of the ramus were intact) or posterior defects that included the condyle were usually reconstructed using soft-tissue flaps unless the cosmetic outcome was the overriding consideration.

Patients were followed up for at least 2 years (range: 24-40 months) because of oncological issues or the need for post-irradiation assessment. The success of soft-tissue flap placement in terms of mandibular reconstruction was evaluated by scoring flap failure, overall morbidity, and cosmetic outcomes.

Since the study was a retrospective observational analysis, no comparative statistics were done at this point. However, descriptive statistical analysis was performed.

This study was approved by Kemalettin Yıldız and all participants signed an informed consent agreement.

Results

The mean patient age was 59.17 years (range 25-76 years). The mean age of patients receiving LDMC flaps was 57.5 years, and that of patients receiving free flaps was 60.3 years. Although the means of ages were similar in the two groups, both of the patients aged <40 years were in the pedicled flap group. Five of 7 patients in the pedicled flap group had comorbidities, and 6 of 10 in the free flap group. The comorbidities were more severe and more numerous in the pedicled flap group.

Preoperatively, only 4 of the 17 patients (2 in either group) lacked a clinical sign that influenced the choice of surgery. Three patients had edentulous mandibles. Seven patients underwent primary reconstructions using pedicled or free flaps. In 10 patients, the reconstructions were salvage procedures. Among 3 patients with the failure of free flaps, 2 underwent pedicled flap reconstruction and 1 underwent free flap surgery. Tumor recurrence or osteoradionecrosis developed in 6 of the 17 patients (2/7 in the pedicled group and 4/10 in the free flap group).

The complication rates were 5/7 in the pedicled flap group and 3/10 in the free flap group. In the pedicled flap group, neck wound dehiscence secondary to radiotherapy was observed in 2 patients. The flap-associated complications were partial necrosis in 1 patient who died in the early postoperative period, and seromas at the LDMC flap donor sites of 3 patients. In the free flap group, neck wound dehiscence (n=2) and skin necrosis (n=1) secondary to radiotherapy were observed. Wound dehiscence was also evident at one free flap donor site.

Flaps used in ultimate reconstruction survived; partial loss of the externally oriented part of the skin island of a pedicled latissimus dorsi flap was observed in only 1 patient, and the flap healed after careful debridement. The mean operative time (combined resection and reconstruction) was 7.1 h.

The etiologies of the defects were radionecrosis developing after treatment of nasopharyngeal carcinoma in 1 patient, ameloblastoma in 2 patients, mesenchymal sarcoma in 4 and squamous cell carcinoma in 10 patients. The mean age was 57 years (range: 25-78 years). Five patients were aged >60 years, and 2 patients were young. In a 25-year-old patient with radionecrosis, the skin paddle of the pedicled latissimus dorsi flap was attached both intra- and extra-orally via de-epithelialization of the intermediate region (Figure 1). In the other young patient, a free VRAM flap was preferred (Figure 2). A late postoperative assessment is shown in Figure 3.

The mean hospitalization time was 16.8 days. The mean hospitalization time of patients receiving LDMC flaps was 17.5 days, and that of patients receiving free flaps was16.3 days. Detailed data of the patients are listed in Table 1.

The cosmetic and dental occlusion outcomes varied. The mandibular angle was usually blunted, and 4 patients required secondary procedures to reduce flap or pedicle bulk. In most of thepatients, revision surgery was performed under local anesthesia in an out-patient setting. When teeth were present, some malocclusion was always in play as one condyle was missing. However, this was well-tolerated by all patients. Malocclusion is not a priority compared with the other possible morbidities.

Discussion

Boneless mandibular reconstruction of posterior defects has been reported previously (4,5,11,12,14,16,18). Cordeiro and Disa (18) developed an algorithm that considered the number of zones adjacent to the mandibular defect. Intraoral defect reconstruction was assigned the highest priority; soft-tissue flaps afforded favorable results (18). Although malocclusion was not evaluated in the cited work, we were also of the view that the priority was the reconstruction and that occlusion problems were less important. We propose that free VRAM flaps and pedicled LDMC flaps should be placed in selected patients with oromandibular defects.

The immediate reconstruction of mandibular defects using vascularized bone has become widely accepted as the gold standard procedure over the past two decades. With the accumulation of surgical experience, the failure rate, and complications and morbidity associated with reconstruction have decreased (1,19). However, the risk of failure after reconstruction using vascularized bone remains significantly higher than that associated with the use of soft-tissue flaps because flap orientation is determined by alignment of the bone rather than optimal positioning of the pedicle (4). Further, patients who are reconstructed using soft-tissue alone experience less postoperative pain and recover more quickly. Such considerations are important when treating patients with head-and-neck cancer, many of whom require subsequent adjuvant therapy or have short life expectancies (6). Although, in theory, it is preferable to replace absent mandibular tissue with "like" (vascularized bone), we are of the view that this is not mandatory if the defects are entirely posterior.

Patients with head-and-neck cancer in poor general health who require several resections of oral soft tissue and the mandible have low long-term survival rates. In many cases, surgery is not appropriate because of systemic disease and/or a history of heavy tobacco, alcohol, or drug use. Their nutritional status may also be impaired, either because of alcoholism or because the tumor interferes with alimentation. Thus, the extent and complexity of surgical procedures should be minimized in such patients. We prefer to place soft tissue-only flaps in such patients because many patients with advanced cancer require postoperative radiotherapy. In such patients, it may be critical to minimize the time that elapses between surgery and adjuvant therapy to ensure long-term treatment success. Less complex reconstructions are thus appropriate, being associated with minimal peri- and post-operative complications.

Prior bony flap reconstructions failed in some of our patients who were in poor general health and had short life expectancies. Under such circumstances, salvage procedures should be used to cover vital organs and to deal with complications caused by post-surgery defects and radiotherapy.

Table 1. The data of the patients including age and gender, etiological factors, the locations of the defects, preoperative status, comorbidities, surgical preferences, durations of operation and hospitalization, complications, and secondary surgical procedures are shown

Patient number	Age (years) gender	Etiology	Defect location	Preoperative status	Co-morbidity	Surgery	Op time (hours)	Complication	Secondary surgery	Hospitalization (days)
1	39 y/M	Ameloblastoma	Posterior		Bipolar disorder	Pedicled LD	3 h			12
2	25 y/M	Nasopharengeal Ca (ORN)	Posterior	RT (ORN)*		Pedicled LD	4 h	Wound dehissence (neck region)	None (secondary healing)	18
3	60 y/M	Mesenchymal sarcoma	Posterior-lateral	Post fibula flap (RT &TR)	HT	Pedicled LD	6 h	Wound dehissence (neck region)	None (secondary healing)	28
4	61 y/FM	Ameloblastoma	Posterior	FFF	CRF, HT, DM	Pedicled LD	6 h	Partial flap necrosis, seroma	Debridement	14 (exitus)
5	69 y/M	Mesenchymal sarcoma	Posterior-lateral	FFF	DM, HT	Pedicled LD	3 h	Seroma, hematoma		22
6	76 y/FM	SCC	Posterior-lateral	Edentulous	COP, HT	Pedicled LD	6 h	Seroma	Flap debulking	17
7	73 y/M	SCC	Posterior		COPD, DM, HT	Pedicled LD	5 h			12
8	64 y/M	SCC	Anterior	Post fibula flap (RT & TR) anterior fistula		Free VRAM	7 h			14
9	68 y/FM	SCC	Posterior		HT	Free VRAM	6,5 h		Flap debulking	10
10	62 y/M	SCC	Antero-lateral	ORN (post fibula flap RT)	HT	Free VRAM	7 h	Wound dehissence (neck region)	Debridement	25
11	66 y/FM	Mesenchymal sarcoma	Posterior-lateral	Edentulous		Free VRAM	6 h			12
12	63 y/M	SCC	Posterior		HT	Free VRAM	6 h		Flap debulking	14
13	59 y/M	Mesenchymal sarcoma	Antero-lateral	Post fibula flap (RT & TR)		Free VRAM	8 h	Partial skin necrosis and Wound dehissence (neck region)	Debridement and STSG	28

Table 1. Continued

Patient number	Age (years) gender	Etiology	Defect location	Preoperative status	Co-morbidity	Surgery	Op time (hours)	Complication	Secondary surgery	Hospitalization (days)
14	62 y/FM	SCC	Posterior-lateral	Edentulous	DM	Free VRAM	6 h	Wound dehissence (donör area)	None (secondary healing)	11
15	58 y/M	SCC	Antero-lateral	ORN (post fibula flap RT)	HT	Free VRAM	7,5 h		Flap debulking	16
16	56 y/FM	SCC	Antero-lateral	FFF, anterior fistula	DM, HT	Free VRAM	6 h			19
17	45 y/FM	SCC	Posterior-lateral			Free VRAM	6,5 h			14

SCC: Squamous cell carcinoma, RT: Radiotherapy, ORN: Osteoradionecrosis, TR: Tumor recurrence
FFF: Free flap failure, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure

Anterior mandible defects require placement of rigid osseous flaps to prevent the development of the Andy Gump deformity, airway collapse, drooling, and facial distortion. However, if the defects are lateral or posterior, it is not essential to reconstruct the bony mandible; soft-tissue flaps alone are useful in certain scenarios (4,5,11,12,14,18). Thus, we propose the use of an algorithmic approach when evaluating anterior mandibular defects. In the absence of prior free flap failure, osteoradionecrosis, a need for radiotherapy, and tumor recurrence, we use a free fibular osteocutaneous flap. If one or more of these conditions is present, we prefer to use a free rectus myocutaneous flap. Finally, if any one (or more) of these conditions is combined with a medical comorbidity, we choose a pedicled pectoralis myocutaneous flap for reconstruction of the anterior defect (Figure 4).

In terms of posterior mandibular defects, we prefer to use a free VRAM flap in the absence of prior free flap failure, osteoradionecrosis, a need for radiotherapy and tumor recurrence. If one (or more) of these conditions is present, we place a pedicled LD flap. We propose that osteocutaneous free flaps should be placed in patients with postero-lateral defects if all of the conditions mentioned above are absent, and the patients are dentulous. However, if one (or more) of the conditions is present and the patient is edentulous, we choose a free VRAM flap. Finally, if one (or more) of the conditions is present together with a comorbidity, we prefer to use a pedicled LD flap (Figure 4).

An anterolateral thigh flap may serve as a second flap during double-flap reconstruction or as a single bulky flap when some of the vastus lateralis muscle is also harvested. Donor site deformities and morbidities are higher when the flaps include muscle and large skin islands.

In patients with comorbid disease, those who have undergone prior irradiation, those for whom recipient vessels are not available, and those with recurrent disease who will not survive for long, we propose that a pedicled latissimus dorsi flap should be used to obliterate the defect and close the floor of the mouth and crucial neck tissues such as the carotid artery and the jugular veins. This is a salvage procedure.

In patients who are more stable oncologically and medically, we propose the placement of a VRAM flap. This affords many advantages. The long pedicle can cover posterior defects. The versatility of the flap allows reconstruction of multiple areas, and the bulky tissue obliterates large composite defects while providing stable soft tissue tolerant of adjuvant irradiation and possible later revision.

Patients who lack a posterior mandible are usually of near-normal appearance and have acceptable oral function provided that the anterior mandible is located in the correct anatomical position, and the oral lining is adequate (16). Problems arise only when the angle of the jaw loses definition or the TMJ is non-functional. Such prostheses are associated with high long-term complication rates and do not restore the mixed gliding and hinge functions of the original TMJ. However, if the defect

Figure 1. The use of pedicled latissimus dorsi myocutaneous flap in osteoradionecrosis (Case 2 in Table 1)

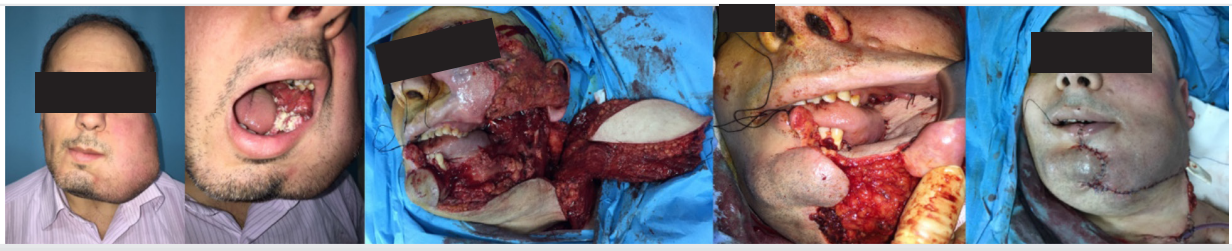

Figure 2. The use of free VRAM flap in the reconstruction (Case 17 in Table 1)
VRAM: Vertical rectus abdominis myocutaneous

is segmental in nature, and the original condyle can be preserved, vascularized bone reconstruction may restore normal mandibular function and is usually the first option considered. As explained above, this may be associated with unacceptable morbidity in certain patients who are in poor general health or have a poor oncological prognosis. In such patients, the use of soft-tissue flaps to reconstruct segmental mandibular defects may be useful.

Oncological resection of a head-and-neck cancer is often followed by adjuvant radiotherapy of the surgical area. This compromises flap survival, increasing fibrosis and the risk of osteoradionecrosis of the mandible or flap. Blood flow to the target area is reduced, causing exposure of the bone or implant. Osteocutaneous flaps are particularly susceptible to radionecrosis, infection, and exposure of fixation material. Bulky myocutaneous flaps feature a robust blood supply to the muscle, covering bone with well-vascularized tissue that may be less susceptible to radionecrosis. After flap irradiation, bulky soft tissue usually shrinks but remains cosmetically acceptable. Foreign materials used for fixation also interfere with radiological imaging, creating artifacts on scans used to screen for tumor recurrence, associated with a risk of misdiagnosis.

Study Limitations

Other soft-tissue flaps, such as anterolateral thigh fasciocutaneous or pectoralis major myocutaneous flaps, are also available. Radial forearm free flaps could perhaps be used to repair some small defects, but most defects created by oncological resection are quite large and require bulky flaps such as the flaps that we have used (i.e., latissimus dorsi or rectus abdominis myocutaneous flaps).

Figure 3. The postoperative view of the case 17 reconstructed with free VRAM flap
VRAM: Vertical rectus abdominis myocutaneous

Conclusion

In conclusion, soft tissue flaps are a feasible option that can be used in posterior and/or posterolateral defects in primary reconstruction or secondary salvage procedures.

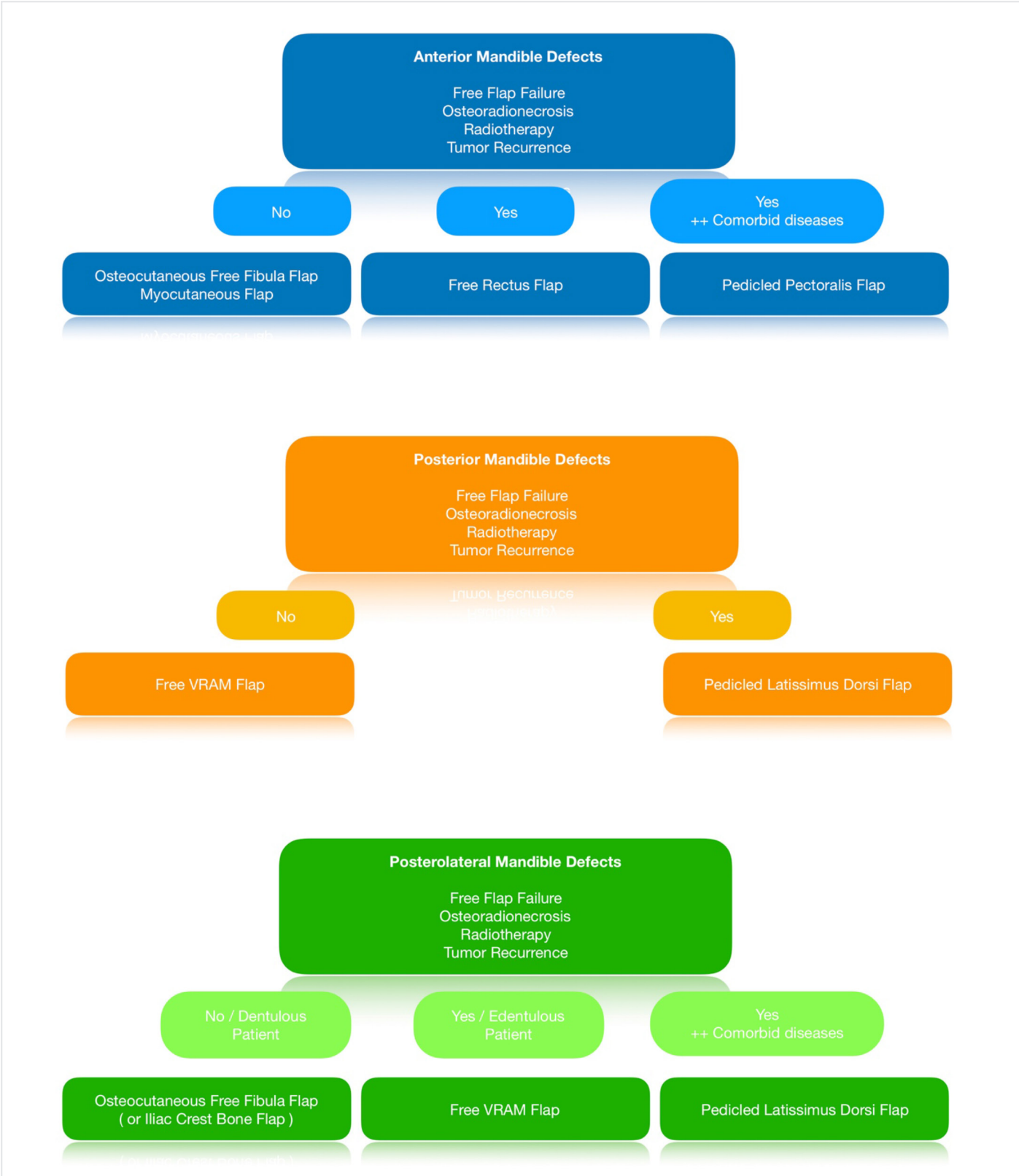

Figure 4. An algorithmic approach in mandible reconstruction. Free flap failure, osteoradionecrosis and tumor recurrence in mandibula reconstructions can be subject to the reconstruction stage with soft tissue flaps. Soft tissue flaps for the composite mandible reconstructions can also be used in selected cases with posterior and/or posterolateral mandible defects in whom radiotherapy is planned and/or who have any comorbidities

VRAM: Vertical rectus abdominis myocutaneous

Ethics

Ethics Committee Approval: Bezmialem Vakıf University Clinical Research Ethics Committee (number: E.21697/date: 208.06.2021).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G., Concept: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G., Design: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G., Data Collection or Processing: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G., Analysis or Interpretation: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G., Literature Search: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G., Writing: K.Y., İ.M.K., R.B.K., O.K., M.V.K., A.K., K.U., E.G.

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Original Article

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Evaluation of Perceptions About Medical Educator and Medical Student Through Metaphors

Tıp Eğiticisi ve Tıp Öğrencisine İlişkin Algıların Mecazlar Yolu ile Değerlendirilmesi

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ABSTRACT

Objective: In the study, it was aimed to reveal the mental images of faculty members in different medical faculties regarding the concept of medical educator and medical student through metaphors.

Methods: A total of 248 faculty members from five different faculties participated in this qualitative research in phenomenology design. The data were collected with a questionnaire form. Faculty members were asked to describe the medical educator and student with a metaphor and to state the reason for the metaphor they used. The research was conducted on a voluntary basis. Content analysis was made on the metaphors. Ethics committee approval was obtained for the study.

Results: Faculty members produced 134 medical educator metaphors. These metaphors were grouped under nine conceptual categories; "source/transmitter of information"; "shaper"; "raiser/feeder/grower"; "guiding/inspiring"; "professional"; "altruist/altruistic/developing identity"; "role model"; "counselor" and "scary" medical educator. One hundred and twenty-nine metaphors developed for medical student were collected under seven categories. The categories of medical students were "recipient/reflector of knowledge", "the constructor/transformer of knowledge", growing/developing, "processed/valued", "working/making effort", "discoverer" and "negatively connotating".

ÖZ

Amaç: Bu çalışmada, farklı tıp fakültelerindeki öğretim üyelerinin tıp eğiticisi ve öğrencisi kavramına ilişkin sahip oldukları zihinsel imgeleri mecazlar aracılığıyla ortaya çıkarmak amaçlanmıştır.

Yöntemler: Olgu bilim desenindeki nitel olan araştırmaya beş farklı eğitim modeli uygulayan fakülteden toplam 248 öğretim üyesi katılmıştır. Araştırmada veriler bir anket formu ile toplanmıştır. Öğretim üyelerinden tıp eğiticisi ve tıp öğrencisini bir mecazla tanımlamaları ve kullandıkları mecazın nedenini belirtmeleri istenmiştir. Araştırma gönüllülük zemininde yapılmıştır. Araştırmada öğretim üyeleri tarafından yazılan mecazlar üzerinden içerik analizi yapılmıştır. Çalışma için etik kurul onayı alınmıştır.

Bulgular: Öğretim üyeleri kendileri için 134 tıp eğiticisi mecazı üretmiştir. Bu mecazlar dokuz kavramsal kategori altında toplanmıştır. Bunlar "bilginin kaynağı/aktarıcısı tıp eğiticisi", "şekillendirici tıp eğiticisi", "yetiştiren/besleyen/büyüten tıp eğiticisi", "yol gösterici/ilham verici tıp eğiticisi", "profesyonel tıp eğiticisi", "özgeci/fedakar/kimlik geliştiren tıp eğiticisi", " rol model tıp eğiticisi", "danışman tıp eğiticisi" ve "korkutucu tıp eğiticisi" idi. Tıp öğrencisi için geliştirilen 129 mecaz yedi kategori altında toplanmıştır. Bu kategoriler "bilginin alıcısı/yansıtıcısı", "bilginin inşacısı/dönüştürücüsü", "büyüyen/gelişen", "işlenen/değerlenen", "çalışan/çaba harcayan", "keşfeden" ve "olumsuz çağrışım yapan" tıp öğrencisi kategorileri idi.

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Conclusion: It was observed that "traditional" understanding was dominant about learning and teaching among all the medical faculties. Medical educators continue to maintain their traditional educator-centered understanding, despite the paradigmatic transformation in medical education.

Keywords: Medical faculty, educator, student, metaphor

Sonuç: Tüm tıp fakültelerinde öğrenme ve öğretmeye ilişkin "geleneksel" anlayış hakimdir. Tıp eğitimindeki paradigmatik dönüşüme rağmen, tıp eğiticileri geleneksel eğitici merkezli anlayışlarını sürdürmeye devam etmektedirler.

Anahtar Sözcükler: Tıp fakültesi, eğitici, öğrenci, metafor

Introduction

The metaphor, derived from the word "metapherein" meaning transferring and transmission in Greek, is replacing the normal use of a word with a new usage (1). It can also be defined as a way of expressing a concept or situation with another concept or situation (2). People often use metaphors when expressing their feelings, thoughts, ideas, and suggestions. Metaphors are the language of experiences in terms of giving meaning to individuals' personal experiences (3,4).

In the field of education, there are various metaphor studies but in the field of medicine metaphor studies are generally related to the perception of the physician but are not related to educational process (5-11).

The role of educator is changing and roles and competencies of medical educator have also been redefined (12). Harden and Crosby (13) defined 12 roles for a good educator. Nikendeı et al. (14) defined 13 main themes reflecting the roles of medical educators. In studies, the characteristics of a good medical educator are clinical knowledge, clinical and technical skills, positive relations with students, supportive learning environments, communication skills, enthusiasm/excitement, altruism, intellectual achievement, personal skills and the search for truth, adopting adult learning principles, innovative spirit, and humanitarian behavior (12-22).

In the realization of these defined roles, it is important for trainers to adapt and internalize these roles. Accordingly, it will be valuable to reveal how the medical trainers in our country position themselves as educators. However, there are almost no studies examining the metaphors regarding the concept of students in the field of education. Studies conducted are generally on the positioning of educators in primary education institutions regarding the student (6,23). It is very valuable to understand the perceptions of the trainer towards herself/himself and the medical student in this period, where the necessity of a student-centered educational environment is emphasized more by putting the student first.

In this study, it is aimed to reveal the mental images of faculty members in medical faculties regarding the concept of medical educators and medical students through metaphors.

Method

This was a qualitative study of the phenomenological type. The study group of the research consisted of faculty members of medical faculty who applied different educational models in the 2016-2017 academic year. While forming the study group, one of the purposeful sampling techniques, "maximum diversity sampling" was used. It was planned to include twenty lecturers from basic, clinical, and surgical sciences from each university, and a total of sixty lecturers from each. However, at the end of the study, a total of 248 faculty members could be reached; 60 from Selçuk University Faculty of Medicine (student-centered, problem-based, integrated, community-based, elective and systematic education model), 55 from Erciyes University Faculty of Medicine (integrated education model), 45 from Ondokuz Mayıs University Faculty of Medicine ["Problem-Based Learning (PBL)" in the first three years and "Task-Based Learning (TBL)" in the 4th and 5th years], 42 from Ankara University Faculty of Medicine (systematic and integrated learning including problem-based, community-based, competency-based learning an integrated education model) and 46 from Akdeniz University Faculty of Medicine (student-centered, problem-solving, integrated, community-based, systematic education model with electives). The educational models of these universities were defined as problem-based for Ondokuz Mayıs University Faculty of Medicine, mixed for Selçuk, Ankara and Akdeniz University Faculty of Medicine and integrated for Erciyes University Faculty of Medicine. There was no PBL in Erciyes University Faculty of Medicine. There were different proportions of PBL and other student-centered practices in the curriculum in medical schools that applied a mixed model.

The data collection tool used in the study was a questionnaire form consisting of two parts. In the first part, there were questions about the socio-demographic characteristics of the faculty members. In the second part, faculty members were asked to describe both the medical educator and the medical student with a metaphor and to state the reason for the metaphor they used. For this purpose, they were asked to complete the sentences "Medical educator is like ……. Because ……." and "Medical student is like ……. Because……..….".

The study was conducted on a voluntary basis. The purpose of the study was explained to the faculty members and then they were asked to fill in the questionnaire with their own handwriting. These forms constituted the data source of the research. Content analysis was made through the metaphors written by the academic members in the research. During the data entry, empty forms that did not specify a metaphor, forms that specified metaphor but did not specify a reason, and forms indicating more than one metaphor were not included in the analysis. For these reasons, 17 faculty members' questionnaires for medical educator metaphors and 33 faculty members' questionnaires for medical student metaphors were not included in the analysis.

The metaphors that faculty members determined for themselves and students were entered in the Excel program. Among the metaphors listed, it was checked whether there was a distinctly repeating metaphor. During the content analysis metaphors formed by the faculty members were analyzed by two researchers in terms of the subject, source and the relationship between the subject and source. As a result of this examination, metaphors were grouped in nine different conceptual categories for the medical educator and seven for the student, with the collaboration of the two faculty members. In the process of naming conceptual categories, studies that included the definitions of medicine, educators, and students were examined (24-26). As a result of this process, the two researchers reached a complete consensus between them. The alphabetical list of the final conceptual categories and metaphors determined was presented to the opinion of another researcher. Reliability of conceptual categorization was calculated by using the formula = (consensus/consensus + disagreement). The coding reliability was based on a confidence percentage of at least 70% (27). As a result of the calculations made in this study, it was found that there was a consensus of 96.2% in the separation of conceptual categories in medical educator metaphors and 82.3% in student metaphors.

Ethics committee approval was obtained for the study from Selçuk University Faculty of Medicine (meeting date: 22/12/2015; decision number: 2015/20). Written informed consent was obtained from the participants.

Statistical Analyses

The data were transferred to the SPSS 22.0 package program and the graphics were drawn in this program.

Results

Of the 248 faculty members participating in the study 54.4% (n=135) were females and 45.6% (n=113) were males. The average age was 46.5±7.2 years. The distribution of faculty members according to their scientific fields and titles is given in Table 1.

Metaphors Developed for Medical Educator

The 231 faculty members included in the analysis produced 134 medical educator metaphors for themselves. Among these, the most repetitive ones were the master (18), the sun (12), the tree (9), and the candle (9). Nine conceptual categories determined for medical educator were as follow; source/transmitter of information; shaper; raiser/feeder/grower; guiding/inspiring; professional; altruist/altruistic/developing identity; role model; counselor and scary medical educator. The metaphors produced by the faculty members for the medical educator are shown in Table 2.

There were 26 metaphors in the category of medical educators as the *source/transmitter of knowledge*. Of the faculty members (60 faculty members) 26.0% uttered a metaphor in this group. The most frequently repeated metaphors were the master, the tree, and the book: "The medical educator is like a *master*. Because he transfers his knowledge and experience to his future colleagues.", "The medical educator is like a *tree*. Because it will convey its knowledge to all students with its branches." and "Medical educator is like a *book*. Because it contains a lot of information."

There were 16 metaphors in the category of *shaper medical educators*. The most frequently repeated metaphors were sculptors, craftsmen, and artist. Of the faculty members (19 faculty members) 8.2% uttered a metaphor in this group: "The medical educator is like a *sculptor*. Because it shapes the student.", "The medical educator is like a *craftsman*. Because craftsmen are like a gem. It processes other ores." and "Medical educator is like an *artist*. Because he is like an actor who appears on the stage and shapes people, while he is raising a physician for six years by giving lectures".

Ten metaphors were produced under the category of "*raiser/feeder/grower medical educator*"; soil, gardener, and water metaphors were mostly written by faculty members. Of the faculty members (23 faculty members) 10% wrote a metaphor from this group: "Medicine educator is like *soil*. Because it grows, feeds, yields.", "The medical educator is like a *gardener*. Because he grows flowers." and "The medical educator is like *water*. Because it feeds, grows, cleans, and refreshes."

In the *guider/inspiratitor medical educator* category, 33 metaphors belonging to 68 (29.4%) faculty members were produced, and under this category, the metaphors of the sun, candle, lantern, and compass were most frequently repeated. "The medical educator is like the *sun*. Because it guides and helps to direct.", "The medical educator is like a *candle*. Because it melts itself, but reflects its light to those around it.", "The medical educator is like a *lantern*. Because it shows the way." and "The medical

Table 1. Distribution of faculty members according to their scientific fields and titles

	Titles				
Scientific field	Professor	Associate professor	Doctor lecturer	Other	Total n (%)
Basic science	38	29	17	2	86 (35.1)
Internal science	46	33	15	3	**97 (39.6)**
Surgical science	21	21	18	2	**62 (25.3)**
Total*	**105**	**83**	**50**	**7**	**245 (100.0)**

*One person did not specify his/her title; two did not specify the department they work in

Table 2. Metaphors of the faculty members for "medical educator"

Category	
Source/transmitter of Information	**Master (18), Tree (9),** Book (6), Teacher (3), Encyclopedia (2), Flower (2), Hose (1), Transcription factors of genes on DNA (1), Library (1), Poet (1), Tap (1), Packer (1), Explorer (1), Ballpoint pen (1), Great plane (1), Emitter (1), River (1), Ocean (1), Spring (1), Jug (1), Water tank with fountain (1), Wise (1), Taxpayer (1), Composer (1), Stream (1), Hose irrigating the garden (1).
Shaper	Sculptor (2), Craftsman (2), Artist (2), Dough kneader (1), Sculptor (1), Painter (1), Mozart (1), Pottery (1), Brush (1), Clay artist (1), Artist (1), Cook (1), Paint on the painter's palette (1), Iron beater (1), Blacksmith (1), Tailor (1).
Raiser/feeder/grower	Soil (5), Gardener (4), Water (4), Fruit grower (3), Sheep (2), Oak tree (1), Auto mechanic (1), Rain (1), Drop of rain (1), Fire (1).
Guider/inspiratitor	**Sun (12), Candle (9),** Lantern (4), Compass (4), Lighthouse (3), Locomotive (3), Bulb (2), Philosopher (2), Coach (2), Navigation device (2)), Ship captain (2), Captain (2), 360-degree rotating lamp (1), Leader (1), Wind (1), Virtuose (1), Road guide (1), Moon (1), Light source (1), Basketball coach (1), Power plant (1), Light (1), Coach (1), Torch (1), Guidewire (1), Rainbow (1), Comedian (1), Guide (1), Luck necklace (1), Path (1), Star (1), Unlocking master (1).
Professional	Conductor (3), Chameleon (2), Donkey (2), Science (1), Don Quixote (1), Medicine Cabinet (1), Sunflower (1), Pansy (1), Tortoise (1), Monkey (1), Hamal (1), Swiss Army knife (1), Clown (1), Rodeo player (1), Wizard (1), Manager (1), Watermelon (1), Fruit (1), Clock (1), Patience (1), Tante shaped robot (1), Waterdrop dripping on the soft rock (1), Bee (1), Cloud (1), Sea (1), Ostrich (1), World (1), Update is always on a program (1).
Altruist/devoted/ developing identity	Parents (6), Mother (4), Head of the family (1), Kartal (1), Gift (1), basic (1), General donor (1), Professional parent (1).
Role model	2nd parent (1), Parent teaching to walk (1), Computer programmer (1), Parent (1), Mirror (1), Model (1), High expectant parent (1), Example (1), Group leader holding a torch (1).
Counselor	Owl (1), Call center (1).
Scary	Dictator (1), Steroid (1).

educator is like a *compass*. Because it makes the student find his way through difficulties."

The most written metaphors in the *professional medical educator* category were the conductor, the chameleon, and the donkey. In this category, there were 28 metaphors belonging to 32 faculty members (13.8%): "A medical instructor is like a *conductor*. Because he coordinates the students who are like talented orchestra members who play different instruments and produce excellent works.", "The medical educator is like a *chameleon*. Because it has to change shape according to the student profile. Otherwise, it cannot reach the same level of education and training for every student. Adjusting to the student and approaching him from the frequency of empathy is the shortest and easiest way to reach the goal." and "The medical educator is like a *donkey*. Because it is a cute animal, it can be used for any job and any job can be undertaken with it."

In the *altruist/devoted/developing ıdentity medical educator* category, 8 metaphors belonging to 16 faculty members (6.9%) were produced and the most frequently repeated metaphors were parents and mothers: "Medical educator is like *parent*. Because he keeps trying to entrust the young people to whom he will entrust his future." "The medical educator is like a *mother*. Because she is loving and giver."

In the *role model medical educator* category, nine faculty members (3.9%) produced nine metaphors: "Medical educator is like a *computer programmer*. Because he is a good role model, loving and giver.", "The medical educator is like a *parent*. Because he is a role model." and "Medical educator is like a *model*. Because with his attitude in basic medicine and his approach to the patient in the clinic, he is a role model for the assistants and medical students he has trained with the treatment methods."

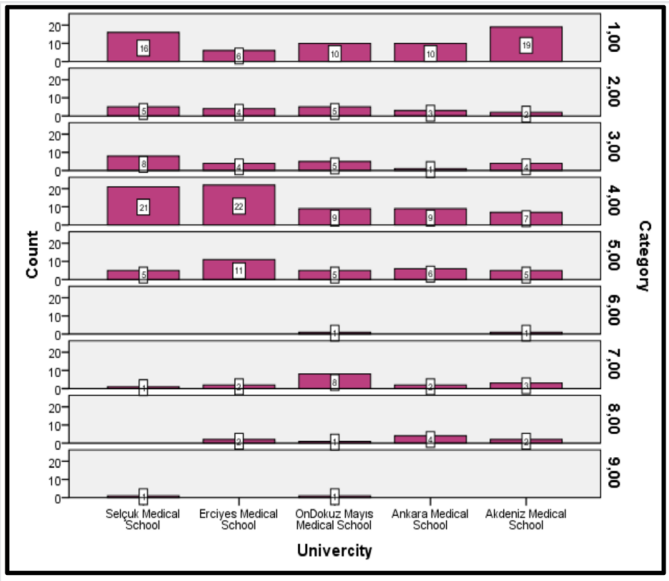
Owl and call center metaphors were included in the *counselor medical educator* category produced by two faculty members (0.9%): "The medical educator is like an *owl*. Because all his experiences have given him the role of a wise consultant in the medical field." and "The medical educator is like a *call center*. Because students call their instructors whenever they have difficulties, or whenever they have trouble."

In the *scary medical educator* category, two metaphors (steroid and dictator) were produced by two faculty members (0.9%): "The medical educator is like a *dictator*. Because he doesn't listen to the student." and "A medical trainer is like *steroids*. Because it is beneficial and suppressive at the same time. Its dosage should be adjusted well."

Distribution charts of metaphor categories of medical educators according to universities, gender, and field of science are given in Figures 1, 2, and 3.

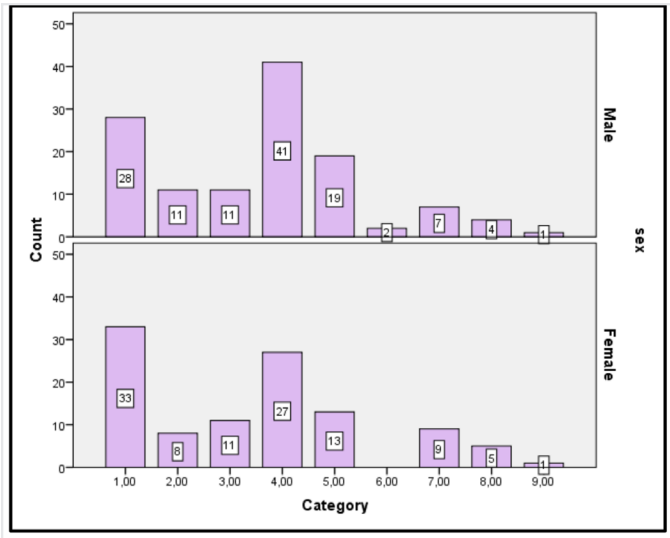
It was observed that the guiding/inspiring medical educator category was more frequent in Selçuk and Erciyes Medical Faculties and in Ondokuz Mayıs, Ankara and Akdeniz Medical Faculties the category of the source/transmitter of knowledge medical educator was more frequent.

Male faculty members wrote more about metaphors in the guider/inspirator medical educator category, on the other hand, female faculty members wrote more about the metaphors in the category of the source/transmitter of knowledge medical educator.



1. source / transmitter of information medical educator, 2. shaper medical educator, 3. raiser/feeder/grower medical educator, 4. guiding / inspiring medical educator, 5. professional medical educator, 6. scary medical educator, 7. altruist / altruistic / developing identity medical educator, 8. role model medical educator, 9. counselor medical educator

Figure 1. Distribution of medical educator categories by universities



1. source / transmitter of information medical educator, 2. shaper medical educator, 3. raiser/feeder/grower medical educator, 4. guiding / inspiring medical educator, 5. professional medical educator, 6. scary medical educator, 7. altruist / altruistic / developing identity medical educator, 8. role model medical educator, 9. counselor medical educator

Figure 2. Distribution of medical educator categories by gender of faculty members

Faculty members working in the field of basic and internal medicine used metaphors in the guiding/inspiring medical educator category and faculty members in the field of surgery members mostly mentioned the metaphors in the category of source/transmitter of information.

Metaphors Developed for Medical Students

Two hundred fifteen faculty members produced 129 metaphors for medical students. The most repeating ones among these were the apprentice (18), the sponge (10), the seed (9), and the bee (9). Seven conceptual categories were determined for the student: "recipient/reflector of knowledge", "the constructor/transformer of knowledge", growing/developing, "processed/valued", "working/making effort", "discoverer" and "negatively connotating". The metaphors produced by the faculty members for "medical students" according to the categories are shown in Table 3.

There were 31 metaphors in the ***recipient/reflector of the knowledge*** category. The most frequently repeated metaphors by 47 faculty members (21.9%) were the sponge, canvas, and the moon. "Medical student is like a ***sponge***. Because he must take the information given to him intensely.", "Medical student is like a ***canvas***. Because each medical educator reflects his own art on this canvas with his own interpretation. Finally, work is completed that neither of them would know exactly how it would be in the first place." and "A medical student is like the ***moon***. Because it reflects the information it collects when the time comes."

There were 14 metaphors in the ***constructor/transformer of the knowledge*** medical student category. The metaphors under this category were (6.5%): "The medical student is like a ***cargo ship*** because carrying tons of information on his back, dealing with the many challenges he faces in deserted oceans. He has to deliver the right cargo to the right address on time." and "A medical student is like ***kidney***. Because he filters the knowledge and skills coming from his professors and other sources, keeps what he thinks will be needed in exams, and in his future life, he throws away what he considers unnecessary."

Under the ***growing/developing*** medical student category, there were 29 metaphors produced by 73 faculty members (33.9%). The apprentice, seed, flower and sapling metaphors were the most written ones by faculty members: "A medical student is like a ***seed***. Because it is a useful and beautiful end product.", "A medical student is like a ***flower***. Because as he gets information, it develops and grows." and "The medical student is like a ***sapling***. Because he is ready to grow and develop."

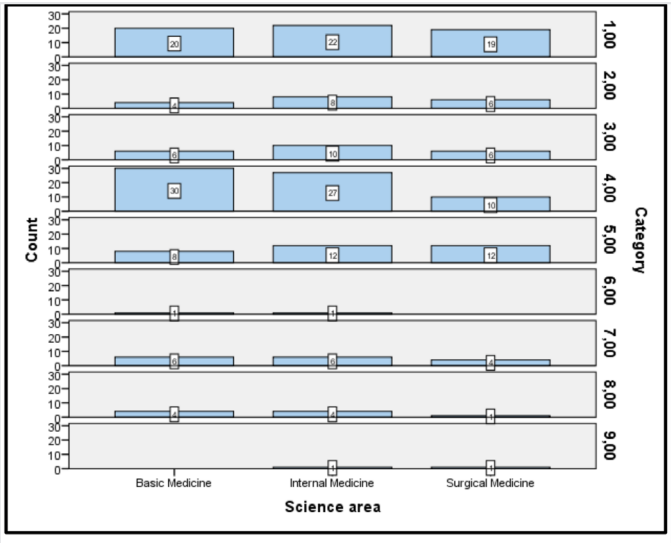
In the ***processed/valued*** medical student category, 21 metaphors were produced by 33 faculty members (15.3%), and under this category, the metaphors of dough, ore and diamond were most frequently repeated: "Medical student is like ***dough***. Because how you knead and shape, it will take that shape.", "A medical student is like a ***ore***. Because it has many valuable aspects. It is open to processing and development" and "A medical student is like a ***diamond***. Because it is valued as it is processed.

The most frequently written metaphors in the ***working/making effort*** medical student category were bee and ant. Thirty one faculty members (14.4%) produced a total of 17 metaphors: "Medical student is like a ***bee***. Because it works hard." and "The medical student is like an ***ant***. Because it always works."

In the ***discoverer*** medical student category, 5 metaphors were produced, and the most frequently repeated ones were explorer and traveler. Ten faculty members (3.2%) selected a metaphor

Table 3. Metaphors of faculty members for "medical students"

Categories	
Recipient/reflector of the knowledge	**Sponge (10),** Canvas (3), Moon (3), Satellite receiver (2), Rainbow (2), Shoes (1), Computer (1), Dark (1), Painting canvas (1), Chest (1), Product (1), A page with random doodles (1), Heavy worker (1), Empty barrel (1), Empty jar (1), Chameleon (1), Bowl (1), Bottomless well (1) , Receiver (1), Earth's moon (1), Planet (1), Hard disk (1), Scout (1), Paper boat (1), Mirror (1), Container (1), Hurricane hose (1) , Match (1), Duckling (1), Tin (1), Honey does not make bee (1).
Constructor/transformer of the knowledge	Cargo ship (1), Yılkı horses (1), Standing library (1), Neurons open to knowledge and learning (1), Unfinished novel (1), Kidney (1), Mill (1), Ship (1), Sun energy (1), Orchestra (1), Digestive system (1), Socrates students (1), Water (1), Poetry reader (1).
Growing/developing	**Apprentice (18), Seed (9),** Flower (6), Sapling (6), Child (4), Baby (4), Kid (2), Fertile soil (2), Sunflower (1), Kindergarten student (1), Sunflower (1), Plant (1), Newborn baby (1), Egg (1), Bird getting ready to fly from the nest (1), Plant seed (1), Branch (1), Sapling branch (1) , Fish grown in the pond (1), Ear of wheat (1), Fruit (1), Minute hand (1), Fruit tree sapling (1), Sweet flower (1), Flower in a pot (1), Fresh willow branch (1) Newborn (1), Nestling bird waiting (1), Child learning to walk (1), Sculpture material (1).
Processed/valued	Dough (8), Ore (4), Diamond (2), Gold (1), Silver (1), Soft rock (1), Carbon (1), Rug (1), Yeast dough (1), Earth (1)), Ready-to-knead dough (1), Paper (1), Marble to be turned into a sculpture (1), Precious silk cloth (1), Unprocessed iron (1), Iron (1), Processed jewelry (1), Clay (1), Metal (1), Diamond (1), Green wood (1).
Working/making effort	**Bee (9),** Ant (7), Hungry wolf (1), Hungry chicken (1), Cook (1), Fire (1), Marathon runner (1), Warrior (1), Kitten (1), Athlete (1), Honey bee (1), Very hungry person (1), Handicapped runner (1), Donkey (1), Porter (1), Glutton man (1), Donkey cub (1).
Discoverer	Explorer (4), Traveler (3), Passengers curious about the ocean and seamanship (1), Contemporary art museum (1), Einstein (1).
Negatively connotating	Antisocial (1), Battery (1), Son of the circus owner (1), Food (1), Sandbag (1), Tramp mine (1), Traveler in foreign countries (1).



1. source / transmitter of information medical educator, 2. shaper medical educator, 3. raiser/feeder/grower medical educator, 4. guiding / inspiring medical educator, 5. professional medical educator, 6. scary medical educator, 7. altruist / altruistic / developing identity medical educator, 8. role model medical educator, 9. counselor medical educator

Figure 3. Distribution of medical educator categories according to the fields in which faculty members work

in this category: "A medical student is like an ***explorer***. Because he is the person who is not satisfied with what has been given to him and who discovers new worlds himself and will guide his discovery." and "Medical student is like a ***traveler***. Because medical students are travelers trying to find their way."

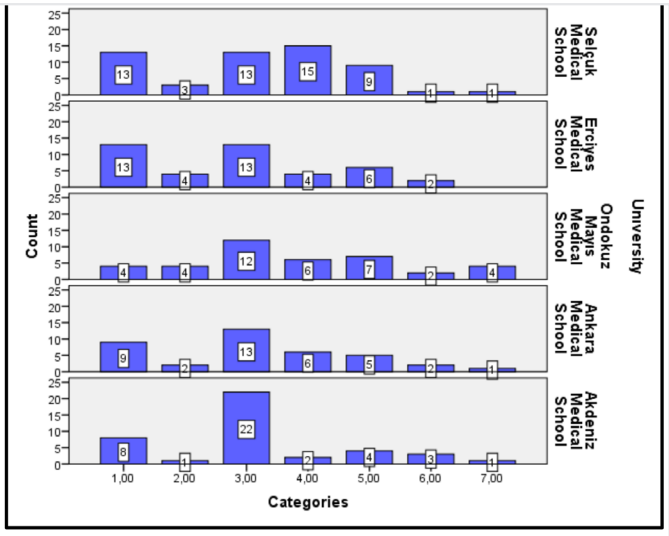
Seven metaphors were produced by 7 faculty members (3.3%) in the medical student category as ***negatively connotating***: "Medical student is like a ***battery***. Because it gets consumed as you read it" and "Medical student is like ***food***. Because it has spicy, sour, sweet. Some leave marks on the palate, some do not hurt for years. Some are fast food. It is consumed immediately, some taxpayers are at the table, it is consumed for a long time. But eventually, it all runs out."

The distribution of medical student conceptual categories created in the study according to the universities where the faculty members work are shown in Figure 4.

The most used metaphors related to medical students were as follows; processed/valued in Selçuk Medical faculty; growing/developing and the recipient/reflector of knowledge in Erciyes Faculty of Medicine; the growing/developing in Ondokuz Mayıs-Ankara and Akdeniz Medical Faculties.

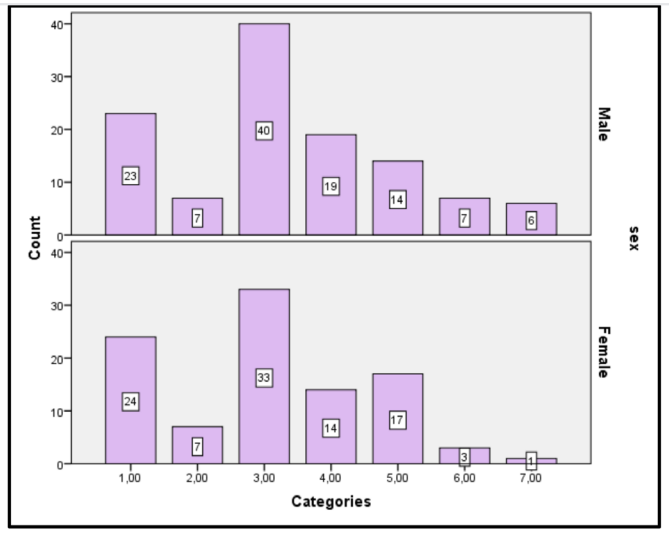
The distribution of medical student categories according to the gender of the faculty members and the fields of science in which they work is shown in Figures 5 and 6. It was observed that the growing/developing category of medical students stood out in both genders. The metaphors in the category of medical students with negative connotations were written more by male faculty members.

In faculty members working in the field of basic medicine, the recipient/reflector of knowledge and the growing/developing



1. medical student as recipient/reflector of knowledge 2. medical student as the constructor/transformer of knowledge 3. growing/developing medical student 4. processed/valued medical student 5. working/making effort medical student 6. discoverer medical student 7. negatively connotating medical student

Figure 4. Distribution of medical student categories by universities



1. medical student as recipient/reflector of knowledge 2. medical student as the constructor/transformer of knowledge 3. growing/developing medical student 4. processed/valued medical student 5. working/making effort medical student 6. discoverer medical student 7. negatively connotating medical student

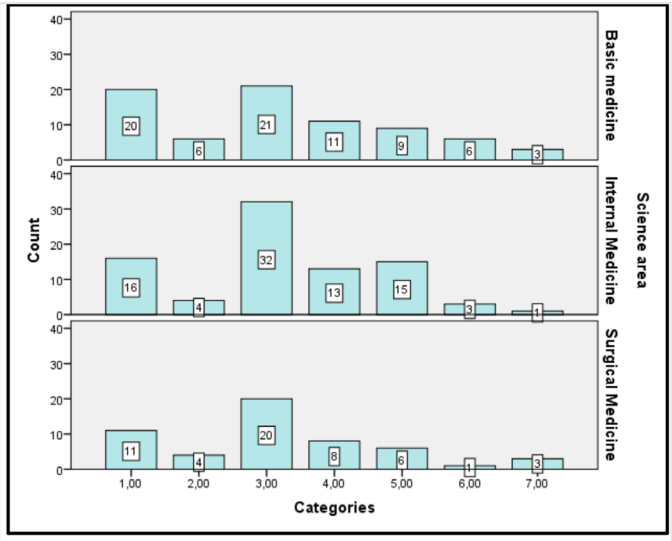
Figure 5. Distribution of Medical Student Categories by Gender of Faculty Members

medical student categories were in the foreground. The growing/developing category of medical students stood out among faculty members working in the field of internal and surgical medicine.

Discussion

In this study, in which the metaphors of medical educators and medical students were determined according to the perspectives of medical faculty members, the mental images created by the faculty members for themselves and the students pointed to a wide range of different metaphors. One hundred thirty four metaphors were produced for the medical educator and 129 for the medical student. Although faculty members produced mostly positive metaphors for both themselves and students, it was observed that some metaphors with negative connotations were also expressed. Yob emphasized that it was important to create a large number of metaphors in a wide perspective whenever a metaphor was done on any subject (28). In this context, 129 metaphors and 7 categories related to the student, and 134 metaphors and 9 categories for the medical educator were produced in this study.

A medical educator should be a master of the field, role model, mentor, leader, manager, researcher, should participate in learning and teaching processes (program design, training, assessment, and evaluation), good at teamwork, act professionally, and have successful communication (12). In the realization of these defined roles, it is important for trainers to adopt and internalize these roles. There is no study on how medical educators define themselves in Turkey. In this study, when the mental images formed by the faculty members as medical educators were examined, it was seen that the categories included the roles defining the role of the medical educator in education, which changed as a result of developments and changes in medical



1. medical student as recipient/reflector of knowledge 2. medical student as the constructor/transformer of knowledge 3. growing/developing medical student 4. processed/valued medical student 5. working/making effort medical student 6. discoverer medical student 7. negatively connotating medical student

Figure 6. Distribution of Medical Student Categories According to the Fields of Science Faculty Members Work in

education. The categories of guider/inspector medical educator (29.4%) and information source/transmitter medical educator (26.0%) stood out in the study.

Traditionally, it has been assumed that a physician starting academia demonstrates the ability to teach even though he or she does not receive training for this. It is seen that they are expected to be trainers before they are ready for their educator roles. In this process, most of the physicians who are faculty members are experts in what to teach rather than how they will teach (12). It is thought that a subject matter expert who knows a lot of things

can easily convey them to others, but this is not the case (29). In this study, it was seen that one of the prominent categories in the mental images of academicians was the medical educators as the source/transmitter of knowledge. Medical educators, while demonstrating their educational role, draw on previous experiences, knowledge, and perceptions associated with learning and teaching. These perceptions generally function positively or negatively in the display of educational competencies without reaching the level of awareness; they also play an important role in educators' acceptance of their roles as educators, shaping themselves and choosing teaching methods (30). Perhaps, for this reason, medical educators have produced negative metaphors about themselves. In our study, the widespread understanding of master-apprentice in medicine showed itself and the master and apprentice were the most used metaphors. In the study, it was observed that the view of "medical educator as the source/transmitter of the information" and the view of the "information recipient/reflector" medical student were directly proportional. However, the purpose of education and training should be to enable people to learn, that is, to transform the learner, not to transfer information (29). Therefore, nowadays, the role of the educator is evolving into the role of counselor-facilitator-director, who provides information without transferring information. The role of the learner is shifting towards the learner who works independently, has choices about what to learn and how to learn, and has opportunities to build their learning on intrinsic motivation and natural curiosity (31). In our study, it was observed that academicians also highlighted the category of "guider/inspiratitor medical educator" for themselves. In education, students are expected to direct their own learning under the guidance of the trainer and take this responsibility (12). In this respect, the trainers' perception of themselves supports this. While the reflection of the category of "guider/inspritor medical educator" in the students was expected to be categorized such as the "constructor/transformer of the knowledge" (6.5%) medical student and the "discoverer" medical student in the facult members, but the situation was very different. When the perceptions of faculty members towards medical students were examined, it was observed that different metaphors were pointed out. Conceptual themes that were popular in the mental images of faculty members regarding the concept of medical student were "growing/developing" (33.9%) "and "recipient/reflector of knowledge" (21.9%) medical students. Less frequently mentioned conceptual themes were the "constructor/transformer of knowledge" (6.5%) and the "discoverer" medical students (4.6%). In the study, it was observed that medical faculty members expressed more frequently the metaphors for medical students that fit the definitions of passive listening and being ones that shoul be shaped and taught. It can be concluded that educators see university students as children whose typical task is to be conveyed information, to be raised, and to work. Popularly adopted categories represent the "traditional" understanding of education. Faculty members have positive feelings about students, but perceive them as passive information receivers of the education and training process. Whereas, the categories of "knowledge constructor/ transformer" medical student and "discoverer" medical student represent constructivist learning conceptions and argue that learning is about structuring, creating, exploring, and developing knowledge, rather than being accepted by the learner (32).

Another remarkable finding in this study was that although there were different education models in all schools and educators had similar tendencies. Considering that education is organized as a process of transferring information to students in some schools, it is not surprising that educators perceive themselves as the source of information. However, considering that student-centered education that turned students into active from the passive position, that is, the inclusion of students in educational activities, it was surprising that this was also the case in schools that had adopted these practices. The situation did not differ according to the basic, clinical, and surgical disciplines or the gender of the instructor. There were educator development programs in all medical faculties participating in the study, and within the framework of this program, the practices in which students were taken to the center were reviewed and the importance of these practices was emphasized. Despite the change of curricula, increase in small group work like PBL etc, or educational development programs, it would be appropriate to reveal with further studies why the perceptions of students were like this.

The themes in the studies conducted with the aim of revealing the mental images about the concept of students in teachers and teacher candidates in our country were the themes dominated by the traditional understanding of education such as "student as a developing entity" and "student as raw material" (6,23). The rate of "students as constructors of their own knowledge" was very low (23). The results of this study showed that the metaphors produced by medical faculty members regarding the medical student were similar to those of the other two studies. There is no change for undergraduate students.

In this study, the use of metaphors as a developing, growing, processed, valued entity for medical students shows the importance given to student learning and development. However, in most of the explanations regarding these metaphors, educators emphasize that the student is shaped by the instructor. This study showed that medical educators continued to maintain their traditional educator-centered understanding, despite the paradigmatic transformation in medical education. However, the very knowledgeable person, who constituted the most valuable human type of ancient times, left his place to the person who knew where and how to find information when necessary. Again, the type of human who believes that knowledge is unchangeable and permanent for ages has evolved into the type of human who believes that knowledge changes and gets old in a short time and therefore constantly tries to improve herself/himself in pursuit of new information (33).

Conclusion

As a result, in this study, it was observed that the "traditional" understanding of learning and teaching was dominant among faculty members of medical faculties, regardless of which model was applied in their faculties. The paradigmatic change in

medical education, the importance of the diversity of strategies and methods, and the different roles of the medical educator have been reflected in educational programs especially in the last decade. These basic topics are also covered in educators' training. Despite all these efforts, the fact that the mental images/thoughts of the trainers remained in a traditional position could be considered as proof that there was no effective change in process from teaching to learning. It is now necessary to stop dealing with what is superficial/forced/apparent and to dig deeper into the subject. More effort and work are needed to change/improve the thinking/prejudice/belief and attitude of the trainers.

Ethics

Ethics Committee Approval: Selçuk University Non-Invasive Clinical Research Ethics Committee (date: 22.12.2015/no: 2015/20).

Informed Consent: Informed consent was taken.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.M.A.K., Design: A.M.A.K., Data Collection or Processing: A.M.A.K., Z.B., Ö.M., M.D., Y.Ş., Analysis or Interpretation: Z.B., Ö.M., M.D., Y.Ş., Literature Search: Z.B., Ö.M., M.D., Y.Ş., Writing: Z.B., .Ö.M., Y.Ş.

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

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Original Article

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Comparison of Mood, Physical Symptoms, Cognitive Failure and Life Satisfaction in Women with Premenstrual Dysphoric Disorder, Premenstrual Syndrome and No/Mild Premenstrual Syndrome: A Controlled Study

Premenstrüel Disforik Bozukluk, Premenstrüel Sendrom ve Hafif Premenstrüel Sendromu Olan/Olmayan Kadınlarda Duygudurum, Fiziksel Belirtiler, Bilişsel Durum ve Yaşam Doyumunun Karşılaştırılması: Kontrollü Bir Çalışma

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ABSTRACT

Objective: This study aimed to compare the mood, physical symptoms, cognitive failure, and life satisfaction in women with premenstrual dysphoric disorder (PMDD), premenstrual syndrome (PMS), and No/Mild PMS (No/Mild PMS).

Methods: Totally 195 women participated in this study. The participants were divided into three groups according to the scores they received from premenstrual symptom screening tool. premenstrual symptom screening tool, beck depression inventory, beck anxiety inventory, cognitive failures questionnaire, and satisfaction with life scale were applied to all participants.

Results: The study findings demonstrated that there was a significant difference between the groups in terms of the mean scores of anxiety, depression, cognitive failure, and life satisfaction ($p<0.05$). Women with PMDD group had significantly higher anxiety, depression, and life satisfaction scores than women with PMS and No/Mild PMS ($p<0.05$). There was a significant difference between the groups in terms of CFQ ($p<0.05$); however, the difference between groups was not significant in post-hoc comparisons.

ÖZ

Amaç: Bu çalışma, premenstrüel disforik bozukluk (PMDB), premenstrüel sendrom (PMS) ve hafif PMS Olan/Olmayan (PMS Yok/Hafif PMS) kadınlarda duygudurum, fiziksel belirtiler, bilişsel durum ve yaşam doyumunu karşılaştırmayı amaçlamıştır.

Yöntemler: Çalışmaya toplam 195 kadın katılmıştır. Katılımcılar premenstrüel belirti tarama aracından aldıkları puanlara göre üç gruba ayrıldı. Tüm katılımcılara premenstrüel belirti tarama aracı, beck depresyon envanteri, beck anksiyete envanteri, bilişsel durum ölçeği ve yaşamdan memnuniyet ölçeği uygulandı.

Bulgular: Araştırma bulguları, anksiyete, depresyon, bilişsel durum ve yaşam doyumu puan ortalamaları açısından gruplar arasında anlamlı bir fark olduğunu göstermiştir ($p<0,05$). PMDB grubundaki kadınların anksiyete, depresyon ve yaşam doyumu puanları, PMS'li ve PMS'siz/Hafif PMS'li kadınlara göre anlamlı düzeyde daha yüksekti ($p<0,05$). CFQ açısından gruplar arasında anlamlı fark vardı ($p<0,05$); ancak post-hoc karşılaştırmalarda gruplar arasındaki fark anlamlı değildi.

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Conclusion: Women with PMDD had higher anxiety, depression, and physical symptoms and lower life satisfaction than women with PMS and No/Mild PMS. The results suggest that health professionals should be sensitive to the emotional and cognitive sides of PMDD/PMS. Holistic intervention programs may be developed considering current study findings.

Keywords: Premenstrual syndrome, premenstrual dysphoric disorder, depression, anxiety, cognitive failure, life satisfaction

Sonuç: PMDB'li kadınlar, PMS'li ve PMS'siz/hafif PMS'li kadınlara göre daha yüksek anksiyete, depresyon ve fiziksel semptomlara ve daha düşük yaşam doyumuna sahipti. Sonuçlar, sağlık profesyonellerinin PMDB/PMS'nin duygusal ve bilişsel yönlerine duyarlı olması gerektiğini göstermektedir. Mevcut araştırma bulguları dikkate alınarak bütüncül müdahale programları geliştirilebilir.

Anahtar Sözcükler: Premenstrüel sendrom, premenstrüel disforik bozukluk, depresyon, anksiyete, bilişsel durum, yaşam memnuniyeti

Introduction

The etiology of premenstrual syndrome is unknown, although this syndrome is linked to the menstrual cycle. Premenstrual syndrome (PMS) is defined as physical, psychological, and behavioral symptoms that occur two weeks before a woman's monthly period. It is diagnosed as PMS when symptoms are severe enough to disrupt daily activities and negatively affect well-being (1). Psychological symptoms such as sadness, irritability, tension, or anxiety and physical symptoms such as bloating and breast tenderness are seen before menstruation and lost with the follicular phase (2). The American College of Obstetricians and Gynecologists estimates that 85% of menstruating women have at least one PMS symptom as part of their monthly cycle. Most of these women have mild symptoms that do not require treatment (3). Others (about 3% to 8%) have a more severe form of PMS, called premenstrual dysphoric disorder (PMDD) (4). PMDD is characterized by prominent symptoms such as irritability, anger, tension, mood swings, and dysphoria (1). PMDD leads to serious functional impairment and decrease in women's quality of life (QOL) (4).

Women with PMS/PMDD reported that they experienced more anxiety and depression in the premenstrual period (5-7) and this depressive mood returned to normal in the post-menstrual period (8). Authors stated that women with PMS/PMDD were more diagnosed as having depression and anxiety disorder (9), attempted more suicide (10) and had more communication problems with others (11) due to mood swings. That's why it is of utmost importance to assess the mood of women with PMS/PMDD.

Women suffering from PMS/PMDD also report cognitive difficulties in addition to psychological symptoms. According to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), the lack of concentration is addressed in emotional symptoms in the diagnostic criterion of PMS/PMDD (12). Some researchers have found impairments in cognitive performance regarding concentration, attention, and memory in PMS/PMDD (13,14). Impairment in cognitive performance measured by neuropsychological tests was associated with PMS/PMDD (15-17). Studies provided evidence that women with PMS/PMDD had lower concentration and lower performance in cognitive tasks in the menstrual period than other times (15,16). There was a difference in the luteal and follicular phase in terms of cognitive performance; after menstruation, these problems disappeared (15,17). Therefore, PMS can be interpreted as a temperamental disorder that may affect some aspects of a woman's cognition (18).

Cognitive failures include perceptual, attentional, memory, and action-related mental errors or everyday slips. Some examples of cognitive failure include forgetting an appointment and the names of people, losing things in public places, failure to notice street signs and failure to remember daily plans, shopping list, taking the drugs, telephone numbers, addresses, and important events (19). Women with PMS reported temporary cognitive difficulties such as distractibility, forgetfulness, or poor concentration (20). In other words, these cognitive difficulties experienced by women with PMS/PMDD may be at the level of daily errors. The previous studies provide at least two possible explanations why more cognitive failure may occur during the premens-period. These are fluctuating levels of estrogen and progesterone hormones during menstruation (17). Second, cognitive failure has been reported as a personality trait in PMS (13). Previous studies indicated cognitive impairments in PMS and PMDD. Reed et al. (15) showed that women with PMDD performed worse on cognitive tasks than women without PMDD in their luteal phase. Similarly, Yen et al. (16) demonstrated that the working memory deficit was more severe in women with PMDD than women without PMDD in the luteal phase. Kumari and Corr (21) showed that women with PMS had fewer correct answers and more errors. Also, they responded less carefully. Slyepchenko et al. (14) stated that women with moderate to severe PMS experienced subtle working memory and selective attention difficulties. To our knowledge, there were limited studies investigating cognitive failure in premenstrual disorders. Cognitive failure was investigated in samples such as mothers involved in child care (22), multiple sclerosis (23), university students (24) and patients with hypertension (25). Only one study examined cognitive impairment during pregnancy and demonstrated higher cognitive failure scores in women who suffered from PMS before pregnancy. The authors argued that women participating in the study were more susceptible to hormonal change (26). Hence, hormonal changes may lead to cognitive failure in PMS/PMDD. However, a review stated that studies remained unclear to show the effect of the menstrual cycle on cognitive functioning and direct effect of hormonal dysregulation impacting cognition (27). Therefore, one aim of the current study was to evaluate whether there was a difference in terms of cognitive failure among women with PMDD, PMS, and No/Mild PMS.

The PMS has troublesome effects on women's overall life and impacts their occupational and social roles (28). Life satisfaction is a subjective definition of QOL (29) and is defined as cognitive judgments of one's life satisfaction and well-being. The psychological, cognitive, and physical symptoms of PMS/PMDD may cause a decrease in womens' life satisfaction. There is ample evidence that women with PMS/PMDD have impaired QOL (28,30,31); however, there is no study comparing the three groups in terms of life satisfaction in the literature. Karimiankakolaki et al. (31) only compared three groups, women with PMDD, PMS, and the general population in terms of QOL. Therefore, the study aimed to compare the mood, physical symptoms, cognitive failure, and life satisfaction in women with PMDD, PMS, and No/Mild PMS groups.

Methods

Participants

A total of 212 volunteer women between the ages of 18-40, who were admitted to the Occupational Therapy Department of Hacettepe University, and whose menstrual cycle continued, participated in the study. Participants were eligible for the study if they met the following inclusion criteria: having regular menstrual periods (21-40 days), being over 18 years old, being a volunteer, and never treated for PMS. Exclusion criteria were determined as being pregnant, taking any hormone medication, having a psychiatric disorder, and having any known health problem except premenstrual symptoms. Seventeen women were excluded from the study because of the irregular cycles (i.e. more than 35 days in length), missing data and some other medical problems (depression, gynecologic disorder etc). Eventually, 195 eligible women who were 24.04±7.45 years old and graduated from the university were included.

This study protocol was conducted in line with the Declaration of Helsinki. It was approved by the Hacettepe University Non-Invasive Clinical Research Ethics Committee (number: 2016/10/date: 10.05.2016). All women received written and oral information before assessment. All participants gave their informed written consent for participation.

Procedures and Data Collection

Demographic and clinical characteristics such as age, body mass index (BMI), and cycle length were collected using a patient information form filled out by all participants. Premenstrual Symptom Screening Tool (PSST), satisfaction with life scale (SWLS), Beck anxiety inventory (BAI), Beck depression inventory (BDI), visual analog scale for physical symptoms and cognitive failures questionnaire (CFQ) were applied to all participants face to face and checked out by researchers. The participants were divided into three groups, PMDD, having moderate to severe symptoms of PMS, or mild to no symptoms of PMS according to the scores they received from PSST. PSST is suggested as a screening tool to identify women who suffer from severe PMS/PMDD and specific criteria are defined for the three groups by Steiner et al. (32). The scale was used to screen for females with moderate to severe premenstrual symptoms, which was defined as (A) presence of at least 1 of the first 4 of the 14 symptoms, (B) presence of at least 4 of any 14 symptoms, and (C) a score of 3 or 4 (ie, moderate to severe, respectively) on at least 1 of the 5 items for assessing functional impairment. The first group consisted of 66 (32.7%) women who fully met the DSM-5 PMDD criteria. To meet these criteria, women had to report at least one of the four core symptoms (irritability, dysphoria, tension, lability of mood) as severe and at least 4 additional symptoms (for a total of 5) as moderate to severe. They also had to report that their symptoms interfered severely with their ability to function in at least one of the five domains (work efficiency, productivity, social life, home responsibilities, relationship at work, or relationships at home for defined, so that it could be identified as PMDD. The second group consisted of 83 women (41.1%). These women reported at least one of the four core symptoms as moderate to severe and at least four additional symptoms as moderate to severe, and their symptoms interfered moderately to severely with their ability to function in at least one of the five domains. This group was evaluated as moderate to severe PMS (Premenstrual Syndrome). Fourty six women (22.8%) in the third group did not meet any of the above criteria and were evaluated as the group with mild or no symptoms (32).

Instruments

Premenstrual Symptom Screening Tool (PSST): PSST was developed by Steiner et al. (32) to assess PMDD, moderate to severe PMS, and No/Mild PMS. The PSST evaluates severity of each of 14 symptoms on a scale from 1 (absence of symptom) to 4 (extremely severe symptom) according to experience of premenstrual symptoms. Five 4-point items were also used to assess impairment of function in work, relationships with coworkers and family, social life activity and home responsibility. It is on a 4-point rating (not at all, mild, moderate, severe). The Turkish version of PSST was formed by Özdel et al. (33). PSST is a reliable and valid instrument in Turkish culture. Internal consistency is excellent (Cronbach α=0.928) for the items of the tool.

Satisfaction with Life Scale (SWLS): SWLS is an inventory that measures global life satisfaction using five statements about the QOL. It was developed by Diener et al. (34). Participants are asked to indicate their level of agreement with the statements on a 7-point Likert-type scale (1= strongly disagree to 7= strongly agree). According to the SWLS, higher scores indicate greater life satisfaction. The total scores of participants on the SWLS range from 5 to 35. The Turkish version of the scale was formed by Durak et al. (35). SWLS is a reliable and valid instrument in Turkish culture. As a result of validity and reliability studies in two different sample groups, SWLS showed high internal consistency in the elderly (0.86). SWLS demonstrated a high internal consistency in the correctional officers' sample (0.81). Confirmatory Factor Analysis revealed that the scale consisted of a single factor in all three samples, and the fit indices were sufficient. The concurrent validity and discriminant validity of the scale were sufficient. In terms of co-validity, a significant correlation was observed between the total score obtained from the scale and life satisfaction and the variables belonging to

similar structures (for example, self-esteem, positive mood, etc.). The alpha reliability for the present sample was 0.77.

Beck Depression Inventory (BDI): BDI was developed by Beck et al. (36) to assess depressive symptoms using 21 items rated on a 4-point Likert-type scale. According to the BDI, higher scores indicate higher levels of depression. The total score ranges from 0 to 63, with a cut-off score of 17. Validity and reliability studies were performed for the Turkish form by Hisli (37). In a psychiatric sample of 63 patients, the correlation coefficient between the MMPI-D scale and the BDI was found to be r=0.63. In university students (N=259); two half-test correlations were reported as r=0.74 and internal consistency coefficient (Cronbach Alpha) as 0.80.

Beck Anxiety Inventory (BAI): It is a self-report inventory developed by Beck et al. (38) to assess the severity of anxiety symptoms using 21 items. The items are rated on a 4-point scale ranging from 0 (not at all) to 3 (severely). The total score ranges from 0 to 63. According to the BAI, higher scores indicate higher levels of anxiety. Validity and reliability studies were performed for the Turkish form by Ulusoy et al. (39). They determined the Cronbach Alpha internal consistency coefficient as 0.928. The item-total test correlation coefficients ranged between 0.45 and 0.72, and the test-retest reliability coefficient was 0.57.

Visual Analog Scale for Physical Symptoms: Physical symptoms in PMS include breast tenderness, headache, joint pain, muscle pain, bloating, and weight gain. Physical symptoms were scored from 0 to 10 points using visual analog scale in our study.

Cognitive Failures Questionnaire (CFQ): CFQ is a self-report questionnaire measuring everyday cognitive errors. The questionnaire was developed by Broadbent et al. (40) to assess the frequency of lapses in three areas; perception, memory, and motor function. CFQ consists of 25 items, and the subjects answer the items on a 5-point Likert-type scale ranging from 0 (never) to 4 (very often). Scores for the CFQ can range from 0 to 100. A high score indicates an increased tendency to cognitive failure. The Turkish version of the questionnaire was formed by Ekici et al. (41). CFQ is a reliable and valid instrument in Turkish culture. Cronbach's alpha coefficients and ICC's at time 1 and time 2 were as follows: 0.90 [confidence interval (CI) 95%; 0.85-0.94]; 0.93 (CI 95%; 0.89-0.96).

Statistical Analysis

Data analysis was performed using SPSS 17 (SPSS Inc., Chicago, USA) and included frequency distribution and descriptive analysis for overall mean scores. First, the Kolmogorov-Smirnov test was applied to check normal distribution. As the data did not meet normal distribution assumptions, the Kruskal-Wallis test was used to compare the scores. Kruskal-Wallis and Mann-Whitney U test were applied to analyze the change for inter-group comparisons. The level of significance was 0.05. A three-fold comparison with the Bonferonni corrected Kruskal-Wallis test was made where p was considered significantly less than 0.017. To determine inter-group differences, the means were compared using Mann-Whitney U test according to Bonferroni Correction as p<0.017.

Results

Sample Characteristics

The mean age was 26.71±8.29 in the PMDD group, 21.92±5.24 in the PMS group, and 23.82±8.00 in the No/Mild PMS group. The mean BMI was 22.48±2.88 in PMDD group, 21.49±3.34 in PMS group, and 22.61±4.52 in No/Mild PMS group. Participants were considered overweight or obese if their BMI was > 25. The mean cycle duration was 27.09±3.82 in PMDD group, 27.96±3.26 in PMS group, and 28.43±2.97 in No/Mild PMS group. The three groups were analyzed in terms of age, BMI, and cycle length (Table 1). The groups were homogenous concerning BMI and cycle length; however, they were not homogenous for age (p>0.05). The demographic and cycle length details of the participants are depicted in Table 1.

Physical Symptom, Mood, Cognitive Failure and Life Satisfaction

The women with PMDD had significantly higher physical symptoms (breast tenderness, headache, joint pain, muscle pain) and weight gain scores compared to women with PMS and No/Mild PMS (p<0.05). The women with PMS reported higher breast tenderness, headache, joint pain, muscle pain, weight gain scores than the women with No/MildPMS (p<0.05). The mean bloating scores in the PMDD group were higher than the PMS No/Mild group (p<0.05). The inter-group comparison of physical symptoms severity related to PSST of the participants is depicted in Table 2.

Table 1. Demographic data and cycle length of the study population (n=195)

	No/Mild PMS Group I (n=46) Mean ± SD	PMS Group II (n=83) Mean ± SD	PMDD Group III (n=66) Mean ± SD	P~	I versus II^	I versus III^	II versus III^
Age (yrs)	23.82±8.00	21.92±5.24	26.71±8.29	0.001*		0.002•	0.001•
BMI (kg/m²)	22.61±4.52	21.49±3.34	22.48±2.88	0.059			
Cycle length (day)	28.43±2.97	27.96±3.26	27.09±3.82	0.063			

~Kruskal-Wallis test, ^Post-hoc Mann-Whitney U test: *P<0.05 statistically significant; According to Bonferroni Correction •p<0.017; BMI: Body mass index, PMDD: Premenstrual dysphoric disorder, PMS: Premenstrual syndrome, No/Mild PMS: No/Mild premenstrual syndrome

Table 2. Inter-group comparison of DSM-5 physical symptoms severity related with PSST by diagnostic group (n=195)

VAS (0-10 cm)	No/Mild PMS Group I (n=46)		PMS Group II (n=83)		PMDD Group III (n=66)		P~	I versus II^	I versus III^	II versus III^	η2
	Med	IQR	Med	IQR	Med	IQR					
Breast tenderness	2.00	7.00	5.00	6.00	6.00	5.00	0.001*	0.004•	0.001•		0.064
Headache	0.00	2.12	2.00	4.00	4.00	5.38	0.001*	0.005•	0.001•	0.001•	0.165
Joint pain	1.00	5.00	4.00	4.80	5.00	4.25	0.001*		0.001•	0.002•	0.120
Muscle pain	3.00	6.00	5.00	5.10	6.00	3.78	0.001*		0.001•	0.002•	0.092
Bloating	4.00	7.80	5.00	6.00	6.97	5.25	0.004*		0.002•		0.055
Weight gain (kg)	0.00	1.00	0.00	1.00	1.00	1.00	0.011*		0.012•	0.012•	0.053

~Kruskal-Wallis test, ^Post-hoc Mann-Whitney U test: *P<0.05 statistically significant; According to Bonferroni Correction •p<0.017; PMDD: Premenstrual dysphoric disorder, PMS: Premenstrual syndrome, No/Mild PMS: No/Mild premenstrual syndrome

Table 3. Inter-group comparison of anxiety, depression, life satisfaction and cognitive failure scores (n=195)

	No/Mild PMS Group I (n=46)		PMS Group II (n=83)		PMDD Group III (n=66)		P~	I versus II^	I versus III^	II versus III^	η2
	Med	IQR	Med	IQR	Med	IQR					
BAI	9.00	9.25	15.00	11.00	19	24.25	0.001*	0.001•	0.001•	0.002•	0.175
BDI	7.00	7.25	11.00	9.00	19	12.25	0.001*	0.001•	0.001•	0.001•	0.229
SWLS	26.50	8.25	21.00	07.00	18.00	8.00	0.001*	0.001•	0.001•	0.001•	0.040
CFQ	38.50	24.25	42.00	22.00	47.00	19.25	0.026*				0.182

~Kruskal-Wallis test, ^Post-hoc Mann-Whitney U test: *P<0.05 statistically significant; According to Bonferroni Correction •p<0.017; BAI: Beck anxiety inventory, BDI: Beck depression inventory, SWLS: Satisfaction with life scale, CFQ: Cognitive failure questionnaire, PMDD: Premenstrual dysphoric disorder, PMS: Premenstrual syndrome

There was a significant difference between the groups in terms of anxiety, depression, cognitive failure, and life satisfaction (p<0.05). Women with PMDD had significantly higher anxiety, depression, and lower life satisfaction scores than women with PMS and No/Mild PMS (p<0.05). Women with PMS had significantly higher anxiety, depression, and lower life satisfaction scores than the PMS No/Mild group (p<0.05). There was a significant difference between the groups in terms of CFQ (p<0.05); however, the difference between groups was not significant in post hoc comparisons. Although not statistically significant, women with PMDD were found to have higher median cognitive failure scores 47.00 (19.25) than women with PMS 42.00 (22.00) and women without PMS/Mild PMS 38.50 (24.25). Inter-group comparison of anxiety, depression, life satisfaction, and cognitive failure scores is depicted in Table 3.

Discussion

Women in PMDD, PMS, and No/Mild PMS were analyzed in terms of mood, physical symptoms, cognitive failure, and life satisfaction in this research. The results of the current study demonstrated that women with PMDD (1) had higher depression and anxiety; (2) had higher physical symptoms; (3) had lower satisfaction with life than women with PMS and No/Mild PMS. Although not significant, cognitive failure scores were higher in the PMMD group. Also, women with PMS experienced more significant changes in depression, anxiety, physical symptoms, and life satisfaction than women with No/Mild PMS.

In our study, physical symptoms were higher in women with PMDD women than women with PMS and No/Mild PMS. Women with PMS also reported more physical symptoms than women with No/Mild PMS. Our study findings showed that both women with PMDD and PMS experienced almost all physical symptoms. Similarly, Steiner et al. (32) showed that physical symptoms were observed in 84.8% of the women with moderate to severe PMS and 88.5% of the women with PMDD. Furthermore, our findings demonstrated that weight gain was higher in the women with PMDD and PMS. Reed et al. (15) showed that women with PMDD desired and ate more foods, especially carbohydrates, during the luteal phase compared to the follicular phase. Our data showed that women with PMDD and PMS experienced more physical symptoms and weight gain than women with No/Mild PMS. Therefore, strategies to control physical symptoms and weight may help to improve women's QOL. Psychoeducation and awareness programs have been shown to reduce symptoms and increase coping skills in women with PMS. Bastani and Hashemi (42) showed that a web-based lifestyle education on female students with PMS led to improvements in overall health and a decline in the severity

of PMS symptoms. Similarly, after the education program, young adolescent girls reported a decrease in PMS symptoms (43). Therefore, educational programs may be beneficial for the management of PMS symptoms by providing information about PMS/PMDD and supporting women coping better with menstrual-related problems.

Our study findings showed that mood measures related to anxiety and depression were significantly higher in women with PMDD than women with PMS and No/Mild PMS. Also, women with PMS had higher depressive and anxiety symptoms than women with No/Mild PMS. The results of our study confirmed previous studies documenting mood changes in women with PMS and PMDD (6,13). Similarly, the women with PMDD had higher depression and anxiety scores than the women with PMS (7,44). KarimianKakolaki et al. (31) found that women with PMDD and PMS had lower mean scores in the aspect of emotional problems. Also, Halbreich et al. (45) reported that the impairments in women with PMDD were almost the same in women with depression. Depression and anxiety scores can be high due to mood swings and dysphoria in the premenstrual term. Women with PMS are more pessimistic, have a sense of more failure, dissatisfaction, guilt, self-dislike, and indecision during the luteal phase compared to the follicular phase (46). In this case, the risk of being depressed or anxious in the premenstrual period may increase. Our study findings emphasize the importance of assessment of depression and anxiety in both women with PMS and PMDD. Therefore, collaborating with mental health professionals and providing people with skills to cope with depression and anxiety can improve their QOL.

This study also evaluated whether there were any differences in cognitive failure among the three groups. The difference between the groups was not statistically significant; however, cognitive failure mean scores of women with PMDD were higher than the other two groups. On the other hand, impairment in cognitive functions of women in the premenstrual period has been mentioned in the literature. Researchers revealed that women had more accidents, and worse work and academic performance during the menstrual period (47,48). Steiner et al. (32) showed that women with PMDD reported decreased interest in work, home, social life, and difficulty concentrating than the PMS group. Shehadeh and Hamdan-Mansour (49) reported that PMDD symptoms impaired students' academic performance. Therefore, premenstrual changes may cause more cognitive errors in the premenstrual period. Although it was not found significant in our study, we recommend that the cognitive difficulties that negatively affected the QOL of women should be investigated in future studies. As Le et al. (27) emphasized that cognitive research findings were lack of consistent findings and were in its infancy, so our findings demonstrated that more detailed studies about cognitive impairment in PMS/PMDD were needed in clinical and larger samples.

In the present study, women with PMDD had lower life satisfaction than women with PMS and No/Mild PMS; women with PMS had lower life satisfaction than women with No/Mild PMS. To our knowledge, there are no previous studies that measure life satisfaction in women with PMS/PMDD. Most studies examined the relationship between PMS/PMDD and QOL. These earlier studies found that QOL decreased during the premenstrual phase (28,30,44). Our finding was consistent with the study of Karimiankakolaki et al. (31). Karimiankakolaki et al. (31) compared the QOL in the three groups, women with PMDD, PMS, and overall population. Women with PMDD reported poor health-related QOL. The QoL was considerably lower in women with PMS and PMDD versus the general population. Women with PMS had significantly poorer QOL than women without PMS (4). Also, Iacovides et al. (50) showed the effect of menstrual pain on health-related QOL. Sut and Mestogulları (51) reported that PMS led to a decrease in work-related quality in nurses. PMS/PMDD disrupted the women's QOL and led to impaired social and occupational functioning. From this current study finding, PMS/PMDD requires biopsychosocial perspective and interdiscipliner approach. More comprehensive programs may be needed for women with PMS/PMDD to improve life satisfaction and wellness. In addition, individual differences should be taken into account.

This study still represents one of the first controlled studies to compare three groups, PMDD, PMS, No-Mild PMS, including life satisfaction, mood, physical symptoms, and cognitive failure measures in women. This study is also valuable in addressing cognitive failure in women with PMS/PMDD for the first time. Further studies are needed to gain a clearer understanding of how the menstrual cycle affects cognitive failure. Our findings suggest that CFQ may be useful and functional in evaluating women with PMS/PMDD who complain of cognitive difficulties due to time limitations in clinical settings.

There are several limitations to our study. First, our population consisted of primarily educated women. It might lead to a bias in the results due to high awareness. Second, participants were examined only in the premenstrual period. We could test both the luteal and follicular phases of the menstrual cycle. Evaluating the differences between these cycles in terms of cognitive failure could be significant. Third, PSST was used to differentiate the groups -PMDD, PMS, and No/Mild PMS. Also early studies suggested Daily Record of Severity of Problems and PSST to be used together (52). They concluded that PSST underreported the PMS diagnosis and over-estimated the PMDD diagnosis. Therefore, in our study, PMDD symptoms might be overestimated by the participants. Fourth, these data were based on self-reports and were not validated by physical or psychiatric examination. Finally, the groups were not homogenous concerning age. We don't know if it may affect the results. Therefore, our study results should be evaluated carefully. In literature, it is stated that being in the young age group is a risk factor for PMS (53,54). Younger women may be more affected by premenstrual changes. On the other hand, some studies showed that symptoms of PMS/PMDD increased with age (55,56). The current study findings need to be replicated. In addition, it is important to consider the age-related risk factor in studies in order to increase the QOL of women and to take early precautions.

Conclusion

This study aimed to compare women with PMDD, PMS, and No/Mild PMS in terms of life satisfaction, mood, and cognitive failure. The results revealed that women with PMDD had higher anxiety, depression scores, physical symptoms and lower life satisfaction scores than women with PMS and No/Mild PMS. These results showed that women with PMDD need more psychological support.

In clinical practice, the focus is on symptoms and not psychological and cognitive difficulties that reduce life satisfaction. The results suggest that health professionals should focus on emotional, cognitive and physical symptoms of PMDD/PMS. Holistic intervention programs and psychological counseling services that support women with PMDD/PMS should be integrated into women's health units.

Ethics

Ethics Committee Approval: Hacettepe University Non-Invasive Clinical Research Ethics Committee (number: 2016/10/ date: 10.05.2016).

Informed Consent: All women received written and oral information before assessment. All participants gave their informed written consent for participation.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: G.E., Design: G.E., Data Collection or Processing: S.E.D., G.E., Analysis or Interpretation: G.E., B.E., Literature Search: S.E.D., Writing: S.E.D.

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Original Article

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Comparison of Coronavirus Stress and Anxiety Levels in Covid-19 Positive and Negative Healthcare Professionals in a Pandemic Hospital, İzmir Example

Bir Pandemi Hastanesinde Covid-19 Pozitif ve Negatif Sağlık Çalışanlarında Koronavirüs Stres ve Anksiyete Düzeylerinin Karşılaştırılması, İzmir Örneği

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ABSTRACT

Objective: In this study, it is aimed to detect the presence of anxiety in healthcare professionals who are and are not infected with the new type of coronavirus (Covid) and to reveal the underlying causes of this anxiety.

Methods: This analytical and descriptive study was conducted with 188 healthcare professionals working at University of Health Sciences Turkey Tepecik Training and Research Hospital between 1-30 July 2020. Covid anxiety and perceived stress scale were administered to the participants along questionnaire.The statistics of the study were made with the SPSS 18.0 program. The statistically significant if the "p" value was less than 0.05.

Results: 40.43% (n=76) of the whole group consisted of individuals who were positive for the polymerase chain reaction test 59.57% (n=112) were health workers who were not diagnosed with Covid-19. Those who worked in Covid-19 wards or outpatient clinics were more likely to be infected with coronavirus and was statistically significant (p=0.014). No statistical significance was observed in terms of the total score of the Coronavirus Anxiety Scale between those infected with Covid-19 and those not (p=0.349).

Conclusion: There are data that all healthcare professionals are concerned and exhausted during the Covid-19 pandemic. The lack of a difference in anxiety levels between those infected with Covid-19 and those not indicates that healthcare professionals still

ÖZ

Amaç: Bu çalışmamızda; yeni tip koronavirüs (Covid) ile enfekte olan ve olmayan sağlık çalışanlarında anksiyetenin varlığını tespit etmek ve bu anksiyetenin altında yatan sebeplerin varlığın ortaya çıkarmak hedeflenmiştir.

Yöntemler: Kesitsel ve tanımlayıcı nitelikte olan bu çalışma 01-30 Temmuz 2020 tarihleri arasında Sağlık Bilimleri Üniversitesi Tepecik Eğitim ve Araştırma Hastanesi'nde çalışan 188 sağlık çalışanı ile yapılmıştır. Katılımcılara Covid anksiyete skalası ve algılanan stres ölçeği uygulanmıştır. Araştırmanın istatistiği SPSS 18.0 programı ile yapıldı. "p" değerinin 0,05'ten küçük olması istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma grubunun %40,43'ünü (n=76) polimeraz zincir reaksiyonu testi pozitif bireyler oluştururken %59,57'sini (n=112) ise Covid-19 tanısı almamış sağlık çalışanları oluşturmaktaydı. Covid-19 servislerinde veya polikliniklerinde görev alanlarda coronavirüs ile enfekte olma durumu daha fazlaydı ve istatistiksel olarak anlamlıydı (p=0,014). Covid-19 ile enfekte olanlar ile olmayanlar arasında coronavirüs anksiyete skalası toplam skoru açısından istatistiksel bir anlamlılık gözlenmedi (p=0,349).

Sonuç: Covid-19 pandemisi sürecinde tüm sağlık çalışanlarının kaygılı, endişeli ve tükenmiş olduklarına dair veriler bulunmaktadır. Covid-19 ile enfekte olanlar ile olmayanlar arasında anksiyete düzeyleri açısından fark olmaması sağlık çalışanlarının pandemi

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have concerns about the pandemic. A widespread and effective psychosocial support provided by institutions will reduce the negative atmosphere in the health system.

Keywords: Covid-19, healthcare professionals, Coronavirus anxiety scale

konusunda hala endişelerinin olduğunu göstermektedir. Kurumların vereceği yaygın ve etkin bir psikososyal destek sağlık sistemindeki olumsuz havayı azaltacaktır.

Anahtar Sözcükler: Covid-19, sağlık çalışanları, Koronavirüs anksiyete skalası

Introduction

Coronavirus disease-19 (Covid-19) has been defined as a coronavirus disease that has been declared as a pandemic by the World Health Organization (WHO) and develops due to the newly defined severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). Covid belongs to a large family of viruses and it is known to cause diseases such as common cold, pneumonia and SARS-CoV (2). According to WHO, published on March 3, 2020, the fatality rate of coronavirus is 2.4% worldwide (3). Covid-19 is spread through droplets from symptomatic or asymptomatic patients (4). The first patient in our country was detected on March 10, 2020 (5). Measures such as social distancing, hand washing and using masks have been taken to prevent rapid spread (6). In addition to these measures, curfew restrictions started in our country, as in many countries (7). In addition, a 14-day quarantine rule was applied to suspicious patients and people from abroad. By these measures, the spread rate of the virus was reduced and a plateau effect in the case-time curve was achieved (8). On June 1, 2020, a step in the normalization process was taken in our country with a decrease in the number of patients. However, as the number of patients increased again in our country with the end of the summer season, curfew restrictions restarted in the last period of November (9).

Healthcare professionals have spent a lot of effort in this difficult process in which dynamic and continuous rapid decisions have been made. With the establishment of pandemic hospitals, many healthcare professionals in different positions have switched to a new working order (10). Reasons such as intense work pace, variable working hours and constant use of personal protective equipment have caused fatigue and wear out in healthcare professionals over time. The fact that 601 (3.8%) of the patients diagnosed at the beginning of April were medical personnel increased the concern (11). In the ongoing process, the rights of all healthcare professionals to leave and quit were restricted starting in mid-March (12). This restriction, which was temporarily lifted during the summer period, was re-applied during the second peak period (13). Along with all these, the continuous updating of diagnostic/follow-up/treatment algorithms related to Covid-19 has caused instability and then anxiety and despair in healthcare professionals. Although the success of some pharmaceutical companies in Vaccination Studies against Covid-19 in the last quarter of 2020 has raised hopes, it can be said that the Covid-19 pandemic will not end in the short term (14,15).

The purpose of this study was to determine the level of anxiety in healthcare professionals who were infected and who were not infected with coronavirus, to reveal the presence of emotional stress caused by coronavirus and to identify other triggers underlying this anxiety.

Method

It is a cross-sectional descriptive study. While 76 healthcare workers with positive Covid-19 polymerase chain reaction tests were used as the study group, 112 healthcare workers who were not diagnosed as having Covid-19 constituted the control group. The necessary approval for the study was obtained from The University of Health Sciences Turkey İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (decision no: 2020-7-15/date: 08.06.2020).

Participants and Procedure: Our study was conducted with 188 healthcare professionals active in our hospital between 1-30 July 2020, which coincided with the first (1) peak period of coronavirus in our country. The data were collected on a purely voluntary basis with the consent and permission of the individuals. The questionnaire was prepared on the internet in accordance with the social distance rule. The internet address associated with the questionnaire was delivered via text message to the mobile phones of healthcare professionals. In the questionnaire developed by the researchers, questions were examining sociodemographic characteristics (age, gender, marital status, etc.), the working order of healthcare professionals in the Covid-19 pandemic period and whether they received mental support during this period. The Turkish version of the "Covid anxiety scale" and the short form of the "perceived stress scale (PSS)" were also applied in the questionnaire.

Coronavirus Anxiety Scale: The Coronavirus anxiety scale is a 5-question scale with robust reliability (α=.93) based on a study with n=775 people (16). In our study, it was determined as (α=0.95). Cronbach is often used in Alpha Likert-type scales. Cronbach is defined as unreliable if Alpha is 0<R2<0.40, low reliable if 0.40<R2<0.60, very reliable if 0.60<R2<0.80 and highly reliable if 0.80<R2<1.00 (17). The Turkish version of the Coronavirus anxiety scale was translated by Evren et al. (18), and its validity and reliability were approved. The necessary permission was obtained from the author at this stage, provided that it was properly cited. Questions on this scale are; "*I felt dizzy, dazed or unconscious when I read or listened to the news about the*

coronavirus, I had trouble falling asleep or staying asleep because I thought about the coronavirus, I felt paralyzed or frozen when I thought about the coronavirus or was exposed to information, I lost interest in eating when I thought about the coronavirus or was exposed to information, I felt nauseous or had stomach problems when I thought about the coronavirus or was exposed to information". The answers to these questions and the score equivalent are: "*None=0, Rare, Less than one or two days=1, More than a few days=2, More than seven days=3, Almost every day in the last two weeks=4*".

Perceived Stress Scale: The PSS was developed by Cohen, Kamarck and Mermelstein (1983) and designed to measure the degree of several situations which were perceived as stressful in an individual's life. In addition to the long-form with 14 items, it has two other forms with 10 and 4 items (19). In this study, a 4-question short form was used. Two questions are with straight statements and 2 questions are with reverse expressions. These questions are: "*How often did you feel that you couldn't control the important things in your life last month? How often have you relied on your ability to address your personal problems in the past month? How often did you feel that everything was going well in the last month? In the last month, how often did you feel that problems had accumulated so much that you couldn't overcome them?*" The answers to these questions and the score equivalent are: "*Very often =4, Quite often =3, Sometimes =2, Almost never =1, Never =0*". It is known that PSS scores have a significant and positive relationship with life events and depression, and a negative and significant relationship with life satisfaction, self-esteem and social support (19). A high total score means that the perceived stress level is high (20). Considering that the predicted reliability levels for the scales planned to be used in the studies were 0.60 and 0.80, the Cronbach's alpha score of the scale for this study was 0.61 and showed internal consistency (20-22).

Measures

While determining the sample, it was aimed to reach all healthcare workers infected with Covid-19. The study was terminated due to the presence of health workers who did not accept to participate in the study and the end of the first peak period in the pandemic.

Statistical Analysis

Statistical evaluation was made with SPSS 18.0 program. Validity and reliability analysis of applied Likert-type questionnaires were performed. The compliance of continuous variables to normal distribution was tested. Comparisons of independent groups were made using the "Student's t-test for variables conforming to the normal distribution, and the "Mann-Whitney U" test for those not conforming to the normal distribution. Categorical variables were presented as frequencies and percentages with cross-tables and their distributions were compared with "chi-square" test methods. In all statistical comparison tests, the margin of error of the first type was determined as α:0.05, and the difference between groups was considered statistically significant if the value of "p" was less than 0.05.

Results

One hundred eighty eight health workers, including the control group, participated in our study. Of participants 40.43% (n=76) tested positive for Covid-19. Of them, 59.57% (n=112) were not diagnosed as having Covid-19, and this group constituted the control group (Table 1).

Of the health workers who tested positive for Covid-19, 76.31% (n=58) were in the 20-39 age range. Of the control group 54.48% (n=61) were in the 20-39 age range. Of healthcare professionals who tested positive for Covid-19 36.8% (n=28) were male and 63.2% (n=48) were female, while 34.8% (n=39) of the control group were male and 65.2% (n=73) were female (Table 1).

There was a significant association between Covid-19 negative status and age increase (p=0.002). While there was no significant relation between Covid-19 negative status and gender and marital status, a significant relationship was found between Covid-19 negative status and high educational level (p=0.049). It was significant that the physician group was less Covid-19 positive than the nurses/obstetricians and other assistant healthcare personnel (p=0.001). In addition, there was a statistically significant relation between the increase in years of work and a lower rate of Covid-19 positivity (p=0.008) (Table 1).

The percentage of health workers who considered themselves at risk, including the control group, was 84.04% (n=158), while the percentage of health workers who said they had anxiety during this process was 88.30% (n=166). Although there were numerically many anxious health workers, the rate of those who said they needed psychological support during the pandemic period was 38.83% (n=73). However, the percentage of those receiving psychological support was 21.80% (n=41). Of those who received support, only 29.27% (n=12) received professional support. The percentage of those who thought their job was always stressful was 44.68% (n=84) (Table 2).

The health workers were more likely to be infected with Covid-19 when there was at least one of the family member diagnosed as having Covid-19 (p=0.000). The health workers were less likely to be infected with Covid-19 if they were assigned in another unit by leaving the current unit of work (p=0.000) (Table 3).

There was a significant relationship between the status of getting infected with Covid-19 and serving only on the day shift (08:00-17:00) (p=0.015). The higher levels of Covid-19 negative status were significant in those who served in pandemic services or outpatient clinics than those who did not (p=0.014). It was statistically significant that those whose working time did not change during the pandemic had a higher level of Covid-19 positivity than those whose working time did (p=0.003) (Table 3).

The average Coronavirus anxiety scale score of all participants was 3.03, while the average value of the total score of the PSS short form, another important scale, was 8.04 (Table 4).

No statistical significance was observed in terms of the total score of the Coronavirus anxiety Scale between those who tested

Table 1. Comparison of sociodemographic data with control group

			Covid-19 Positive	Negative	p
Age	40 years and older	n	18	51	*0.002*
		%	23.68%	45.52%	
	Ages 20 to 39	n	58	61	
		%	76.31%	54.48%	
Gender	Male	n	28	39	0.776
		%	36.8%	34.8%	
	Female	n	48	73	
		%	63.2%	65.2%	
Education status	High school/elementary	n	17	12	*0.049*
		%	22.37%	10.71%	
	University	n	59	100	
		%	77.63%	89.29%	
Task	Auxiliary medical personnel	n	23	28	*0.001*
		%	30.26%	25.00%	
	Nurse/obstetrician	n	29	19	
		%	38.16%	16.97%	
	Doctor	n	24	65	
		%	31.58%	58.03%	
Year of work in the profession	16 years and over	n	17	46	*0.008*
		%	22.37%	41.07%	
	0-15 years	n	59	66	
		%	77.63%	58.93%	

Covid-19: Coronavirus disease-19

positive for Covid-19 and the control group (p=0.349). Similarly, no statistical significance was observed in terms of the total score of the PSS (short form) between those with positive Covid-19 test and the control group (p=0.290) (Table 4).

Compared to the educational level of all participants and the total score of the Covid anxiety scale; it was statistically significant that the anxiety level decreased as the educational level increased (p=0.006). When the total score of Covid anxiety scale was compared with working in pandemic outpatient clinics or services, it was found that the anxiety level did not increase statistically (p=0.504). The Covid anxiety scale score of those receiving mental support was high, and it was statistically significant that those with high anxiety levels also needed mental support (p=0.001) (Table 5).

Considering the answers given in the Covid anxiety scale, the sample size and the statistical significance value, when we accepted the cut off value as "1", no statistically significant difference was observed in terms of the scale value between Covid-19 positive group and the control group (p=0.556). Also, no statistically significant difference was observed in terms of the scale value between participants who worked for 16 years or over and who worked for 0-15 years, and between those who worked in outpatient clinic or service and who did not (p=381 and p=474, respectively) (Table 6).

Discussion

Healthcare professionals, who have to work 24 hours a day without interruption under the stress of being primarily responsible for health, experience psychological and physiological disorders due to the increased workload (23). These can occur in the form of health problems such as chronic insomnia, fatigue, fear of causing malpractice, burnout syndrome, concentration disorders, chronic diseases, and some types of cancer (24). Furthermore, trying to fight an pandemic that they did not know about before has affected medical personnel too much (25,26). In our study, no relation was found between coronavirus infection status and both the Covid anxiety scale and the PSS scores. It can be said that those who fully carry out infection protocols/procedures have both avoided being infected with coronavirus and that their stress level has not changed. Although the presence of a continuous infection creates a persistent level of anxiety, it can be said that being infected with Covid-19 does not cause much variability on the anxiety.

In our study, it was observed that anxiety levels decreased as education levels increased, and stress increased in the presence of infected or suspected patient contact with Covid-19. Some studies showing that anxiety and insomnia are more common in doctors and nurses who come into contact with possible or diagnosed patients (27,28). We can say that those with a high

Table 2. Anxiety status of all participants (n=188)

		n	%
Which process are you in now?	I'm in isolation.	9	4.79
	My treatment was completed, but I didn't start work because I was on leave or a report.	10	5.32
	My treatment was completed and I'm back to work.	57	30.32
	My Covid-19 PCR test is negative (I have not been diagnosed with Covid-19)	112	59.57
Do you consider yourself at risk?	Yes	158	84.04
	No	30	16.96
Has anyone (mother, father, siblings, wife, child) been diagnosed with Covid-19 in your family?	Yes	20	10.64
	No	168	89.36
Did you have any concerns during the Covid-19 pandemic?	Yes	166	88.29
	No	22	11.71
Have you experienced burnout syndrome?	Yes	61	32.47
	No	127	67.53
Do you think you needed psychiatric/psychological support during the pandemic?	Yes	73	38.83
	No	115	61.17
Did you receive psychological support during the pandemic?	Yes	41	21.80
	No	147	78.20
Do you think your job is stressful?	Always	84	44.68
	Often	54	28.72
	Sometimes	39	20.74
	Rarely	9	4.79
	Never	2	1.07

Covid-19: Coronavirus disease-19, PCR: Polymerase chain reaction

level of education can access sufficient data in the light of evidence-based medicine, and accordingly, the level of anxiety decreases. On the other hand, we believe that when it comes to contact with a suspicious patient, it creates an exacerbation of the anxiety level again.

Chan and Huak (29). found that doctors were 1.6 times more likely to experience psychiatric symptoms than nurses. Another study showed high levels of sleep problems, anxiety, and depression symptoms in healthcare professionals (30). In addition, Ataç et al. (31) stated in the study that while anxiety symptoms in nurses/obstetricians and dentists were higher than other professions, doctors constituted the occupational group with the least anxiety symptoms. In our study, it was found that the physician group was less likely to be infected with coronavirus than the nurse/obstetrician and other auxiliary medical personnel. As the years of working in the profession increased, the rate of Covid-19 positivity decreased. It can be concluded that a doctor with high experience in the profession has a low level of being infected with Covid-19, while other healthcare professionals have a higher level of being infected with Covid-19 and a higher level of anxiety than doctors.

In a study on the anxiety levels of individuals, Tutku et al. (2) found that women's health anxiety perception levels were high. Moreover, another study found that levels of anxiety and depression in women were significantly associated with the Covid-19 pandemic (32). Our study is similar to this aspect. We believe that being a woman, as well as being a medical staff, deepens the level of anxiety in this process.

Looking at the researches on Covid-19, some studies are showing that lower levels of psychological impact, depression and anxiety are detected with more preventive measures (33). Ataç et al. (31) found that there was no significant difference in anxiety and insomnia both according to the current task unit and according to the new tasks carried out during the pandemic period. Polat and Coşkun (34) found that healthcare professionals who used their personal protective equipment appropriately when necessary had low depression, anxiety and stress scores. Likewise, in a study conducted in China, it was reported that individuals with high mask-wearing rate who took part in this process had lower DASS depression and anxiety subscales scores (35). In our study, similarly, working in Covid-19 outpatient clinics or services did not increase the level of anxiety. Those who did not work in Covid-19 outpatient clinics or services had a higher rate of Covid-19 than those who worked. Based on this, strict measures taken at the first point of close contact can be considered to have reduced the level of anxiety. On the

Table 3. Comparison of Covid-19 pandemic working order with control group

			Covid-19		p
			Positive	Negative	
Has anyone (mother, father, siblings, wife, child) been diagnosed with Covid-19 in your family?	Yes	n	17	3	*0.000*
		%	22.37%	2.68%	
	No	n	59	109	
		%	77.63%	97.32%	
Has the service or space you worked in during the Covid-19 pandemic been changed?	Yes	n	20	61	*0.000*
		%	26.32%	54.46%	
	No	n	56	51	
		%	73.68%	45.54%	
How was your working order during the Covid-19 pandemic?	Just a shift	n	12	21	*0.015*
		%	15.79%	18.75%	
	Only full-time working every day (8.00-17.00)	n	21	11	
		%	27.63%	9.82%	
	Only flexible working hours	n	13	28	
		%	17.11%	25.00%	
	Both shift and overtime together if necessary	n	30	52	
		%	39.47%	46.43%	
Did you serve in the Covid-19 outpatient clinic or service?	Yes	n	33	69	*0.014*
		%	43.42%	61.61%	
	No	n	43	43	
		%	56.58%	38.39%	
Any changes in your working time compared to before the Covid-19 pandemic?	My working time has increased	n	12	28	*0.003*
		%	15.8%	25.0%	
	My working time hasn't changed	n	35	25	
		%	46.1%	22.3%	
	My working time has been reduced	n	29	59	
		%	38.2%	52.7%	

Covid-19: Coronavirus disease-19

Table 4. Comparison of coronavirus survey scale and perceived stress scale of Covid-19 negative and positive individuals (n=188)

Coronavirus anxiety scale		n	Mean SD med.	Min-max	p
Covid-19 state	Positive	76	2.70±3.91 (1.00)	(0.00-17.00)	0.349
	Negative	112	3.25±4.56 (1.00)	(0.00-20.00)	
	Total	188	3.03±4.31 (1.00)	(0.00-20.00)	
Perceived stress scale		n	Mean SD med.	Min-max	*p*
Covid-19 state	Positive	76	7.75±2.91 (8.00)	(0.00-14.00)	0.290
	Negative	112	8.24±3.02 (8.00)	(0.00-16.00)	
	Total	188	8.04±2.98 (8.00)	(0.00-16.00)	

SD med.: Standart deviation median, min: Minimum, max: Maximum

other hand, it can be interpreted that those who do not work in Covid-19 departments are more easily infected by assuming that they are away from the danger zone.

Anxiety disorders are known to become more pronounced with a decrease in interpersonal communication and with the cessation of social support (36). It should be noted that all kinds of psychological events disrupt the general functioning of the body with prolonged stress, laying the ground for not only Covid-19 but many infections or exacerbating psychosomatic diseases (26). In a multicenter study in Turkey; the perception of stigma score in those who received psychological support during the Covid-19 pandemic and who had psychological disorders during or before the Covid-19 pandemic outbreak were found

Table 5. Comparison of data with Coronavirus anxiety scale (n=188)

		n	Mean SD med.	Min-max	p
Year of work in the profession	16 years and over	63	3.32±4.70 (1,00)	(0.00-20.00)	0.946
	0-15 years	125	2.88±4.11 (1,00)	(0.00-20.00)	
Age	40 years and over	69	3.30±4.56 (1.00)	(0.00-20.00)	0.721
	Ages 20 to 39	119	2.87±4.17 (1.00)	(0.00-20.00)	
Education level	University	159	2.71±4.06 (1.00)	(0.00-20.00)	*0.006*
	High school/secondary education	29	4.76±5.24 (4.00)	(0.00-20.00)	
Did you receive psychological support during the pandemic?	Yes	41	5.17±5.51 (4.00)	(0.00-20.00)	*0.001*
	No	147	2.43±3.72 (1.00)	(0.00-20.00)	
Has the service or space you worked in during the Covid-19 pandemic been changed?	Yes	81	2.91±3.84 (1.00)	(0.00-17.00)	0.902
	No	107	3.11±4.65 (1.00)	(0.00-20.00)	
Did you serve at the Covid-19 outpatient clinic or service?	Yes	102	3.43±4.98 (1.00)	(0.00-20.00)	0.504
	No	86	2.55±3.32 (1.00)	(0.00-16.00)	
Did you have contact with a patient who was diagnosed with Covid-19 while working?	Yes	113	3.00±3.79 (2.00)	(0.00-17.00)	*0.012*
	No	34	1.50±3.03 (0.00)	(0.00-16.00)	

SD med.: Standart deviation median, min: Minimum, max: Maximum, Covid-19: Coronavirus disease-19

Table 6. Comparison of data by cut-off value "1" on the coronavirus anxiety scale

			Coronavirus anxiety scale cut-off		p
			1+	<1	
Did you serve at the Covid-19 outpatient clinic or service?	Yes	n	27	75	0.474
		%	60.00%	52.45%	
	No	n	18	68	
		%	40.00%	47.55%	
Year of work in the profession	0-15 years	n	27	98	0.381
		%	60.00%	68.53%	
	16 years and over	n	18	45	
		%	40.00%	31.47%	
Covid-19	Positive	n	16	60	0.556
		%	35.56%	42.96%	
	Negative	n	29	83	
		%	64.44%	58.04%	

Covid-19: Coronavirus disease-19

to be significantly higher (37). In our study, those who said they needed mental support had a higher score in the Covid anxiety scale, while those who had high anxiety levels also needed mental support. We believe that the morale and motivation of health workers should be increased throughout the pandemic and that institutions should provide all kinds of support in terms of psychological support.

No cut-off value was detected for the Covid anxiety scale in studies (16,18). In the score table, when the cut off value "9" was taken as a basis, 90% sensitivity and 85% specificity were found, and 71% sensitivity and 74% specificity were found when "5" was taken as a basis (16,18). In our study, we considered the cut-off as "1". Accordingly, no significant difference was found between those with "*1 and above*" and those with a "*0*" in terms of the frequency of Covid-19. It can be concluded that there is no change in the individual's current level of anxiety, whether the person is infected with coronavirus or not.

Study Limitations

The limitations of our study were that the Covid anxiety scale used in our study did not have a certain cut-off value and the sample size did not include primary health care institutions.

Conclusion

Those fighting on the front lines against the pandemic are healthcare professionals. A staff with a high level of anxiety does not have any change in the anxiety level after being infected, indicating that the individual is now hopeless and bored. The fact that the healthcare professionals' anxiety level does not decrease indicates that their concerns about Covid-19 persist. The service of a disenchanted healthcare professional will reduce the quality of health, as well as lead to dangerous consequences such as medical malpractice, burnout or suicide.

At this point, we believe that institutions should be as committed to protective equipment as they are to social or psychological support. A widespread, effective and sustainable psychosocial support will lead to efficient service in the health system.

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Ethics

Ethics Committee Approval: University of Health Sciences Turkey İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (decision no: 2020-7-15/date: 08.06.2020).

Informed Consent: Informed consent was obtained from the patients for this study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.M.U., N.Y., D.S., Design: M.M.U., H.P., N.T., Data Collection or Processing: M.M.U., N.Y., Analysis or Interpretation: M.M.U., H.P., N.Y., D.S., N.T., Literature Search: M.M.U., H.P., N.T., Writing: M.M.U., H.P., D.S., N.T.

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Original Article

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Investigation of Bioactive Components, Antioxidant and Antimicrobial Activities of Traditional Turkish Beverage Hardaliye

Geleneksel Türk İçeceği Hardaliyenin Biyoaktif Bileşenleri ile Antioksidan ve Antimikrobiyal Aktivitelerinin İncelenmesi

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ABSTRACT

Objective: In our study, it was aimed to make the chemical analysis of hardaliye products (H1 and H2), which are commercially available by different manufacturers, and to examine their antioxidant and antimicrobial activities.

Methods: Antioxidant activity, organic acid and phenolic compounds, and antimicrobial activity in Hardaliye products (H1 and H2) were determined by using 1.1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, [liquid chromatography-high resolution mass spectrometry (LC-HR/MS)] and liquid microdilution methods, respectively.

Results: Ascorbic acid and fumaric acid from organic acids were determined by chemical analysis of hardaliye samples by LC-HR/MS method. While ascorbic acid concentrations were 21.295 mg/L and 26.84 mg/L in H1 and H2, respectively, fumaric acid concentrations were 59.55 mg/L in H1, and 224.562 mg/L in H2. While the phenolic component with the highest concentration in H1 was resveratrol (44.57 mg/L), it was observed that the phenolic component with the highest concentration in H2 was p-coumaric acid (31.87 mg/L). In terms of antioxidant activity, diphenyl-2-picrylhydrazylfree radical scavenging activity of hardaliye samples was determined as 2.07±0.004% and 2.49±0.004% in H1 and

ÖZ

Amaç: Çalışmamızda farklı üreticiler tarafından ticari olarak satışa sunulan geleneksel Türk içeceği hardaliye ürünlerinin (H1 ve H2) kimyasal analizinin yapılması, antioksidan ve antimikrobiyal aktivitelerinin incelenmesi amaçlanmıştır.

Yöntemler: Hardaliye ürünlerinde (H1 ve H2) antioksidan aktivite 1,1-diphenyl-2-picrylhydrazyl (DPPH) serbest radikal giderim aktivitesiyle, organik asit ve fenolik bileşenler sıvı kromatografi-yüksek çözünürlüklü kütle spektrometre [liquid chromatography-high resolution mass spectrometry (LC-HR/MS)] yöntemiyle, antimikrobiyal etkinlik sıvı mikrodilüsyon yöntemleriyle araştırılmıştır.

Bulgular: LC-HR/MS yöntemiyle hardaliye örneklerinin kimyasal analizi yapılarak organik asitlerden askorbik asit ve fumarik asit saptanmıştır. Askorbik asit konsantrasyonları H1 ve H2'de sırasıyla 21,295 mg/L ve 26,84 mg/L iken, H1'de fumarik asit konsantrasyonları 59,55 mg/L, H2'de ise 224,562 mg/L olarak saptanmıştır. H1'de konsantrasyonu en yüksek fenolik bileşen resveratrol (44,57 mg/L) iken, H2'de konsantrasyonu en yüksek fenolik bileşenin p-kumarik asit (31,87 mg/L) olduğu gözlenmiştir. Antioksidan etkinlik açısından hardaliye örneklerinin diphenyl-2-picrylhydrazyl serbest radikal giderim aktivitesinin H1 ve H2'de

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H2, respectively. It was determined that hardaliye samples showed inhibitory effect [H1 minimum inhibitor concentration (MIC): 15.625 µg/mL, H2 MIC: <3.9 µg/mL] against only *S. epidermidis* ATCC 49461 strains among the tested microorganisms.

Conclusion: In our study, it was determined that two different commercial Hardaliye products contained very low concentrations of phenolic compounds compared to the data in the literature, and therefore it was thought that tested Hardaliye products did not show antioxidant activity.

Keywords: Hardaliye, phenolic component, antioxidant

sırasıyla %2,07±0,004 ve %2,49±0,004 olduğu tespit edilmiştir. Hardaliye örneklerinin test edilen mikroorganizmalardan sadece *S. epidermidis* ATCC 49461 kökenine karşı inhibitör etki [H1 minimal inhibisyon konsantrasyonu (MİK): 15,625 µg/mL, H2 MİK: <3,9 µg/mL] gösterdikleri saptanmıştır.

Sonuç: Çalışmamızda ticari olarak üretilen iki farklı hardaliyenin literatürdeki verilere kıyasla fenolik bileşenleri oldukça düşük konsantrasyonlarda içerdiği saptanmış olup, bu sebeple antioksidan aktivite göstermediği düşünülmüştür.

Anahtar Sözcükler: Hardaliye, fenolik bileşen, antioksidan

Introduction

Plants produce the main metabolites necessary for their growth and development. Furthermore, it is known that plants produce bioactive components known as phytochemicals that have beneficial effects on human health as a result of their secondary metabolism. Phenolic compounds formed by the attachment of one or more hydroxyl groups to the benzene ring constitute a crucial part of phytochemicals (1).

Phenolic compounds are found in many parts of plants, such as stems, leaves, and flowers, in various fruits and vegetables, and beverages such as green tea (1). Grape, which is a fruit, is among the richest fruits in terms of phenolic components. These phenolic compounds are distributed in various parts of the grape. It is known that the phenolic components in grape juice are mainly obtained from grape skins and seeds, and to a lesser extent from the juicy parts of this fruit. The components and amounts of phenolic compounds are related to many factors (type of grape, the soil, geographical location, climatic conditions, harvest time, etc.) (2).

Phenolic compounds have important effects on human health as well as their functions such as taste and aroma in fruits and vegetables. It is known that phenolic compounds can bind free radicals and chelate with metals with their antioxidant effect. In addition, they can utilize anti-inflammatory, anti-allergic, anti-carcinogenic, anti-hypertensive and anti-microbial effects, and modulate the intestinal microbiota by acting as prebiotics (1,3). Due to these beneficial effects on human health, foods rich in phenolic components have become the focus of the field of nutrition.

Hardaliye is a non-alcoholic fermented beverage made from dark-colored grapes (Cabernet, Merlot, Shiraz, etc.). It is presumed that hardaliye production in Kırklareli and the region of Thrace has a history of nearly one and a half centuries. It can be made at home as well as commercially available. It is obtained by adding benzoic acid and crushed mustard seeds to crushed dark-colored and fragrant grapes and undergoing lactic acid fermentation. Benzoic acid prevents or reduces alcohol formation by acting on yeasts. Allyl isothiocyanates in the mustard seed structure largely create the distinctive aroma of mustard. It has also been shown to reduce alcohol formation by reducing yeast activity. Studies have reported that allyl isothiocyanate has antimicrobial activity as well as anti-cancer effect. In people who consume hardaliye, it has been reported that there is a significant decrease in diene conjugate, malondialdehyde and homocysteine concentrations due to the antioxidant capacity arising from the phenolic components contained in hardaliye. Interest in this drink has increased with results from clinical trials (4,5).

In our study, we aimed to evaluate the chemical analysis, antioxidant and antimicrobial activities of the traditional Turkish beverage hardaliye products sold commercially by diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity, LC-HR/MS and broth microdilution, respectively.

Method

Hardaliye Samples

Hardaliye- 1 (H1) and Hardaliye- 2 (H2), produced by different manufacturers and sold commercially, were purchased. Before use, test materials were passed through 0.45 µm filters and stored at + 4 °C until use.

Analysis of Phenolic Compounds by LC-HR/MS

Phenolic compounds in Hardaliye samples were determined by LC-HR/MS method. LC-HR/MS experiments were performed by a Thermo Orbitrap Q-Exactive ESI Mass Spectrometry system (Thermo Fisher Scientific, Waltham, Massachusetts, USA). The samples were separated on a C18 (150x3 mm; 3 µm) column (Fortis Technologies, UK) at 25 °C. The chromatographic conditions, particularly the composition of the mobile phase and its pH, were optimized through several trials to achieve good sensitivity and symmetric peak shapes of analytes. For that purpose, at various flow rates, different solvents of mixtures such as methanol, acetonitrile, formic acid and acetic acid were tested. The best results were acquired using methanol: formic acid as the mobile phase and was applied to the gradient program. The mobile phase was a mixture of mobile phase A (1% formic acid solution in water) and B (1% formic acid solution in methanol), the gradient program of which was 0-1.00 min 50% A and 50% B, 1.01-3.00 50% A and 50% B, 3.01-6.00 0% A and 100% B, 6.01-7.00 min 50% A and 50% B and finally 7.01-10.00 min 50% A and 50% B. The flow rate of the mobile phase was 0.35 mL/min. The injection volume was 10 µL. The dihydrocapsaicin was used as an internal standard.

Determination of Antioxidant Activity

In this study, the antioxidant effects of H1 and H2 were determined using 1,1-DPPH free radical (Sigma Aldrich, Germany) (6). DPPH is a stable free radical with characteristic absorption at 517 nm. DPPH solution when freshly prepared is dark purple and gives maximum absorbance at 517 nm.

The presence of antioxidant activity was evaluated in proportion to the decrease of DPPH's absorbance value at 517 nm. H1 and H2 were dried using a lyophilizer. DPPH solution at a concentration of 40 µg/mL was added to the solutions prepared with ethanol at concentrations of 10, 25, 50, and 100 µg/mL. Ethanol was used as a control. After 30 min of incubation at room temperature, in the dark, at 517 nm, absorbances were measured in a spectrophotometer (Synergy H1 Hybrid Reader, BioTek, U.S.A). The absorbance values of the samples were evaluated against the control. Free radical scavenging activity was calculated using the following equation.

DPPH Radical Scavenging Activity (% inhibition) = [(A control-A sample)/(A control)] x 100

(A control is the absorbance of the control; a sample is the absorbance of the sample).

Investigation of Antimicrobial Efficacy with Minimum Inhibitor Concentration (MIC)

Standard Strains used in the Study

In our study, the antimicrobial activities of hardaliye samples were determined against for Gram-positive with *Staphylococcus aureus* ATCC 25923, *S. epidermidis* ATCC 49461, *Bacillus cereus* ATCC 14579, *Enterococcus faecalis* ATCC 29212; for Gram-negative with *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 70063, *Acinetobacter baumannii* ATCC 19606, *Helicobacter pylori* ATCC 43504; for yeasts *Candida albicans* ATCC 66027 and *C. glabrata* ATCC 2001.

The standard strains were cultured in Sabouraud Dextrose Agar, 5% Sheep Blood Agar, Mac Conkey agar and Columbia agar [(10% defibrinated horse blood and supplement with Vancomycin (10 mg/L), Cefsulodin (5 mg/L), Trimethoprim (5 mg/L) and Amphotericin B (5 mg/L)] for *Candida* species, Gram-positive strains, Gram-negative strains and *Helicobacter pylori*, respectively.

Antibacterial Efficacy

Resazurin Microtiter Assay (REMA)

The resazurin microplate method was used to determine the antibacterial activities and minimum inhibitor concentrations (MICs) of H1 and H2 against standard bacterial strains and the study was repeated twice. Streptomycin (Sigma Aldrich, Germany) was used as the standard drug. Stock solutions of the studied samples at a concentration of 1,000 µg/mL were prepared with DMSO and passed through membrane filters with a diameter of 0.22 µm. Fifty µL of *Brucella* broth (BD BBL, USA) for *H. pylori* and 50 µL of Mueller Hinton Broth (Merck, Germany) for other bacteria were dispensed into the microplates. Serial dilutions of the prepared solutions were made by adding 1,000 µg/mL to the first wells of the microplates and the MIC range was set as 3.9-1,000 µg/mL. Serial dilutions were made by setting the final concentration of streptomycin as 83 µg/mL and adding 50 µL to the first well. Serial dilutions were made by placing dimethyl sulfoxide (DMSO) (Sigma Aldrich, Germany) as a negative control in one column of microplate and 50 µL of standard bacteria as a positive control in one column. Three McFarland in Brucella broth containing 10% Fetal Bovine Serum (Lonza, USA) from colonies of *H. pylori* and 0.5 McFarland standard in Mueller Hinton Broth from other strains were prepared and diluted 1:100. 10 µL of the prepared suspensions were added to the wells. Plates were covered with parafilm, microplates belonging to *H. pylori* were incubated for 72 hours at 37 °C in the microaerophilic environment (Thermo Scientific™ Oxoid™ CampyGen™, UK), and others at 37 °C for 24 hours in aerobic environment. After incubation, 33.75 mg of resazurin (7-Hydroxy-3H-phenoxazin-3-one-10-oxide) (Sigma Aldrich, Germany) and 20% Tween 80 (Merck, Germany) dissolved in 5 mL distilled water were added to all wells. 10 µL was added, plates were left to incubate for 2-4 hours and the results were evaluated visually. The lowest concentration preventing the color change from purple to pink was determined as the MIC value.

Antifungal Efficacy

Resazurin Microtiter Assay (REMA)

The resazurin microplate method was used to determine the antifungal activities and MICs of H1 and H2 against standard yeast strains and the study was repeated twice. Fluconazole (Sigma Aldrich, Germany) was used as the standard drug. Stock solutions of the studied samples at a concentration of 1,000 µg/mL were prepared with DMSO and passed through membrane filters with a diameter of 0.22 µm. 50 µL of Mueller Hinton Broth was distributed to each well, serial dilutions of the prepared solutions were made by adding 1,000 µg/mL to the first well and the MIC range was set to 3.9-1,000 µg/mL. Serial dilutions were made by setting the final concentration of fluconazole as 30 µg/mL and adding 50 µL to the first well. Serial dilutions were made by placing DMSO as a negative control in one column of the microplate and 50 µL of standard strains as a positive control in another column. Suspensions equivalent to 0.5 McFarland standard were prepared from fresh yeast colonies and diluted 1:100. Ten µL of the prepared suspensions were added to the wells. Plates were covered with parafilm and incubated at 37 °C for 48 hours in an aerobic environment. After incubation, 10 µL of 33.75 mg of resazurin dissolved in 5 mL of distilled water and 20%. Tween 80 were added to all wells, the plates were left to incubate for 12-24 hours and the results were evaluated visually. The lowest concentration preventing the color change from purple to pink was determined as the MIC value.

Results

Contents of Phenolic Compounds in Hardaliye Products

In our study, the chemical analysis of commercially sold hardaliye products was made by LC-HR/MS method and 28 components were determined. The phenolic components and their amounts (mg/L) detected in the hardaliye samples are given in Table 1. In Figure 1, some LC-HR/MS chromatograms of H1 and H2 are shown.

In the study, ascorbic acid and fumaric acid were determined as organic acids in both hardaliye products. Ascorbic acid was detected as 21.295 mg/L in H1 and 26.84 mg/L in H2. It was

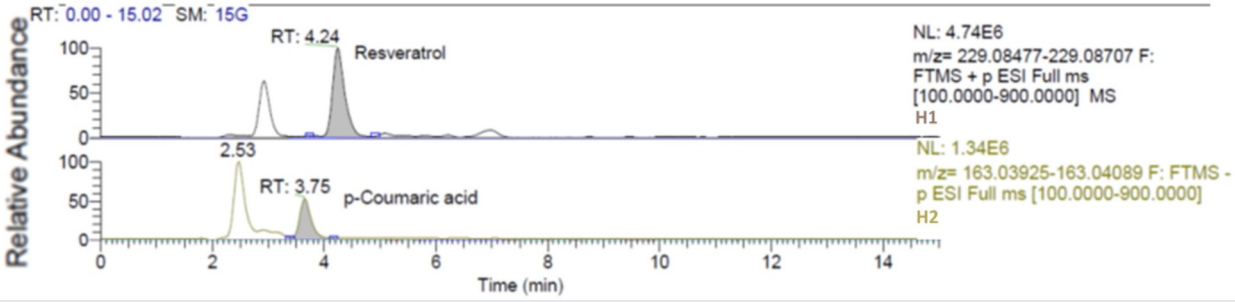

Figure 1. LC-HR/MS chromatograms of resveratrol and p-coumaric acid in H1 and H2

Table 1. Phenolic components and their amounts in selected hardaliye samples

Chemical name	m/z*	Ionization mode	H1 (mg/L)	H2 (mg/L)	U** (%)
Ascorbic acid	175.025	Negative	21,295	26.84	3.94
(-)-Epigallocatechin	307.081	Positive	7,108	2.5859	3.09
(-)-Epigallocatechin gallate	459.092	Positive	0.479	<LOD	3.76
(+)-Catechin	289.072	Negative	4,809	5,381	3.31
Chlorogenic acid	353.088	Negative	0.48	0.575	3.58
Fumaric acid	115.004	Negative	59.55	224,562	2.88
(-)-Epicatechin	289.072	Negative	4,023	9,428	3.17
Verbascoside	623.198	Negative	0.024	0.053	2.93
Orientin	447.093	Negative	<LOD	0.129	3.74
Caffeic acid	179.035	Negative	0.312	1,559	3.06
(+)-Trans taxifolin	303.051	Negative	<LOD	0.246	3.06
Naringin	579.172	Negative	<LOD	0.064	3.57
p-Coumaric acid	163.040	Negative	<LOD	31.87	3.79
Rosmarinic acid	359.077	Negative	<LOD	0.118	3.46
Hyperoside	463.088	Negative	5,067	0.034	2.86
Dihydrokaempferol	287,056	Negative	0.033	0.058	4.30
Ellagic acid	300,999	Negative	0.383	0.423	4.20
Quercitrin	447,093	Negative	0.271	0.001	3.78
Myricetin	317,030	Negative	1,689	0.891	4.18
Quercetin	301,035	Negative	3,305	0.798	2.95
Herniarin	177,055	Positive	0.251	0.082	3.89
Salicylic acid	137,024	Negative	0.626	0.696	1.89
Naringenin	271,061	Negative	0.052	0.032	4.20
Kaempferol	285,040	Negative	0.127	<LOD	3.56
3'-O-methyl quercetin	315,051	Negative	0.118	0.01	3.58
Apigenin	269,046	Negative	0.01	0.01	2.87
Chrysin	253,051	Negative	0.018	0.019	3.24
Resveratrol	229,085	Positive	44.57	16.64	3.17

*m/z: Mass to charge ratio, **U: Measurement uncertainty

observed that fumaric acid with the highest concentration was 59.55 mg/L in H1 and 224.562 mg/L in H2 (Table 1).

Among the phenolic components, the highest amount of resveratrol, (-)-epigallocatechin, hyperoside, (+)-catechin, (-)-epicatechin, quercetin and myricetin were detected in H1, with concentrations of 44.57, 7,108, 5,067, 4,809, 4,023, 3,305, and 1,689 mg/L respectively. The highest number of phenolic components in H2 were p-coumaric acid, resveratrol, (-)-epicatechin, (+)-catechin, (-)-epigallocatechin, caffeic acid and their concentrations were 31.87, 16.64, 9,428, 5,381, 2.5859, and 1,559 mg/L, respectively (Table 1).

Antioxidant Activity of Hardaliye Products

DPPH free radical scavenging activity was studied at four different concentrations (10, 25, 50, 100 µg/mL). Antioxidant effect comparisons were made with BHA (Butylated hydroxy anisole) (Sigma Aldrich, Germany) used as standard. At a concentration of 100 µg/mL, an inhibition rate of 2.07±0.004% and 2.49±0.004% was observed in H1 and H2, respectively. Inhibition values of standard substances and samples are shown in Figure 2.

Antimicrobial Activity of Hardaliye Products

The antimicrobial activities of H1 and H2 on Gram-positive and Gram-negative bacteria and yeasts were performed by broth microdilution method, and the microorganisms and MIC results are given in Table 2. Antibacterial activity of H1 and H2 on *S. epidermidis* ATCC 49461 was observed as MIC: 15,625 µg/mL, MIC: <3.9 µg/mL, respectively. It was determined that neither of the hardaliye products had an inhibitory effect on other bacteria and yeast species (MIC: 250-1,000 µg/mL) (Table 2).

Discussion

Grape is one of the widely grown fruits that has an economic role in the production of wine, fruit juice, jam and raisins, has rich phenolic components and has positive contributions to human health. Grape skin, pulp, juicy parts and seeds are rich in phenolic components. These components can be classified as phenolic acids, flavonoids, stilbenes. Phenolic compounds in fresh grapes and commercial grape juices can play an important role in preventing various diseases related to oxidative stress, such as cancer, cardiovascular and neurodegenerative diseases, related to their antioxidant activity (1-3). Due to their antioxidant properties and abundance in the diet, phenolic compounds have become interesting to researchers and manufacturers.

In recent years, a discipline called "food-omics" has emerged that examines the fields of food and nutrition with the application and integration of advanced omic technologies to protect the health of consumers and ensure their trust (7). In this context, omic technologies such as genomic, epigenomic, transcriptomic, proteomics, metabolomics and metagenomics have been accepted as the basic tools used in food-omics (8). The main purpose of metabolomics in the field of food-omics is to identify

Table 2. MIC results of hardaliye samples against in tested microorganisms

	Test material (µg/mL)	
Microorganisms	**H1**	**H2**
S. aureus ATCC 25923	1,000	1,000
E. coli ATCC 25922	1,000	1,000
P. aeruginosa ATCC 27853	1,000	1,000
E. faecalis ATCC 29212	500	500
A. baumannii ATCC 19606	1,000	250
K. pneumoniae ATCC 70063	500	500
B. cereus ATCC 14579	500	500
S. epidermidis ATCC 49461	15,625	<3.9
C. albicans ATCC 66027	1,000	250
C. glabrata ATCC 2001	1,000	250
H. pylori ATCC 43504	1,000	1,000

MIC: Minimum inhibitor concentration

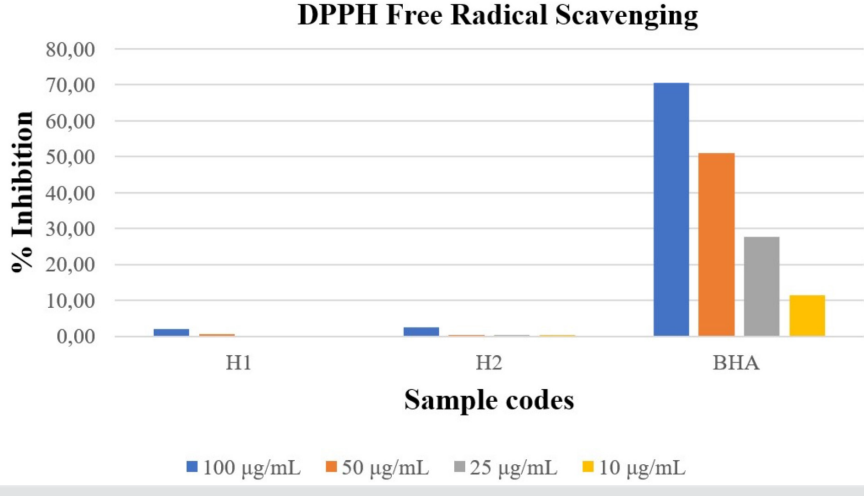

Figure 2. DPPH free radical scavenging activity results
DPPH: Diphenyl-2-picrylhydrazyl

and quantify small (<1,000-1,500 Da) molecules (such as amino acids, lipids, carbohydrates, phenolic compounds, vitamins, organic acids, drugs) in food and nutrition studies. LC-HR/MS has been used in various metabolomic studies due to its wide dynamic range and reproducible quantitative analysis and performs well in profiling secondary metabolites (9,10).

Data in the literature show that products with rich phenolic content reduce oxidative stress and the incidence of chronic diseases. Grape is one of the most important fruits in our diet due to its diversity in terms of phenolic components. With the antioxidant effect of these compounds, the consumption of products derived from grapes reduces the risk of cardiovascular disease. In addition, these components have been shown to have anti-cancer, anti-microbial and anti-inflammatory activities. The most common phenolic compounds found in grapes are in the group of flavonoids, phenolic acids and stilbenes. The most dominant class among the flavonoids found mostly in the core and skin part of the grape is flavan-3-ols, and this group includes compounds such as (+)-catechin, (-)-epicatechin, (-)-epigallocatechin. Another important group of flavonoids is flavanols, and compounds such as quercetin, myricetin, hyperoside (quercetin-3-O-galactoside) are included in this group. Phenolic acids, on the other hand, are mostly found in the skin and pulp of grapes. Phenolic compounds such as p-coumaric acid, caffeic acid are included in this group. Another phenolic component found in grape and grape products is resveratrol, which is in the class of stilbenes (1-3).

Studies on grape-derived products have shown that many factors can affect phenolic composition. Concentrations of (+)-catechin and (-)-epicatechin were determined as 500.52±12.33 and 53.48±19.78 mg/L, respectively, in grape juices obtained from red grapes of the genus *Vitis labrusca* L. produced by organic farming in Brazil. It has been reported that these data are higher than those obtained by traditional agriculture (79.89±30.19, 14.40±0.77 mg/L, respectively) (11). In the study conducted by Faikoğlu et al. (12) in 2016, hardaliye was produced from various grapes collected in the Tekirdağ region in the laboratory environment and the (-)-epicatechin concentrations in Adakarası and Kalecik black grapes were determined as 21.89 ± 0.072 mg/100 mL and 20.55±0.028 mg/100 mL, respectively. Silva et al. (13) investigated the effect of different processing technologies such as "Hot press", "Cold press", "Hot break" (HB) and "Artisanal" used to produce grape juice on the content of phenolic components. The highest concentrations of (-)-epigallocatechin, (-)-epicatechin (17.23 mg/L, 50.30 mg/L, respectively) were detected in grape juices obtained with HB (13). In our study, (-)-epicatechin and (+)-catechin concentrations in H1 were 4.023 mg/L and 4.809 mg/L, respectively, while it was 9,428 mg/L and 5,381 mg/L in H2. The concentration of (-)-epigallocatechin was 7,108 mg/L in H1 and 2.5859 mg/L in H2. Compared to the data in the literature, the concentrations of (+)-catechin, (-)-epigallocatechin and (-)-epicatechin in hardaliye samples were observed to be quite low in our study.

Another group of flavonoids is flavanols. It is reported that compounds such as quercetin, myricetin, and hyperoside in this group have antioxidant, anti-inflammatory and anticarcinogenic properties (1-3). In the study conducted by Amoutzopoulos et al. (14) from our country, quercetin concentration in hardaliye samples was reported as 65.5±0.37 mg/L. While the concentrations of myricetin were 7.99±0.99 and 6.98±0.90 mg/L in organic and traditional red grape juices, respectively, this amount was quite low in white grape juices (1.85±0.46 mg/L) obtained by traditional agriculture. In the same study, it was observed that the concentration of quercetin was 3.91±0.08 mg/L in red grape juices obtained by organic farming, while it was 4.27±0.54 mg/L in traditional cultivation (11). In the study reported by Balea et al. (15) in 2020, hyperoside concentrations in the fresh and fermented pulp of *Vitis vinifera* L. Feteasc ă neagr ă grapes grown in Romania were found to be 0.804±0.06 mg/100 mL and 10.813±0.18 mg/100 mL, respectively, and hyperoside could not be detected in Pinot Noir grapes. In our study, hyperoside, quercetin, and myricetin concentrations in H1 were 5,067 mg/L, 3,305 mg/L, and 1,689 mg/L, respectively, while in H2, they were found to be 0.034 mg/L, 0.798 mg/L, and 0.891 mg/L, respectively. It is lower than the data in the literature (Table 1). Caffeic acid and p-coumaric acid concentrations, which were among phenolic acids with antimicrobial, anticancer and anti-inflammatory activities, were reported as 60±1.15 mg/L and 21±1.71 mg/L, respectively, in the study conducted by Amoutzopoulos et al. (14). In the study conducted by Toaldo et al. (11) in 2015, the caffeic acid and p-coumaric concentrations (29.95±1.57, 11.23±0.16 mg/L, respectively) in red grape juices obtained by organic farming were compared to traditionally obtained red grape juices (14.08±0.17, 10.73±0.51 mg/L, respectively) and they were observed to be higher. In our study, while the concentration of p-coumaric acid was undetectable in H1, it was 31.87 mg/L in H2. Caffeic acid concentrations were found to be 0.312 and 1.559 mg/L in H1 and H2, respectively. It has been reported that resveratrol, which is in the stilbenes group among phenolic compounds, has a protective effect against many diseases, especially cancer and heart diseases (1-3). Trans-resveratrol concentration was determined as 2.72±0.28 mg/L in the study reported by Amoutzopoulos et al. (14) in 2013. The data of this study are similar to the resveratrol concentration (2070±260 μg/L) detected in commercially available hardaliye products in the study reported by Ilıkkan et al. (16) from Edirne in 2017. Resveratrol concentrations in hardaliye samples in our study were determined to be 44.57 mg/L in H1 and 16.64 mg/L in H2, and the determined amounts were considerably higher than the data in the literature. Considering the literature data, we think that the reason why the results we obtained in our study differ from the data in the literature is due to factors such as the type of grape used in the production of hardaliye, the geographical region where it is grown, the type of agriculture, harvest time, product processing conditions, and climatic conditions.

Phenolic compounds are known to have an important role in preventing various health problems such as cancer, cardiovascular and neurodegenerative diseases associated with oxidative stress due to their antioxidant activity (1-3). Many studies have mentioned the relationship between phenolic compound composition and free radical scavenging activities. In a study

reported from Brazil in 2013, the DPPH free radical scavenging activity of grape juices obtained from grapes harvested at different times of the year in 2010 was found to be 100%, and this ratio showed high correlation with the anthocyanin content varying between 44.3±2.01-129.5±2.82 mg/100 mL (17). In the study reported by Nile et al. (18) from Korea, they compared the phenolic content and antioxidant activity of grape skins and pulp in different grape varieties. While the antioxidant activity of extracts in grape peel was between 12.5% and 60.2%, this rate varied between 35.4% and 84.5% in extracts obtained from grape pulp. A statistically significant correlation was observed between the phenolic content obtained from the extracts and free radical scavenging activity (18). In the study conducted by Gündüz et al. (19) in 2019, DPPH free radical scavenging activity was reported to be between 80-90% in homemade hardaliye and 70-80% in commercial hardaliye, and the total phenolic content in hardaliye products was observed to be between 2029.30-2193.08 mg/L. In our study, the antioxidant activity in H1 and H2 was determined as 2.07±0.004% and 2.49±0.004% respectively. Compared to the data in the literature, the phenolic component contents and thus free radical scavenging activity of the hardaliye samples in our study are quite low. For this reason, it cannot be mentioned that the products in our study show antioxidant activity.

Ascorbic acid is thought to be a functional food ingredient, as it is an important bioactive compound found naturally in fruits and vegetables with antioxidant properties. For this reason, grapes and products derived from grapes also constitute an important part of the daily diet, as they contain varying concentrations of vitamin C (20). In 2013, Amoutzopulos et al. (14) reported the vitamin C concentration in hardaliye products as 2.35±0.07 mg/L. In a study conducted in Algeria in 2014, the ascorbic acid content of various grapes varied between 12.33±0.01-30.80±4.98 mg/100 mL (21). In our study, it was found as 21.295 mg/L in H1 and 26.84 mg/L in H2. Studies have reported that ascorbic acid content in fruit and vegetables may vary depending on factors such as climatic conditions (exposure to sunlight and weather), agricultural practices (fertilizers), crop maturity, harvest method, post-harvest processing conditions (storage), species, genotype (22,23).

Fumaric acid is an organic acid that is used as an acidifier in beverages and is responsible for the sour taste (24). Studies have reported that mold species such as Ding et al. (25) produce fumaric acid. It has been observed that the addition of fumaric acid to foods and beverages causes bactericidal activity against foodborne pathogens (26). In a study reported in China in 2020, trace amounts of fumaric acid (0.002-2.18 mg/100 mL) were detected in grape juices obtained from different grape varieties (27). Similarly, in the study reported from Spain in 2021, trace amounts of fumaric acid were detected in the hydro-ethanol extracts of purple grape seeds (28). In our study, fumaric acid concentrations were found as 59.55 mg/L and 224.522 mg/L in H1 and H2, respectively (Table 1). Although fumaric acid concentrations were higher in the samples analyzed in our study compared to these studies, the antibacterial activity could not be detected (Table 2).

When the literature data are reviewed, it has been reported that phenolic compounds show antimicrobial efficacy (1-3). Filocamo et al. (29) showed that white grape juice extracts were effective against *S. aureus* ATCC 6538P (MIC: 3.9 µg/mL), *S. epidermidis* ATCC 49134 and *S. epidermidis* ATCC 35984 (MIC: 15.62 µg/mL) strains in Italy. In the study conducted by Xu et al. (30) in 2015, the highest ratio of catechin and epicatechin was found among the flavonoid components identified in the pulp obtained from grapes grown in Virginia. It has been reported that these fibers show antibacterial activity against *L. monocytogenes* ATCC 7,644 and *S. aureus* ATCC 29213 (30). In the study conducted by Gündüz et al. (19), it was determined that homemade and commercial traditional hardaliye beverages produced from grapes grown in our country showed antimicrobial activity on *S. aureus, B. cereus, Salmonella typhimurium* (MIC 4.53-150 mg/mL). In a study conducted in 2021 in Spain, it was reported that extracts obtained from grape seeds of the Albariño genus *Vitis vinifera* had high concentrations of catechin and oligomers and that these extracts were effective against multiple resistant *S. aureus* strains (MIC: 5 mg/mL) (28). In our study, it was found that hardaliye samples showed antibacterial activity only on *S. epidermidis* ATCC 49461 strain (H1, MIC: 15.625 µg/mL; H2, MIC: <3.9 µg/mL), it was ineffective on other bacteria and *Candida* species (MIC: 250-1,000 µg/mL) was determined.

Study Limitations

There is no study in the literature investigating the effectiveness of hardaliye on *H. pylori*. However, studies have reported that various grape extracts are effective on *H. pylori* (31). In our study, it was observed that hardaliye samples did not show antibacterial activity (MIC: 1,000 µg/mL) on the strain of *H. pylori* ATCC 43504.

Conclusion

In the studies in the literature, it has been observed that the phenolic composition of grapes and products obtained from grapes may vary depending on the type of the grape, the geographical region where it is grown, climate, harvest and post-harvest processes. When grape juices obtained from grapes and grapes are evaluated in terms of antioxidant activity, free radical scavenging activity is compared with the amount of phenolic component. It was observed that the phenolic component concentrations determined in our study were generally lower than the literature findings. Therefore, the low DPPH free radical scavenging activity in hardaliye products was thought to be related to the low concentrations of phenolic components. To produce higher quality products and improve their biological activities on human health, it is necessary to support the factors affecting the phenolic composition in hardaliye production.

Ethics

Ethics Committee Approval: Since our study is not a clinical study, it does not require ethics committee decision and patient consent information.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Concept: P.Y.M., R.Ç., Design: P.Y.M., R.Ç., Data Collection or Processing: S.P.S, H.Ö.D., B.B.A., P.Y.M., Analysis or Interpretation: S.P.S., H.Ö.Y., B.B.A., P.Y.M., Ö.A., B.S., R.Ç., Y.A.Ö., Literature Search: Ö.A., B.S., Y.A.Ö., Writing: S.P.S., P.Y.M., R.Ç.

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

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Original Article

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The Effects of the COVID-19 Pandemic on Perceived Stress, State and Trait Anxiety and Work-Related Strain in Healthcare Professionals

Sağlık Çalışanlarında COVID-19 Pandemisinin Algılanan Stres Durumluk-Sürekli Kaygı ve İş Gerginliği Üzerindeki Etkileri

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ABSTRACT

Objective: In Coronavirus disease-19 (COVID-19), as in all pandemics, employees are the human force fighting against the disease at the forefront, and they face the risk of infection for themselves and their relatives during this struggle. In this study, it was aimed to determine the stress, anxiety and work-related strain levels of healthcare employees dealing with the treatment of infected patients during the COVID-19 pandemic and the factors affecting these levels.

Methods: This descriptive study was conducted in Karadeniz Technical University Farabi Hospital. Healthcare employees who were deemed to be at high/low risk in terms of Covid-19 transmission were included in the study. Perceived stress scale (PSS), state and trait anxiety inventory (STAI-S, STAI-T), and work-related strain inventory (WRSI) were used.

Results: Stress,anxiety and work-related strain levels were high in the high-risk group.This difference was significant in PSS (p=0.000). Stress, anxiety and work-related strain levels of those working in the high and low-risk work areas and who weren't satisfied with their work were higher.This difference was significant according to WRSI (p=0.000). Stress, anxiety and work-related strain levels of men were higher in high-risk group and women in low-risk group. In high-

ÖZ

Amaç: Tüm pandemilerde olduğu gibi Koronavirüs hastalığı-2019 (COVID-19) salgınında da sağlık çalışanları hastalığa karşı en ön safta mücadele eden insan gücü olup bu mücadele sırasında kendilerinin ve yakınlarının enfekte olma riskiyle karşı karşıya gelmektedirler. Bu çalışmada COVID-19 pandemisi sırasında enfekte hastaların tedavisi ile uğraşan sağlık çalışanlarının, salgın sırasındaki stres, kaygı ve işe bağlı gerginlik seviyesini ve bu düzeylere etki eden faktörlerin saptanması amaçlandı.

Yöntemler: Tanımlayıcı nitelikte olan bu çalışma Karadeniz Teknik Üniversitesi Farabi Hastanesi'nde yapıldı. COVID-19 bulaş riski açısından yüksek ve düşük riskli kabul edilen sağlık personeli çalışmaya dahil edildi. Algılanan stres ölçeği (ASÖ), durumluk ve sürekli kaygı envanteri (DKE-SKE) ve işe bağlı gerginlik ölçeği (İBGÖ) kullanıldı.

Bulgular: Çalışmamızda yüksek riskli grupta stres, kaygı ve işe bağlı gerginlik düzeylerinin yüksek olduğu ve bu farkın ASÖ ölçeğinde anlamlı olduğu saptandı (p=0,000). Yüksek ve düşük riskli çalışma alanında görev alan ve çalıştığı işten memnun olmayanların stres, kaygı ve işe bağlı gerginlik düzeyleri daha yüksekti ve İBGÖ ölçeğine göre bu fark anlamlı idi (p=0,000). Yüksek riskli grupta erkeklerin, düşük riskli grupta ise kadınların stres, kaygı ve işe bağlı gerginlik

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risk group, this difference was found to be statistically significant according to the STAI-S (p=0.048), in low-risk group this difference was statistically significant according to PSS (p=0.004) and STAI-S (p=0.010).

Conclusion: Increasing stress, anxiety and work-related strain levels with the COVID-19 pandemic negatively affect both healthcare professionals and healthcare services provided by healthcare professionals. Efforts, activities, and measures should be taken to improve and eliminate these negativities.

Keywords: Pandemic, COVID-19, perceived stress, healthcare employee

düzeylerinin daha yüksek olduğu tespit edildi. Yüksek riskli grupta bu fark DKE'ye göre (p=0,048), düşük riskli grupta bu fark ASÖ (p=0,004) ve DKE'ye (p=0,010) göre istatistiksel olarak anlamlı bulundu.

Sonuç: COVID-19 pandemisiyle birlikte artan stres, kaygı ve işe bağlı gerginlik düzeyleri hem sağlık çalışanlarını hem de sağlık çalışanlarının verdiği sağlık hizmetlerini olumsuz etkilemektedir. Bu olumsuzlukları iyileştirmeye ve gidermeye yönelik çaba, faaliyet ve önlemlerin alınması gerekmektedir.

Anahtar Sözcükler: Pandemi, COVID-19, algılanan stres, sağlık çalışanı

Introduction

The Coronavirus disease-19 (COVID-19), which was caused by severe acute respiratory syndrome coronavirus, emerged in China in December 2019, spread the entire world within 4 months, and caused a serious public healthcare problem in the world today like the previous pandemics (1). The service capacity of healthcare systems is exceeded in pandemics that affect the entire world, and the healthcare employees whose workload increases in this process are also affected mentally. As in all pandemics, healthcare employees make up the human power fighting against the disease, and they face the risk of being infected during this fight. According to an article published in China, in a study with 138 series infected with COVID-19 and who developed pneumonia, 40 (29%) of the cases were healthcare employees (1). Despite the use of personal protective equipment, it is inevitable that healthcare employees who fight against a disease face a high risk of transmission and mortality (2), feel stressed in all kinds of invasive attempts that are performed when necessary. The optimum level of mental health of healthcare employees as the most important human factor in the fight against pandemics in this period is proportional to the success of the fight against the pandemic. However, it was reported in studies that investigated the mental health of healthcare employees in pandemic periods that healthcare employees also had anxiety and stress, and some studies even reported that they experienced mental health disorders as bad as psychosis (3-5).

In this study, our purpose was to determine the stress, anxiety and work-related strain levels of healthcare employees who dealed with the treatment of infected patients during the COVID-19 pandemic and the factors that affected these levels, to make recommendations to reduce these levels to minimize, to increase the comfort of healthcare employees, and to increase the quality of healthcare. This study can be a resource for future pandemics, and if the stress, anxiety and work-related strain levels of healthcare employees can be reduced to the lowest level, it can contribute to the development of healthcare services that will be provided during new pandemics which may occur in the future.

Methods

This descriptive study was conducted in a university hospital. Healthcare employees who were deemed to be at high/low risk in terms of COVID-19 transmission were included in the study. perceived stress scale (PSS), state and trait anxiety inventory (STAI) and Work-Related Strain Inventory (WRSI) were used.

Participants

The study was conducted at a Farabi Hospital of Karadeniz Technical University Faculty of Medicine in Trabzon. The healthcare employees working at hospital emergency department, pediatric emergency department, COVID-19 positive ward, possible COVID-19 ward, COVID-19 intensive care, microbiology and biochemistry laboratory, and in the imaging units (X-ray, tomography, ultrasound, magnetic resonance imaging, and interventional radiology) (doctors, nurses, helping medical staff) were included in the study. Healthcare employees who did not have contact with potential or positive COVID-19 patients/samples were excluded from this study. The healthcare staff working in COVID-19 units of emergency departments, COVID-19 positive ward, and intensive care units were considered to be at high risk because of dealing with high-risk operations, the staff working in other areas were considered to be at low risk. Healthcare employees were interviewed with a distance of at least 1 meter face-to-face using a mask. The data were collected by filling in surveys that were prepared in advance. The ethical approval was taken from the Ethics Committee Presidency of the Karadeniz Technical University Faculty of Medicine in Trabzon (ethics committee approval no: 2020/119).

In our study, healthcare workers were divided into high and low-risk groups in terms of the risk of COVID-19 transmission. Healthcare employees working in the COVID-19 unit of the pediatric and adult emergency deparments, COVID-19 positive services, COVID-19 probable services, COVID 19 PCR laboratory, COVID-19 polyclinic and COVID-19 intensive care unit where suspected COVID 19 and definite COVID 19 cases are treated, were considered as high risk due to their high-risk procedures. Personnel working in other areas (eg, green yellow trauma and monitor area of emergency department, imaging and laboratories) were considered as low risk. In addition, healthcare workers who performed procedures that we thought were high-risk due to the high risk of aerosol formation in terms of the risk of COVID-19 transmission were also considered as high-risk group regardless of the place of work. These risky procedures

were: endotracheal intubation, cardiopulmonary resuscitation, non-invasive mechanical ventilation, aspiration, COVID-19 specimen collection.

Materials

The questionnaire consisted of 6 parts. In the first part, there were questions about demographic characteristics and personal information such as age, gender, occupational group, and working duration, educational status, marital status, number of children, chronic illness, drug use history, cigarettes, and alcohol use history. In the second part, there were questions such as in which unit of the hospital the healthcare employee worked during the pandemic, the way and duration of work, what risky procedures were performed, the factors that caused stress during the pandemic, and the ways to deal with them during the pandemic. In the third part, there were questions about family and community life, such as whether they separated from their homes, families or children since the pandemic started, and whether they imposed restrictions on actions related to their social life such as going to markets and using minibuses or shuttles. In the fourth part "PSS" was used, and the 14 questions were asked to healthcare employees about their personal experiences in March 2020. In the fifth part, "STAI" was used, and 40 questions were asked on how they felt that moment. In the sixth part, the WRSI was used, and 18 questions were asked about their jobs.

Perceived Stress Scale (PSS-14): The scale was developed by Cohen et al. (6) in 1983 as a method of evaluating how much individuals perceived their experiences. Each item on the scale is evaluated with 5-Point Likert Scale ranging from "Never (0)" to "Very often (4). Seven of the items containing positive statements are reverse scored. The PSS-14 scoring system is between 0-56 points, and high scores show higher stress perception levels. If the score is between 11-26 points, the stress level is low, and scores between 27-41 points show moderate, and between 42-56 points show high-stress levels. The Turkish validity and reliability study of the scale was conducted by Eskin et al. (7) The Cronbach Alpha Internal Consistency Coefficient, which showed the reliability of the PSS, was calculated as 0.84.

State and Trait Anxiety Inventory (STAI): The scale was developed by Spielger et al. (8) in 1970 to evaluate state and trait anxiety, and the adaptation to Turkish was performed in 1982 by Öner and Le Compte (9). There are 20 questions in both scales, each of which is evaluated over a Likert-type scale ranging from "None (1)" to "Completely" (4). The score obtained from each scale ranges from 20 to 80. In STAI, high scores show a high level of anxiety of participants. The Cronbach Alpha Reliability Coefficient of STAI was found to be between 0.73 and 0.86 in various applications for trait anxiety scale, and between 0.86-0.92 for state anxiety scale (9).

Work-Related Strain Inventory (WRSI): The scale was developed to evaluate the stress and tension levels of healthcare employees who had to look after serious and terminally ill patients and consisted of 18 items. Each question is scored based on the Likert-type scale ranging from "This does not apply to me at all (1)", and "This applies to me completely" (4). The scoring system of the WRSI is between 18-72 points. The scale was previously translated into Turkish, was applied on a nurse sampling by Aslan et al. (10), and the Cronbach Alpha Internal Consistency Coefficient, which showed the reliability of the scale, was found to be 0.63 and 0.75 in that study.

Statistical Analyses

All the data were transferred to the Statistical Package for the Social Sciences 23.0 (SPSS Inc; Chicago, IL, USA) program. Descriptive statistics of the evaluation results were given as numbers and percentages for categorical variables, and as mean, standard deviation, minimum, and maximum values for numerical variables. The chi-square test was used in independent groups when the differences between the rates of categorical variables were analyzed. The normal distribution of numerical variables was evaluated with the Shapiro-Wilk test. In comparisons of the measurement variables for the data that fit normal distribution between two independent groups, the Student t-test was used, and the Mann-Whitney U test was used in case the data were not distributed normally. The variance analysis was used in comparisons of continuous variables that fit normal distribution between three independent groups, and the Kruskal-Wallis test was used when the data did not fit the normal distribution pattern. The statistical alpha significance level was set at $p<0.05$.

Results

A total of 183 healthcare employee were included in the study. The rate of the male participants was 48.1%, and that of the female participants was 51.9%. Among the participants, 54.09% (n=99) were evaluated as having high risk due to the workplace they worked in the fight against COVID-19. The demographic characteristics according to the risk levels of the participants are compared in Table 1.

The majority of the healthcare employees who were included in the study were working in the emergency department (n=133; 72.7%). It was found that 76 of them worked in a high-risk area, and approximately 19.2% of them (n=19) did not receive any training on the use of personal protective equipment. The changes related to the social lives of the healthcare employees fighting against COVID-19 in the pandemic period are shown in Table 2. Of the participants 82% (n=150) did not change their homes, 91.3% (n=167) continued to live in the same house with their children, and 57.4% (n=105) separated from their relatives who had chronic diseases.

The perceived stress, state and trait anxiety and work-related strain levels of the participants were evaluated with 3 separate scales, and when compared according to risk groups, the perceived stress, state and trait anxiety and work-related strain levels were found to be higher in the high-risk group. However, this difference was only found to be statistically significant in the PSS (p=0.000). The comparison of perceived stress, state and trait anxiety and work-related strain levels of the participants according to risk groups is shown in Table 3.

Table 1. Distribution of demographic characteristics of participants according to risk levels

	High risk		Low risk		Total	
	n	%	n	%	n	%
Age (mean ± SD)	31.30±6.167		35.44±8.061		33.20±7.374	
Gender						
Female	57	57.6	38	45.2	95	51.9
Male	42	42.4	46	54.8	88	48.1
Marital status						
Married	46	46.5	55	65.5	101	55.2
Single	53	53.5	29	34.5	82	44.8
Children						
Yes	33	33.3	48	57.1	81	44.3
No	66	66.7	36	42.9	102	55.7
Profession						
Doctor	60	60.6	3	3.6	63	34.4
Nurse	29	29.3	11	13.1	40	21.9
Other	10	10.1	70			
Paramedic	1	1.0	10	11.9	11	6.0
Employees	7	7.1	15	17.9	22	12.0
Technician	2	2.0	19	22.6	21	11.5
Storage attendant	-	-	2	2.4	2	1.1
Security attendant	-	-	11	13.1	11	6.0
Secretary	-	-	6	7.1	6	3.3
Other	-	-	7	8.3	7	3.8
Educational status						
Primary school			1	1.2	1	0.5
Secondary/high school	9	9.1	30	35.7	39	21.3
University	90	90.9	53	63.1	143	78.1
Chronic disease						
Yes	23	23.2	20	23.8	43	23.5
No	76	76.8	64	76.2	140	76.5

SD: Standard deviation

The comparison of the scale scores according to the risk status is shown in Table 4. According to these data, it was found that the perceived stress, state and trait anxiety and work-related strain levels of men were higher in the high-risk group and these levels of women were higher in the low-risk group. This difference was found to be statistically significant in STAI-S in the high-risk group, and was statistically significant in PSS and STAI-S in the low-risk group. No statistically significant differences were detected according to having a chronic disease, marital status, having children, having a relative with chronic disease at home, working in an isolated area in the emergency department, receiving training on personal protective equipment, and decrease in working duration in the pandemic period. The perceived stress, state and trait anxiety and work-related strain levels were found to be higher in the participants who were not satisfied with the working environment, and this difference was statistically significant in some scales.

Discussion

It was determined in our study that perceived stress, state and trait anxiety and work-related strain levels were higher in the high-risk group in the PSS. The perceived stress, state and trait anxiety and work-related strain levels were higher in the WRSI scale in those who worked in high and low-risk working areas and who were not satisfied with their working environments. It was also found that the perceived stress, state and trait anxiety and work-related strain levels of men were higher in the high-risk group, and these levels of women were higher in the low-risk group. This difference was statistically significant according to STAI-S in the high-risk group; and was statistically significant according to PSS and STAI-S in the low-risk group. No statistically significant differences were detected according to having a chronic disease, marital status, having children, having a relative with chronic disease at home, working in the isolated area in the emergency department, receiving training on personal

Table 2. Changes in social lives of participants in the pandemic period

	High risk		Low risk		Total	
Changing home	n	%	n	%	n	%
I move on as before	75	75.8	75	89.3	150	82.0
I sent other members of my family to another place	9	9.1	5	6.0	14	7.7
We moved to another place as a family	1	1.0	-	-	1	.5
I stay at the hotel provided by the hospital	3	3.0	-	-	3	1.6
We moved to another house form the hospital	9	9.1	2	2.4	11	6.0
Other	2	2.0	2	2.4	4	2.2
Leaving children						
Yes	9	9.1	7	8.3	16	8.7
No	90	90.9	77	91.7	167	91.3
Leaving relatives						
Yes	62	62.6	43	51.2	105	57.4
No	37	37.4	41	48.8	78	42.6
Going to market						
No change	10	10.1	14	16.7	24	13.1
Decreased	81	81.8	60	71.4	141	77.0
Increased	8	8.1	8	9.5	16	8.7
Never	-	-	2	2.4	2	1.1
Taking the service bus to the hospital						
No change	72	72.7	46	55.9	118	64.5
Decreased	9	9.1	16	19.0	25	13.7
Increased	3	3.0	4	4.8	7	3.8
Never	17	17.2	19	22.6	36	19.7
Social contact						
No change	6	6.1	3	3.6	9	4.9
Decreased	83	83.8	73	86.9	156	85.2
Increased			3	3.6	15	8.2
Never	10	10.1	5	6.0	3	1.6

Table 3. Comparison of stress scale scores of participants according to risk levels

Risk level	PSS*		STAI-S**		STAI-T***		WRSI****	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
High risk	28.68	6.636	45.60	9.973	43.11	8.405	38.47	7.142
Low risk	24.58	8.450	43.73	9.879	41.96	7.432	36.70	5.542
	p=0.000	t=3.597	p=0.206	t=1.269	p=0.334	t=0.970	p=0.061	t=1.888

PSS*: Perceived stress scale, STAI-S**: State and trait anxiety inventory-state, STAI-T***: State and trait anxiety inventory-trait, WRSI****: Work-related strain inventory

protective equipment, and decrease in working durations in the pandemic period.

On the one hand, healthcare employees work in close contact with infected or possibly infected patients, and thus, jeopardize their health, on the other hand, they fight against the fear that they may infect their family members and their loved ones; sometimes they leave their homes for an uncertain time to avoid this, or tend to live in separate rooms in their homes to avoid infection. Another difficulty of being a healthcare employee is that the social environment and the community may stigmatize them by considering them as possible infection sources (11). Also, during the pandemic period, increasing workload and social isolation caused that the healthcare employees, who witnessed the worst moments of their patients in hospital, worked in the hospital

Table 4. Comparison of scale scores according to descriptive characteristics and risk status

	High risk (mean ± SD)				Low risk (mean ± SD)			
	PSS	STAI-S	STAI-T	WRSI	PSS	STAI-S	STAI-T	WRSI
Gender								
Female	29.3±6.93	44±11.35	42.5±9.2	37.5±7.18	30 (9-40)	50 (26-66)	43.4±7.65	37.4±5.48
Male	27.8±6.19	47.8±7.32	43.9 ± 7.23	39.7±6.98	24 (7-36)	41.5 (24-67)	40.8±7.12	36.1±5.58
	p=0.280	**p=0.048**	p=0.437	p=0.132	**p=0.004**	**p=0.010**	p=0.116	p=0.283
Profession								
Healthcare employee	29.1±6.55	47 (20-71)	43.4±8.39	38.5±7.17	27.4±9.25	45.2±10.33	41.3±8.05	37.7±5.87
Other	24.4±6.33	42 (38-56)	39.9±8.39	38.2±7.33	23.5±7.91	43.1±9.72	42.2±7.23	36.3±5.4
	p=0.044	p=0.472	p=0.230	p=0.912	p=0.051	p=0.388	p=0.603	p=0.296
Emergency service areas								
Isolated area	28.6±6.27	46.8±9.22	41.9±7.83	38.1±7.7	29±2.83	49±0.0	49±8.49	36 ±1.41
Other	28.7±6.84	45±10.31	43.7±8.66	38.7±6.92	24.5±8.52	43.6±9.97	41.8±7.38	36.7±5.61
	p=0.897	p=0.405	p=0.350	p=0.724	p=0.458	**p=0.000**	p=0.177	p=0.857
Being satisfied with the work environment								
Satisfied	28.3±6.81	45.3±10.09	42.8±8.57	37 (20-55)	24.5 (7-40)	41.0 (24-66)	40.5±6.88	36.0 (25-44)
Not satisfied	30.8±5.31	47.1±9.53	45±7.44	44 (39-56)	30 (12-38)	53.0 (36-67)	45.3±7.66	40.5 (30-54)
	p=0.161	p=0.506	p=0.329	**p=0.000**	p=0.45	**p=0.000**	**p=0.005**	**p=0.000**

*Analyses were made by using the Mann-Whitney U test for the data that were not distributed normally, and median, minimum-maximum values were identified.
SD: Standard deviation, PSS: Perceived stress scale, STAI-S: State and trait anxiety inventory-state, STAI-T: State and trait anxiety inventory-trait, WRSI: Work-related strain inventory

longer, and remained away from activities that might make them feel good. The fact that the personal protective equipment, which is worn for protection from infection, is disturbing and heavy has also moved healthcare employees away from their comfortable area. Although such equipment makes them feel protected from the disease, it also constantly reminds them that they are face-to-face with the infection. In addition, seeing that their patients and colleagues are infected with COVID-19 and that they lose their life threaten the mental health of the employees. Previous studies show that clinical symptoms such as anxiety, uneasiness, insomnia, and depression are frequent in healthcare employees due to all these reasons (12,13).

The endurance of healthcare employees who are exposed to continuous increasing workload causes that optimum yield is obtained from healthcare systems. Endurance is the ability to fit and adapt to conditions causing stress for an individual, and individuals who can endure negative conditions have optimism and confidence in control of conditions even under difficult conditions. The more resistant healthcare employees, the lower levels of anxiety they experience (14). However, it is also known that healthcare employees experience feelings such as anger, fear, disappointment, guilt, helplessness, and anxiety, and are subject to being stigmatized by society and experiencing more trauma symptoms in the long term. In previous studies conducted with STAI-S and STAI-T to determine the anxiety experienced by healthcare employees due to the pandemic, it was found that STAI-S scores were at statistically significant levels in healthcare employees than individuals who did not work in the field of healthcare, and there were no significant differences in terms of STAI-T scores. Again, it was found that STAI-S scores were higher at statistically significant levels in women than in men, in married ones than in single ones, and in nurses than in doctors; and there were no significant differences in terms of STAI-T scores (15). In a study in which STAI was evaluated, it was found that the STAI scores of healthcare employees were high (14). In another study, no significant relations were detected between age, gender and anxiety scores (16). In our study, the perceived stress, state and trait anxiety and work-related strain levels of the female gender were found to be higher in the low-risk group in PSS and STAI-S. The perceived stress, state and trait anxiety and work-related strain levels of the male gender were found to be higher in the high-risk group in STAI-S. We believe that gender has no significant effects on anxiety because of the elevated scores found in different scales in different groups in males and females. The fact that the infection and mortality of the COVID-19 pandemic are independent of gender can be considered as a reason for this.

When the literature data were evaluated, according to the study of Liu et al. (16) using the self-rating anxiety scale, it was determined that the anxiety scores of healthcare workers who had direct contact with COVID-19 were high. According to the study of Lai et al. (17) using the Patient Health Questionnaire, Generalized Anxiety Disorder, Insomnia Severity Index, Impact of Event Scale-Revised scales, the high level of mental health symptoms such as depression (50.4%), anxiety (44.6%), insomnia (34.0%), distress (71.5%) were detected. According to another study of Zhang et al. (18) using the Insomnia

Severity Index, the Symptom Check List-revised, and Patient Health Questionnaire-4 scales, it was found that the prevalences of insomnia, anxiety, somatization, and obsessive-compulsive disorder were higher in medical health care workers compared to non-medical health workers. According to another study of Lu et al. (19) using the "Numeric rating scale", "Hamilton Anxiety Scale", and "Hamilton Depression Scale's, fear, anxiety and depression scale values were found to be higher in health workers when medical health workers and administrative staff were compared. In our study, we found that the levels of perceived stress, state and trait anxiety and work-related strain were higher in the high-risk group in the PSS (Table 3). However, it was found in some studies conducted with healthcare employees working in the field of COVID-19 by using the PSS that no significant differences were detected in PSS between healthcare employees working in risky places and healthcare employees working in other units (20). In a study conducted in 2003 during the SARS pandemic, it was found that the stress levels were higher in the high-risk group compared to the low-risk group, and no statistically significant differences were detected; and this difference was found to be statistically significant in the same health professionals in another study conducted one year after the SARS pandemic was over (21). In our study, the perceived stress, state and trait anxiety and work-related strain levels were higher in the high-risk group in all scales, and these differences were found to be statistically significant according to PSS; however, this difference was not significant according to the WRSI, STAI-S, STAI-T scales. The reasons why the perceived stress levels were found to be higher in employees with high risk in our study in PSS might be increased work life of healthcare employees in the pandemic period, the fear of being infected with the disease, the fear of infecting their children or beloved ones, fear of death, and the restrictions on social life. The reason for no statistically significant differences in other scales might be that the emergency services were very busy, and the stress, anxiety and work-related strain levels of employees in this area were high also before the COVID-19, and that the employees were already familiar with stress, anxiety and work-related strain. Also, it may be considered that pandemics may affect people in social, economic, and psychological terms regardless of being a high-risk or low-risk employee, and the increased stress, anxiety and work-related strain levels in both groups may have hindered the occurrence of statistically significant levels. It was shown in previous studies that the mental effects of the pandemic might continue for months even for years after returning to routine life (22). We are planning to clarify this by repeating the same study on the same individuals 1 year after the pandemic.

People and healthcare employees in particular are affected in terms of social, economic, and psychological aspectsin pandemics. Factors such as the quarantine process and social isolation, the fear of the disease, the fear of being infected with the disease, the stress of treating colleagues infected with the disease, job stress, the fear of being stigmatized by the society due to the fear of carrying the infection, the fear of infecting relatives for whom the healthcare employee is providing care at home affect the lives of healthcare employees (23). In our study, it was found that the majority of the healthcare employees working in both high-risk and low-risk areas did not change their homes, and those who were married did not separate from their children. The reason for this may be that our healthcare employees are used to work in crowded, intense, chaotic emergency services as well as their economic problems.

According to the study of Birhanu et al. (24), healthcare employees constitute an important group that might be affected by workplace stress because of their unique working environments. The stress levels due to the workplace were found to be high in healthcare employees in this study (24). Similar to the literature data, the stress, anxiety and work-related strain levels of healthcare employees who were not satisfied with their working environment were found to be higher in all scales in our study. This difference was found to be significant in the WRSI. Job is an important part of life, and as a result of this, it is expected to affect the quality of life of people. It is inevitable that people who are not satisfied with their work environment have higher stress, anxiety and work-related strain levels.

Although high anxiety scores were detected in single individuals in the study of Zhang et al. (18), no significant relations were detected between marital status and anxiety levels in most studies (15,25,26). In our study, in line with the literature, no significant differences were detected between age, marital status, having children, and perceived stress, state and trait anxiety and work-related strain levels of healthcare employees.

Insomnia, depression, anxiety, and somatization symptoms were detected to be higher in those with non-organic diseases according to the study conducted by Zhang et al. (18). Again, in the same study, when those who lived with their families were compared according to the depression model, it was found that depression levels were higher in those living alone (18). In our study, no significant differences were detected between chronic disease and living alone and the perceived stress, state and trait anxiety and work-related strain levels of employees. The stress, anxiety and strain caused by the fear of transmitting the disease to their loved ones in those living with their families, and the low sociability in the lonely ones may be the reasons for the lack of difference between the two groups that were living alone or living with family.

Study Limitations

The first one was that the number of participants was limited to 183 healthcare employees. The second one was that although there were patients with COVID-19 in the city in the period of the study, their number did not reach peak level. The third limitation was that a pandemic hospital was established in our city, and COVID-19 positive patients were referred to this hospital. As a result, COVID-19 risk remained relatively lower than the pandemic hospital due to the admission of mild and outpatients to our hospital. The fourth limitation was the examination of mental problems such as anxiety levels at one time in pandemics. As a matter of fact, it would not provide accurate results examining psychological problems that would be brought by a pandemic, which started in 2019 and was still

in progress, and whose end was not known. Because the stress, anxiety, work-related strain levels of healthcare employees may vary with increasing positive cases and difficult conditions. To address these limitations, we are planning to evaluate the stress, anxiety and work-related strain levels of our same healthcare employees with the same scales.

Conclusion

Our study can constitute a source for possible pandemics that may occur in the future for healthcare employees to work with more self-confidence and to increase the psycho-social support training for healthcare employees to minimize their perceived stress, state and trait anxiety, work-related strain levels during pandemics. It is among the most important factors for us to improve the mental states of healthcare employees to provide the best quality of healthcare services during pandemics.

Ethics

Ethics Committee Approval: Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee Presidency (number: 24237859-416/date: 03.07.2020).

Informed Consent: Survey study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.K., A.G., V.Ö., Concept: Y.K., A.G., V.Ö., P.Ş., M.İ., S.P., D.S.A., M.T., A.G., Design: Y.K., A.G., V.Ö., P.Ş., M.İ., S.P., D.S.A., M.T., A.G., Data Collection or Processing: Y.K., A.G., V.Ö., P.Ş., M.İ., S.P., D.S.A., M.T., A.G., Analysis or Interpretation: Y.K., A.G., V.Ö., P.Ş., Literature Search: Y.K., A.G., V.Ö., Writing: Y.K., A.G., V.Ö.

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Original Article

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Effect of Position Priority on Physiological Variables in Preterm Newborns Receiving Respiratory Support: Randomized Controlled Trial

Solunum Desteği Alan Preterm Yenidoğanlarda Pozisyon Önceliğinin Fizyolojik Değişkenlere Etkisi: Randomize Kontrollü Çalışma

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ABSTRACT

Objective: This study was designed to evaluate the effect of supine and prone position priority on oxygen saturation and heart rate in preterm newborns receiving respiratory support.

Methods: This was a randomized controlled study. Preterm newborns who were aged <7 days, clinically stable and received respiratory support were included. The sample group consisted of 38 preterm newborns were divided into two groups by randomization according to position priority; Group 1 [supine/prone (S/P)], Group 2 [prone/supine (P/S)].

Results: In both prone and supine positions, the mean oxygen saturation of preterm newborns in Group 2 (P/S) was found to be significantly higher than those in Group 1 (S/P). It was determined that the mean heart rate of preterm newborns in Group 1 (S/P) in the supine position was significantly lower than in Group 2 (P/S).

Conclusion: Giving the prone position first and then the supine position to preterm newborns receiving respiratory support increases oxygen saturation.

Keywords: Heart rate, oxygen saturation, supine position, prone position, preterm newborn

ÖZ

Amaç: Bu çalışma, solunum desteği alan erken doğmuş yenidoğanlarda sırtüstü ve yüzüstü pozisyon önceliğinin oksijen satürasyonu ve kalp hızı üzerindeki etkisini değerlendirmek için tasarlanmıştır.

Yöntemler: Bu çalışma randomize kontrollü bir çalışmadır. Doğum sonrası en fazla yedi günlük olan ve klinik olarak stabil olan, solunum desteği alan preterm yenidoğanlar dahil edildi. Örnek grubunu oluşturan 38 preterm yenidoğan öncelik sırasına göre iki gruba randomize edildi: Grup 1 [sırtüstü/yüzüstü (S/P)], Grup 2 [yüzüstü/sırtüstü (P/S)].

Bulgular: Grup 2'deki (S/P) erken doğmuş yenidoğanların ortalama oksijen satürasyonu, Grup 1'dekilere (S/P) göre anlamlı derecede yüksek bulundu. Grup 1'deki yenidoğanların ortalama kalp hızlarının sırtüstü pozisyonda Grup 2'dekilere göre anlamlı derecede düşük olduğu belirlendi.

Sonuç: Solunum desteği alan preterm yenidoğanlara ilk önce yüzüstü pozisyonu daha sonra sırtüstü pozisyonu verilmesi oksijen satürasyonunu artırır.

Anahtar Sözcükler: Kalp hızı, oksijen satürasyonu, sırtüstü pozisyon, yüzüstü pozisyon, erken doğmuş yenidoğan

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Introduction

Preterm newborns constitute the most important group of newborns hospitalized in the neonatal intensive care unit (NICU) (1). As the birth weight and gestational age of preterm newborns decrease, the lack of maturation in organs and systems and their susceptibility to premature complications increase (2). Since the respiratory center and lungs of preterm newborns are anatomically and functionally immature, respiratory distress is the most common problem they experience (3,4). Respiratory problems (74%) are in the first place in preterm newborns (5). In the NICU, preterm newborns have to get respiratory support due to respiratory distress (6). Respiratory support is used to provide oxygenation and excretion of accumulated carbon dioxide through alveolar ventilation, as well as to relieve and support breathing in newborns with insufficient respiratory function or without breathing (7,8). In the care of the newborn under respiratory support, application of moist and heated oxygen, routine physical examination and close monitoring of vital signs, especially respiratory distress symptoms and blood gases are required (9,10). During respiratory support, the body temperature of the newborn should be preserved, and liquid electrolyte and nutritional support should be provided. One of the important nursing care practices on newborns who receive respiratory support is to lay them in the appropriate position and change their position frequently (11,12).

Proper positioning of preterm newborns in the NICU is one of the important applications of individualized developmental care (13-15). Appropriate positioning is an application that supports newborns to get the least harm from environmental factors (16). Appropriate positioning is an intervention that enables preterm newborns to maintain their body posture and feel safe (17). It has been reported that proper positioning of newborns affects the respiratory system and heart rate of the newborn (18).

Supine, prone and side lying positions, called therapeutic positions, are recommended to prevent excessive tension of the joints of preterm newborns and to maintain the flexion position (19,20). With therapeutic position applications (supine, prone and lying on the side), normal growth and development are facilitated, staying in the same position for a long time is prevented, muscle deformity and asymmetry are prevented, unnecessary energy expenditure and stress are reduced and the newborn is allowed to rest. Within the scope of individualized supportive developmental care, the neonatal calming and physiological stability are increased by ensuring that the newborn feels safe (21,22).

The best lying position for preterm newborns is the prone position. The American Academy of Pediatrics recommends placing preterm newborns in the prone position during their stay in intensive care units, partly due to well-documented physiological effects in sick newborns, particularly those with lung disease (23). In the literature, it is reported that prone position increases oxygenation (24-27) and lung function (28). When the prone position is applied to preterm newborns first and then the supine position, the oxygen saturation and heart rate of the newborn may remain stable. However, no studies were found showing the changes in position priority in oxygen saturation and heart rate.

Methods

Purpose

The aim of this randomized controlled study is to evaluate the effect of priority of supine/prone (S/P) positions on oxygen saturation and heart rate in preterm newborns receiving respiratory support.

Research Hypotheses

(1) Hypotheses 1: The first prone position, then the supine position will provide better regulation of the oxygen saturation of preterm newborns with statistically significant differences compared to the first supine then prone position

(2) Hypotheses 2: The first prone position, then the supine position will provide better regulation of the heart rate of preterm newborns with statistically significant differences compared to the first supine then prone position

Study Design

This was a two-period crossover, experimental, randomized controlled trial. Preterm newborns in the study were divided into two groups by randomization according to position priority; Group 1 (S/P) and Group 2 [prone/supine (P/S)]. In this study, each newborn was both a study and a control group (crossover design).The study protocol prepared on the basis of the literature (24,26,29) was reviewed and approved by Clinical Trials.gov (NCT03895242).

The study was conducted in the NICU of an education and research hospital in Turkey, between February 2015 and June 2016. Study sample was deemed adequate based on sample size calculation performed with PS Power and Sample Size Calculations (Version 3.0). According to the formula of the calculated sample size, for a crossover design with a=0.05, the sample size required to achieve a 90% power was 36. Thus, the sample of the study consisted of 38 preterm newborns who met the inclusion criteria.

Inclusion criteria of the study were; (a) having 25 to 36 weeks of gestation age, (b) receiving respiratory support [mechanical ventilation (intubated) or nasal CPAP at least 12 hours], (c) postnatal age ≤7 days, and (c) being clinically stable.

We excluded newborns who had cardiopulmonary instability, underwent high-frequency oscillating ventilation, had congenital impairment preventing positioning, and received continuous sedative and anticonvulsant drugs.

The closed envelope method was used as a randomization method in the study. Preterm newborns in the research were divided into two groups according to the priority of position; Group 1 (S/P) and Group 2 (P/S). Papers on which “Group 1 (S/P)” or “Group 2 (P/S)” was written were placed one by one into the

opaque sealed envelopes. When deciding a preterm newborn's position, a random envelope was selected among the envelopes by the clinical nurse who was not included in the study. Then the envelope was opened by the positioning researcher and the position of the preterm newborn was determined based on which group was written on the paper. The group of the newborn was determined just before positioning. Due to the nature of the interventions, it was not possible to blind the researcher's intervention to any of those involved. However, assessment of outcome measures was blind.

Procedure

After determining the group of the preterm newborns randomly, routine nursing care was given to the preterm newborns. After supine or prone position was given with positioning materials, the newborns were treated and fed.

The preterm newborns in Group 1 (S/P) were first placed in supine position and were waited for 60 minutes to stabilize after the positioning (no data was collected during this time). From the 61st minute, SpO_2 and HR were recorded with the pulse oximetry for 120 minutes every 15 minutes. Two hours later, the preterm newborns in Group 1 (S/P) was gently turned into the prone position by the investigator and they were waited for 60 minutes to stabilize after the positioning (no data was collected during this time). From the 61st minute, SpO_2 and HR were recorded with the pulse oximetry for 120 minutes every 15 minutes. Figure 1 shows the sample flow and protocol of the study.

In this study, all positioning and data collection procedures were performed by the researcher. The preterm newborns stayed in each position for 3 hours (1 hour for their stabilization and 2 hours for monitoring SpO_2 and HR values). Physiological parameters (oxygen saturation and heart rate) of the newborns were evaluated every 15 minutes for 120 minutes in accordance with the literature (24,26,30). Both groups were positioned in the midline and the head of the bed was raised 15-30 degrees

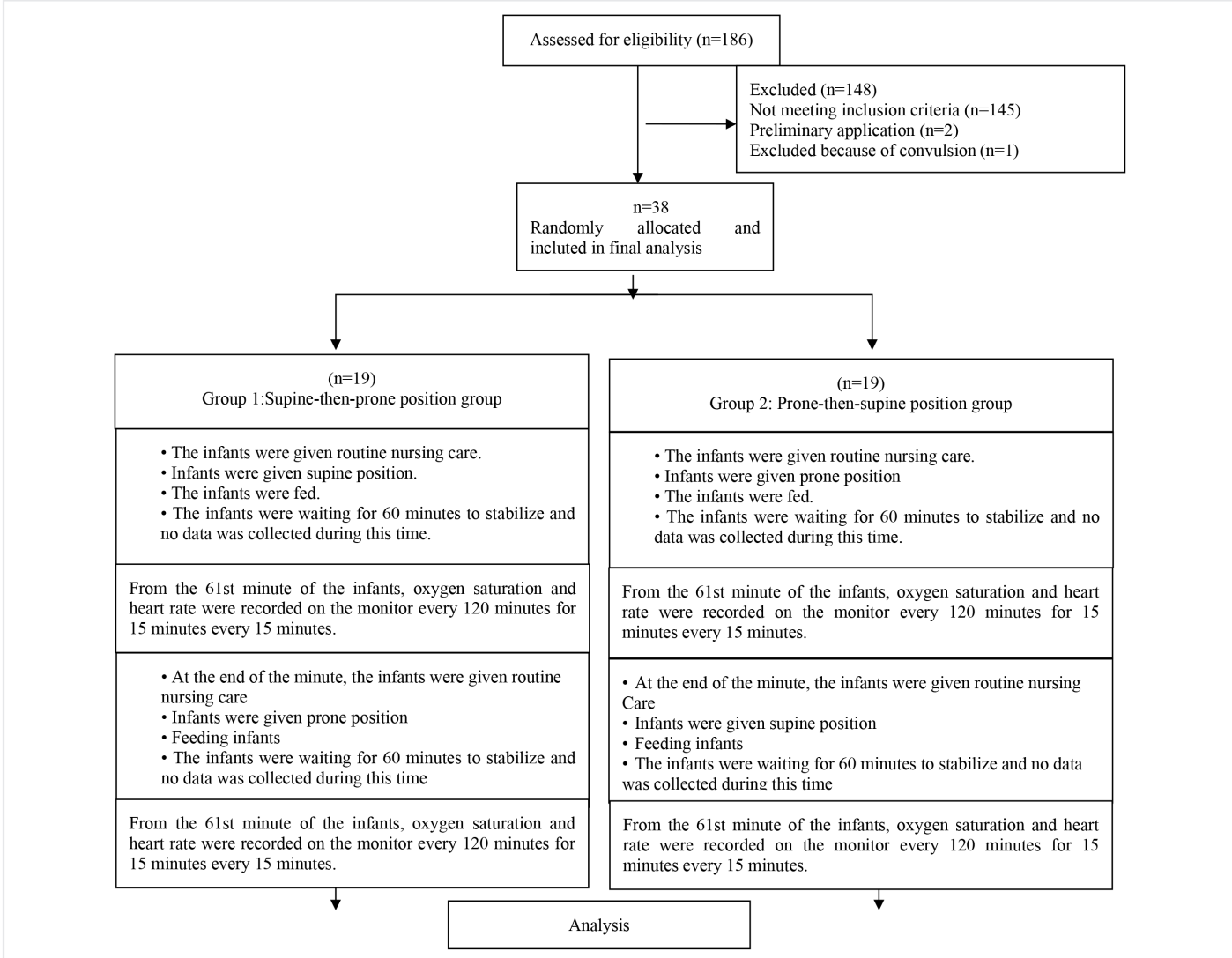

Figure 1. Flowchart based on the CONSORT diagram

(30,31). In all positioning procedures, it was ensured that the extremities were in symmetrical physiological flexion, the neck was slightly flexed (<30 degrees), and the head and body were aligned.

Positioning materials were used to increase the positive effects of positions and to prevent positional deformities (32). Towel rolls were used as materials for positioning the newborns. In the supine position, the head was turned to the midline or to the right or left side. The upper extremities were placed near the chest wall. The lower extremities were given a flexion position by placing a rolled towel under the knees. In the prone position, the head was turned to the right or left side. A towel roll was placed under the head to provide a slight extension. Hands were placed on both sides of the head. The flexion position was given to the lower extremities by placing a towel cover on the abdominal area. The newborns involved in the study were cared for in a incubator and wore diapers only.

Measures

The data collection tools, The Newborn Descriptive Characteristics Form, The Newborn Clinical Variable Form and The Physiological Variable Monitoring Form were specially designed for this study based on the literature (24,30,33). Descriptive characteristics were gender, age, gestational age and birth weight. Clinical variables were respiratory support, treatment with surfactant and caffein. Physiological variables were heart rate (HR) (minimum) and oxygen saturation (% SpO_2). A pulse oximetry (Philips Model) was used to determine HR and SpO_2. The normal vital sign ranges assumed for the study subjects were as follows; 121 to 179 beats per minute for HR and oxygen saturation ≥92% (34). The pulse oximetry was calibrated as recommended by the manufacturer prior to use at the beginning of each shift within the study period. The pulse oximetry probe was attached to the foot.

In order to conduct the study, written permissions were obtained from the hospital. The study was approved by the Institutional Review Board of the University (IRB no: 2015-41) and was conducted in compliance with the Helsinki Declaration. Before starting the study, the parents were informed about the objective, plan, and period of the study, and their written and verbal consents were received.

Statistical Analysis

Data analysis was carried out using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) statistical program. Frequencies, percentages, mean values, standard deviation and range were used as descriptive statistics. Kolmogorov-Smirnov test was used to determine the suitability of variables for normal distribution. All the variables were normally distributed. Accordingly, parametric tests such as variance analysis and t-test were used to determine the differences between the variables of the two groups. Variance analysis was used in repeated measurements of HR and oxygen saturation of preterm newborns at 15-minute intervals. A value of $p<0.05$ was considered statistically significant.

Results

As presented in Table 1, 18 (47.4%) preterm newborns were male, 20 (52.6%) were female. The mean age of the newborns

Table 1. Comparison of descriptive and clinical variables of preterm newborns (n=38)

Characteristic or clinical variables		Group 1 (S/P) (n=19)		Group 2 (P/S) (n=19)		Total (n=38)		p
		n (%) or M (SD)		n (%) or M (SD)		n (%) or M (SD)		
Gender Female		9 (47.4)		11 (57.9)		20 (52.6)		0.516
Male		10 (52.6)		8 (42.1)		18 (47.4)		
Age(days)		2.42 (1.30)		3.05 (1.47)		2.73 (1.40)		0.170
Gestational age (weeks)		31.53 (2.99)		31.26 (3.18)		31.40 (3.05)		0.794
Birth weight (g)		1750.53 (637.29)		1675.79 (646.09)		1713.16 (634.11)		0.722
Respiratory support	MV	11 (57.9)		7 (36.8)		18 (47.4)		0.194
	NCPAP	8 (42.1)		12 (63.2)		20 (52.6)		
Treatment with surfactant	Yes	10 (52.6)		13 (68.4		23 (60.5)		0.319
	No	9 (47.4)		6 (31.6)		15 (39.5)		
Treatment with caffeine	Yes	9 (47.4)		12 (63.2)		21 (55.3)		0.328
	No	10 (52.6)		7 (36.8)		17 (44.7)		
Nutritional status	Parenteral + enteral	9	47.4	9	47.4	18	47.4	1.000
	Parenteral	10	52.6	10	52.6	20	52.6	
Diagnosis	RDS	10	52.6	9	47.4	19	50	0.746
	TTN	9	47.4	10	52.6	19	50	

S/P: Supine/prone, P/S: Prone/supine, MV: Mechanical ventilation, NCPAP: Nasal continuous positive airway pressure, RDS: Respiratory distress syndrome, TTN= Transient tachpynea of newborn, SD: Standart deviation

Table 2. Comparison of heart rate and oxygen saturation according to positions and measurement time of preterm newborns (n=38)

Group	Measurement time (min)	Heart rate		Oxygen saturation	
		Supine M (SD)	**Prone** M (SD)	**Supine** M (SD)	**Prone** M (SD)
Group 1 (supine/prone n=19)	0	136.48 (19.75)	141.84 (14.93)	98.16 (1.42)	97.37 (2.39)
	15	138.58 (16.62)	139.48 (16.20)	98.68 (1.11)	98.05 (1.75)
	30	137.21 (17.81)	139.58 (15.34)	97.63 (1.67)	98.05 (1.87)
	45	138.52 (20.14)	141.37 (13.03)	97.79 (1.78)	98.11 (1.91)
	60	138.21 (21.72)	140.37 (14.42)	97.74 (1.37)	98.16 (2.01)
	75	137.05 (18.19)	142.58 (13.68)	97.79 (1.90)	98.00 (1.70)
	90	138.42 (15.89)	143.63 (14.92)	97.84 (1.74)	97.58 (2.12)
	105	141.42 (17.54)	143.69 (15.47)	96.95 (2.04)	98.11 (1.37)
	120	139.74 (17.52)	142.84 (15.45)	97.42 (1.81)	97.79 (2.25)
	Total	138.40 (18.05)	141.71 (14.58)	97.78 (1.70)	97.91 (1.92)
Group 2 (prone/supine n=19)	0	142.68 (14.84)	136.31 (15.22)	98.11 (2.26)	98.74 (1.69)
	15	145.32 (16.44)	137.90 (12.78)	98.32 (1.86)	99.00 (1.15)
	30	144.84 (13.88)	138.37 (12.76)	98.53 (1.78)	98.79 (0.92)
	45	145.48 (17.97)	141.74 (15.66)	98.84 (1.42)	98.79 (1.44)
	60	144.95 (17.56)	141.11 (15.08)	98.42 (1.64)	98.90 (1.29)
	75	144.05 (15.54)	144.11 (16.88)	98.79 (1.27)	98.58 (1.54)
	90	142.68 (14.73)	144.11 (18.42)	98.58 (1.71)	98.90 (1.29)
	105	142.42 (16.20)	146.16 (17.56)	98.37 (1.64)	98.841 (1.61)
	120	146.37 (17.77)	147.37 (15.95)	98.42 (1.87)	98.21 (1.90)
	Total	144.31 (15.84)	141.91 (15.75)	98.48 (1.71)	98.75 (1.44)
Statistic		**p value**	**p value**	**p value**	**p value**
	Between-groups	0.002	0.904	0.000	0.000
	Change over time	0.998	0.369	0.624	0.851
	Time-group interaction	0.998	0.956	0.398	0.955

SD: Standart deviation, min: Minimum

was 2.73±1.40 days. Among the preterm newborns who received respiratory support, 47.4% were on mechanical ventilation and 52.6% were on nasal CPAP. The groups were homogeneous in terms of these characteristics.

In both prone and supine positions, the means of oxygen saturation of preterm newborns in Group 2 (P/S) was found to be significantly higher than in Group 1 (S/P) (prone: F =20.22, p=0.000, supine: F=14.73, p=0.000). It was determined that the mean HR of preterm newborns in Group 1 (S/P) was significantly lower than in Group 2 (P/S) in the supine position (F=9.92, p=0.002). It was determined that there was no significant difference between the mean HR of preterm newborns in Group 1 (S/P) and those in Group 2 (P/S) in the prone position (F=0.01, p=0.904) (Table 2).

As a result of the statistical analysis in this study, the mean of oxygen saturation of the preterm newborns in the Group 1 (S/P) at the 105th minute was statistically significantly higher in prone position (t=-4.01, p=0.001) (Table 3).

It was determined that the mean of oxygen saturation of the preterm newborns in the Group 2 (P/S) at the 15th minute was statistically significantly higher in the prone position (t=-2.17, p=0.0439) (Table 4).

Discussion

The aim of this randomized controlled study was to evaluate the effect of priority of supine and prone positions on oxygen saturation and HR in preterm newborns receiving respiratory support.

In a study, preterm newborns were divided into two groups as Group 1 S/P and Group 2 P/S and oxygen saturation was compared between the groups. As a result of the study, no difference was found in terms of oxygen saturation between the groups (24). Our results were not similar to the results of the study by Chang et al. (24).

Wu et al. (35) divided 67 newborns who underwent mechanical ventilation (intubation) into two groups as the supine position

Table 3. Comparison of oxygen saturation and heart rate averages of preterm newborns in Group 1 (S/P) according to measurement time and positions (n=19)

Group	Measurement time (min)	Oxygen saturation			
		Supine M (SD)	**Prone** M (SD)	**t**	**p**
Group 1 (supine/prone)	**0**	98.16 (1.42)	97.37±2.39	1.20	0.2444
	15	98.68 (1.11)	98.05±1.75	1.61	0.1241
	30	97.63±1.67	98.05±1.87	-0.85	0.4084
	45	97.79±1.78	98.11±1.91	-0.68	0.5061
	60	97.74±1.37	98.16±2.01	-0.87	0.3973
	75	97.79±1.90	98.00±1.70	-0.45	0.6587
	90	97.84±1.74	97.58±2.12	0.40	0.6915
	105	**96.95±2.041**	**98.11±1.37**	**-4.01**	**0.0008**
	120	97.42±1.81	97.79±2.25	-0.71	0.4876
		Heart rate			
		Supine M (SD)	**Prone** M (SD)	**t**	**p**
	0	136.48±19.75	141.84±14.93	-1.42	0.1733
	15	138.58±16.62	139.48±16.20	-0.29	0.7757
	30	137.21±17.81	139.58±15.34	-0.57	0.5735
	45	138.52±20.14	141.37±13.03	-0.76	0.4576
	60	138.21±21.72	140.37±14.42	-0.50	0.6229
	75	137.05±18.19	142.58±13.68	-1.40	0.1789
	90	138.42±15.89	143.63±14.92	-1.51	0.1472
	105	141.42±17.54	143.69±15.47	-0.59	0.5649
	120	139.74±17.52	142.84±15.45	-1.02	0.3217

SD: Standard deviation, min: Minimum

group and the alternating position group. The oxygen saturations at 8 and 16 hours were recorded after giving 33 of the newborns the supine position (4 hours), and after giving 34 of them the supine position (4 hours) and then the prone position (4 hours). It was found that oxygen saturation was higher in the alternating position group (first supine, then prone) than the supine position group (35).

Hough et al. (36) divided 30 preterm newborns with <32 weeks of gestation and birth weight >750 gwho underwent nasal CPAP or had spontaneous breathing into two groups including semi-prone, prone and supine positions groups. The oxygen saturation was recorded 30 minutes after each position. No difference was found between the order of positions in terms of oxygen saturation (36). Hough et al. (36) followed up preterm newborns who received nasal CPAP or had spontaneous breathing for 30 minutes after each positioning, while we followed up those who were intubated or received nasal CPAP for 120 minutes after each positioning.

Hough et al. (37) found that there was no difference between the order of semi-prone, prone and supine positions in terms of oxygen saturation of preterm newborns who were intubated or breathing spontaneously. Wu et al. (35) determined that the oxygen saturation of the preterm newborn who was given the prone position first was higher.

Although the finding obtained at the 15th minute in our study did not seem to be significant; the finding obtained at the 75th minute after waiting for 60 minutes following positioning was significant. So, the finding obtained at the 15th minute can be evaluated as the finding obtained at the 75th minute. This situation supports that the finding obtained at the 15th minute is a significant finding and that oxygen saturation is higher in the prone position. In addition, when looking at the positions of preterm newborns in the groups; it was observed that those in Group 1 (S/P) were in the prone position at the 105th minute and those in Group 2 (P/S) were in the prone position at the 15th minute. This situation highlights the importance of the positive effect of prone position on oxygen saturation.

In line with these results obtained in our research; it was observed that preterm newborns who received respiratory support in the prone position first had higher oxygen saturation in this position and the prone position kept the oxygen saturation stable. In addition, it was determined that the oxygen saturation was higher and stability continued during the period of supine position in preterm newborns who were given supine position

Table 4. Comparison of oxygen saturation and heart rate averages of preterm newborns in Group 2 (P/S) according to measurement time and positions (n=19)

Group	Measurement time (min)	Oxygen saturation Supine M (SD)	 Prone M (SD)	t	p
Group 2 (prone/supine)	**0**	98.11±2.26	98.74±1.69	-1.43	0.1690
	15	**98.32±1.86**	**99.00±1.15**	**-2.17**	**0.0439**
	30	98.53±1.78	98.79±0.92	-0.62	0.5433
	45	98.84±1.42	98.79±1.44	0.12	0.9093
	60	98.42±1.64	98.90±1.29	-1.69	0.1075
	75	98.79±1.27	98.58±1.54	0.57	0.5778
	90	98.58±1.71	98.90±1.29	-0.92	0.3686
	105	98.37±1.64	98.84±1.61	-1.49	0.1545
	120	98.42±1.87	98.21±1.90	0.39	0.6975
		Heart rate			
		Supine M (SD)	**Prone** M (SD)	**t**	**p**
	0	142.68±14.84	136.31±15.22	2.09	0.0513
	15	145.32±16.44	137.90±12.78	2.10	0.0505
	30	**144.84±13.88**	**138.37±12.76**	**2.77**	**0.0126**
	45	145.48±17.97	141.74±15.66	1.36	0.1917
	60	144.95±17.56	141.11±15.08	1.41	0.1755
	75	144.05±15.54	144.11±16.88	-0.02	0.9822
	90	142.68±14.73	144.11±18.42	-0.47	0.6474
	105	142.42±16.20	146.16±17.56	-1.28	0.2164
	120	146.37±17.77	147.37±15.95	-0.30	0.7671

SD: Standard deviation, min: Minimum

after prone. However, it was observed that oxygen saturation of preterm newborns who received respiratory support in the supine position was not stable for 3 hours. As a result, it is suggested that preterm newborns who receive respiratory support should be given the prone position first and that they can remain in the prone position after 3 hours.

In line with the results, it was determined in our study that the HR of preterm newborns in group 1, who was given the supine position first, was lower. When the literature was examined, it was determined in the studies that the order of the position did not affect the HR (36,37).

Study Limitations

The limitation of the present study was that it was not possible to control the noise due to the personnel and devices. The sample size was limited due to the fact that the study was conducted in a single center.

Conclusion

The results showed that the method of first prone then supine positioning was effective in increasing oxygen saturation but ineffective in reducing HR. Prone position may be preferred primarily to increase oxygenation of preterm newborns receiving respiratory support in the NICU.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Review Board of the University (IRB no: 2015-41) and was conducted in compliance with the Helsinki Declaration.

Informed Consent: The parents were informed about the objective, plan, and period of the study, and their written and verbal consents were received.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Original Article

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Can Anatomical Variations of AICA Loop be a Cause of Hearing Loss which can Affect the Laterality of Tinnitus Also?

AICA Loop Anatomik Varyasyonları Tinnitus Lateralitesini de Etkileyebilecek İşitme Kaybının Bir Nedeni Olabilir Mi?

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ABSTRACT

Objective: We aimed to reveal whether the vascular loop variations created by the antero-inferior cerebellar artery (AICA) in the cerebellopontine angle (CPA) and the internal acoustic canal (IAC) can be a cause, that can affect laterality of tinnitus and cause hearing loss.

Methods: The data and the magnetic resonance imaging scans were collected retrospectively and 109 patients with tinnitus were included in the study. Data were recorded according to the patients' duration and laterality of tinnitus, laterality, type and frequency of hearing loss ,contact type and extension of AICA with remarking the side of the vascular loop.

Results: A statistically significant difference was found in between the left ear high frequency (HF) hearing loss (p=0.042) and extension type of the AICA. Also showed statistically significant results in between left sided tinnitus (p=0.030) and the Chavda classification. Besides the patients who had right sided tinnitus, was found to be in relation with the right sided contact type as the p value was 0.023.

Conclusion: Our results suggest that AICA variations in CPA and IAC can cause HF hearing loss as well as particularly affect the side of tinnitus. Nevertheless, this relationship must be confirmed by more advanced audiological and imaging techniques.

Keywords: Tinnitus, hearing loss, anterior inferior cerebellar artery

ÖZ

Amaç: Anterior inferior serebellar arterin (AICA), serebellopontin açıda (SPA) ve internal akustik kanalda (İAK) oluşturduğu vasküler loop varyasyonlarının, tinnitus hissedilme tarafını etkileyen ve işitme kaybı oluşturabilen bir neden olup olamayacağını ortaya koymayı amaçladık.

Yöntemler: Toplam 109 tinnitus hastasının verileri retrospektif olarak toplandı ve çalışmaya dahil edildi. Hastaların tinnitus süresi ve lateralitesi, işitme kaybının tipi ve kulak tarafı, manyetik rezonans görüntülemede AICA vasküler loop tarafı, temas tipi ve uzantısı, odyolojik ve radyolojik görüntüleme verileri taranarak kaydedildi.

Bulgular: Sol kulakta yüksek frekanslı (YF) işitme kaybı (p=0,042) ile AICA'nın ekstansiyon tipi arasında istatistiksel olarak anlamlı fark bulundu. Ayrıca sol taraflı tinnitus (p=0,030) ile Chavda sınıflandırması arasında istatistiksel olarak anlamlı sonuçlar gözlendi. Bunların yanı sıra sağ tarafta tinnitusu olan hastalar ile sağ taraflı temas tipi arasında anlamlı ilişkili saptandı (p=0,023).

Sonuç: Sonuçlarımız, SPA ve İAK'deki AICA varyasyonlarının YF'li işitme kaybına yol açabileceği gibi kulak çınlamasının tarafını da özellikle etkileyebileceğini ortaya koymaktadır. Yine de bu ilişki daha ileri odyolojik ve görüntüleme teknikleriyle onaylanmalıdır.

Anahtar Sözcükler: Tinnitus, işitme kaybı, anterior inferior serebellar arter

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Introduction

Hearing of a nonexisting sound which is perceived without an external or internal stimuli is called tinnitus. Approximately 12% of the general population suffers from tinnitus worldwide (1-4). Tinnnitus can be both temporary or chronic and can be defined as "ringing in the ears" and as different perceptions of sound including buzzing, rustling, hissing, whistling, pulsing, roaring and clicking. Tinnitus is not a disease in itself, but rather a symptom of another health condition. In most cases, tinnitus is a sensorineural reaction that occurs in the brain and hearing system. While tinnitus is often associated with hearing loss, there is a wide variety of health problems that can cause tinnitus as a symptom however the etiology remains uncertain in some patients (5,6). To determine the possible causes of tinnitus in a patient, physical examination with detailed medical history has to be performed. Neuroradiologic imaging may also help to identify the neuro-otologic causes in mandatory cases. Vascular anatomical variants can also be considered in tinnitus etiology which can be revealed clearly with imaging methods.

Cerebellum folding around the pons and middle cerebellar peduncle forms a V-shaped cleft which is located between the superior and inferior limbs of the cerebellopontine fissure in the posterior fossa called cerebellopontine angle (CPA). The anterior inferior cerebellar artery (AICA) is a branch of the basilary artery and usually courses posterolaterally in the CPA, but various pathways of AICA are defined (7,8). The vestibulocochlear nerve (CNVIII) passes through the internal auditory canal (IAC), travels along anterolaterally in the CPA than enters the brainstem and facial nerve (CNVII) also transmits to the face via CPA through the IAC (9). Vascular compression of CNVIII can be the cause of tinnitus and accompany some other symptoms such as dizziness, hemifacial spasm, trigeminal neuralgia and vertigo. Jannetta (10) depicted that hemifacial spasm, trigeminal neuralgia, hearing loss, tinnitus and vertigo might be associated with vascular loop of AICA within the IAC compressing on cranial nerves (11). There are theories in the etiology of vascular orginated tinnitus. The primary clarification is that changes within the blood stream disturb the laminar stream and newly existing turbulence can cause an audible sound. Besides, physiologically streaming sounds of the vascular structures can be heard more escalated with bone conduction when the impact of outside sound masking effect weakens. The chronic compression of the vessel may be responsible for regional demyelination or impairment of blood flow on the nerve. These impacts can lead to dysfunction of the nerve and also development of symptoms (12).

Computed tomography and magnetic resonance imaging (MRI) have been utilized in the evaluation of microvascular compression (MVC). MRI has appeared to be a more appropriate imaging in determining the vascular loops, besides it is a supportive technique to analyze the other causes of tinnitus (11). The subject of radiological imaging still remains unclear in patients with tinnitus. The candidates can be either patients with unilateral tinnitus and hearing loss or patients with asymmetrical hearing loss or patients with unspecified audiometric results (3,6,13). Despite all these uncertainties, it is obvious that MRI is the best way to identify the AICA vascular loop. But MVC can be detected commonly in general population, so it can bring along a contradiction. Cadaveric studies also revealed that AICA loop in IAC could be found in the prevelance of 40% (7,14).

We aimed to evaluate the association between the laterality of tinnitus and hearing loss with the types of vascular loops of AICA in the CPA and IAC, examining through the MRI scans.

Methods

We carried out a retrospective study in our tertiary referral center with the approval of local ethical committee (app no: 2020/85-1195). The patients were selected from our databasa in between January 2017 and December 2019, and their medical history and physical examination notes were searched thoroughly. Patients who were under 18 years old and who had any other diagnosed otologic, neurologic or systemic diseases in their history were excluded from the study. One hundred nine patients who had tinnitus and also vascular loop in MRI were recorded according to their demographic factors (age and gender), duration and laterality of tinnitus, contact type and extension of the vascular loop, laterality and type of hearing loss (PTA and high frequency). Especially, none of the patients complained from significant pulsation, they mostly complained from buzzing or ringing in the ear.

Data Collection

Radiological Evaluation

The MRIs were performed with a 1.5 T system (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) with a head coil. The standart imaging protocol included transverse T2 weighted [echo time (TE) =110, repetition time (TR) =6,690 ms, slice thickness =5 mm] screening of the whole brain. For the evaluation of CPA; transverse fat-saturated (FS) T1 weighted (TE =9.7 ms, TR =404 ms, slice thickness =2 mm), T2 weighted (TE =111 ms, TR =4,540 ms, slice thickness =2 mm), T2 weighted SPACE (TE =156 ms, TR =1,400 ms, slice thickness =0.6 mm), coronal FS T1 weighted (TE =7.3 ms, TR =697 ms, slice thickness =2 mm), T2 weighted (TE =93 ms, TR =3,720 ms, slice thickness =2 mm), and following gadolinium-based contrast material injection (10 mL, 0.5 mmol/mL, gadoteric acid, Guerbet, Roissy, France), transverse FS T1 weighted (TE =9.7, TR =120 ms, slice thickness =2 mm) and coronal FS T1 weighted (TE =7.3, TR =150 ms, slice thickness =2 mm) images were used.

The previous reports of the images were not taken into consideration as MRIs were newly evaluated by a single radiologist blinded to the clinical history and findings. The radiologist examined MRIs for the location of AICA loops in the IAC and position of the loops relative to nerve(s), and also any other pathologic abnormalities in CPA, cochlea and/or vestibulum were noted. The location of AICA loop in the IAC was graded according to the Chavda classification (Type I: lying within the CPA but not entering the IAC, Type II: entering but not extending >50% of the length of the IAC, Type III: extending >50% of the IAC) (15). The position of the

loop relative to nerve(s) was evaluated in transverse view and described in terms of the type of contact to the nerve(s) (Type A: crossing 2 (vestibular and cochlear nerve) or 4 nerves in the IAC (as a bridge), Type B: crossing only one nerve, Type C: running parallel to the nerves but not crossing them) (16).

Audiologic Tests

Auditory testing results of all patients who were included in the study were obtained by searching the audiologic archives. Tests were performed in a soundproof cabin with Radioear- 3045 earphones (Therapeutic Technologies, Bournemouth, UK). Pure tone average (PTA) was calculated from auditory thresholds recorded at 0.5, 1, and 2 kHz and high frequency (HF) hearing levels at 4 and 8 kHz were recorded also with Interacoustics AC 40 Clinical audiometer (Interacoustics, Assens, Denmark). The tresholds which were higher than 25 dB were accepted as hearing loss. According to their test results, the patients were classified as having normal hearing treshold, right sided asymmetric hearing loss, left sided asymmetric hearing treshold, bilateral symmetric hearing loss (difference at least 20 db between ears) in PTA treshold and also in HF levels (4 kHZ - 8 kHZ).

Statistical Analysis

The data were analyzed with SPSS 23.0 (IBM, Armonk, NY, USA). The descriptive data results were given as mean ± standard deviation and median (minimum-maximum). Chi-square test was used to compare the categorical variables in the groups and results were presented as frequency (n) and also in percent (%). Statistical significance level was stated as $p<0.050$.

Results

Demographic Data

There were 109 patients in this study consisting of 63 male and 46 female patients with a mean age of 43.6±17.5 (range 18-80). Fourty two (38.5%) patients had tinnitus symptom less than 1 year, 43 (%39.4) patients had symptom for 1 to 3 years, 14 (12.8%) patients had tinnitus for 3 to 5 years and 10 (9.2%) patients suffered from tinnitus over 5 years. While 43.1% (n=47) of patients had bilateral symmetrical tinnitus, 33% (n=36) of them had tinnitus only on the right and 23.9% (n=26) of them only on the left side. According to the gender of the patients, there was no statistically significant difference in terms of the distribution of AICA extension and contact in IAC for both ear ($p>0.050$).

Audiometric Findings

Audiometric results revealed that 54.1 % (n=59) of patients had normal hearing level treshold in PTA while 17.4% (n=19) of them had right sided asymmetrical, 12.8% (n=14) left sided asymmetrical and the rest 15.6% (n=17) had bilateral symmetrical hearing loss. In HF audiometry test, 49.5% (n=54) of the patients had symmetrical hearing loss while 21.1% (n=23) had normal hearing tresholds. There was no relationship between hearing loss and tinnitus (Table 1).

MRI Findings

According to the Chavda classification; the frequency of Type I AICA placement was 47.7% (n=52), the frequency of Type II was 41.3% (n=45) and the frequency of Type III was 11% (n=12) in right IAC. For the left IAC, the frequency of Type I extension of AICA was 70% (n=64.2) (Figure 1). The frequencies of Type II and Type III extensions were 29.4% (n=32) and 6.4 % (n=7), consecutively in left ear. In the MRI evaluation, Type A contact was also found in high percentages for both ears as 91.7 % (n=100) and 88.1% (n=96) (Figure 2), respectively in the right and the left ears of the patients.

The patients who had right sided tinnitus were found to be in relation with the right sided contact type ($p=0.023$). Among the patients who had right sided tinnitus, 94.4% (n= 34) of them had Type A (Figure 3) and 5.6% (n=2) (Figure 4) of them had Type B contacts in the right IAC. Besides, there was statistically significant relationship between the Chavda classification of the left ear and left sided tinnitus ($p=0.030$). Of the patients 46.2% (n=12) who had left sided tinnitus had Type I and 50% of them (n=13) had Type II extensions into the left IAC (Table 2).

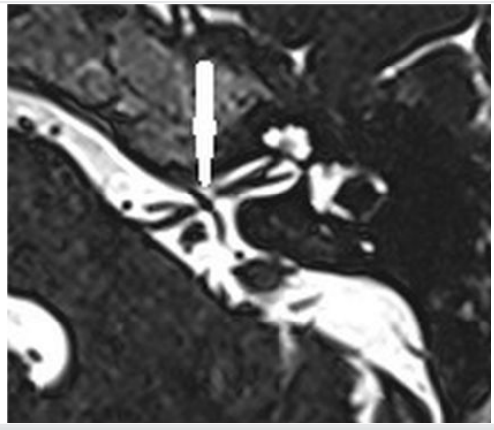

Figure 1. Transverse T2 SPACE image demonstrates vascular loop located in left cerebellopontine angle, crossing over the nerves (white arrow) (Type I A)

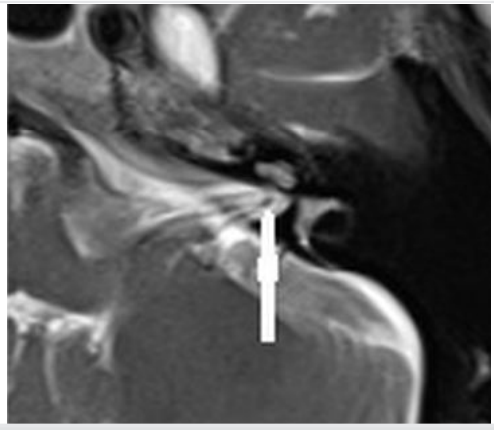

Figure 2. Transverse T2 weighted image demonstrates vascular loop entering and extending >50% of left internal acoustic canal, crossing over the nerves (white arrow) (Type III A)

Table 1. The comparison of PTA and HF acording to the ear with tinnitus symptom

	Right sided n (%)	Left sided n (%)	Bilateral n (%)	Total n (%)	p value
PTA					
Normal threshold levels	16 (44.4)	16 (61.5)	27 (57.4)	59 (54.1)	0.471
Right sided asymmetrical HL	9 (25)	4 (15.4)	6 (12.8)	19 (17.4)	
Left sided asymmetrical HL	3 (8.3)	3 (11.5)	8 (17)	14 (12.8)	
Bilateral symmetrical HL	8 (22.2)	3 (11.5)	6 (12.8)	17 (15.6)	
HF					
Normal threshold levels	8 (22.2)	5 (19.2)	10 (21.3)	23 (21.1)	0.844
Right sided asymmetrical HL	7 (19.4)	4 (15.4)	4 (8.5)	15 (13.8)	
Left sided asymmetrical HL	6 (16.7)	4 (15.4)	7 (14.9)	17 (15.6)	
Bilateral symmetrical HL	15 (41.7)	13 (50)	26 (55.3)	54 (49.5)	

number (% percentage), PTA: Pure tone avarage, HF: High frequency, HL: Hearing loss,
*p value of chi-square test statistics which are statistically significant (p<0.050)

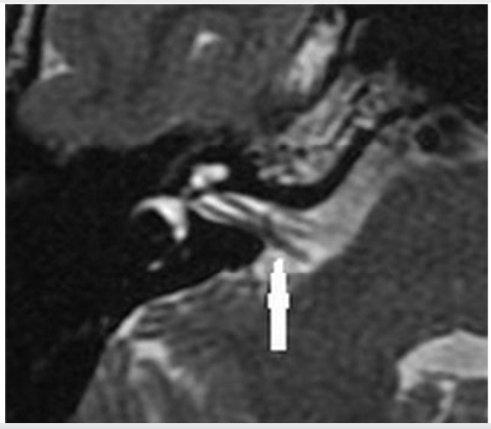

Figure 3. Transverse T2 weighted image demonstrates vascular loop entering and extending <50% of right internal acoustic canal, crossing over the nerves (white arrow) (Type II A)

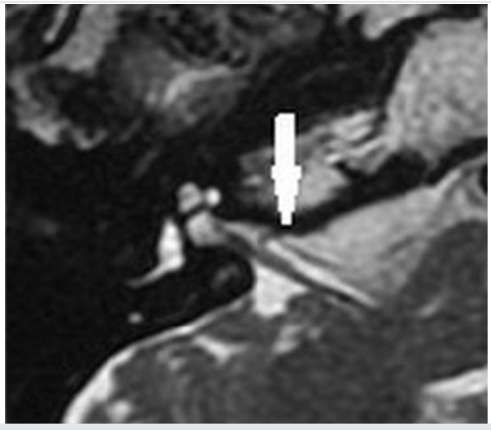

Figure 4. Transverse T2 weighted image demonstrates vascular loop entering and extending <50% of right internal acoustic canal, in contact with one nerve (white arrow) (Type II B)

Although there was no relationship between the HF audiologic findings and contact type of AICA in both ears (p>0.050), a statistically significant relationship was found between the left ear HF hearing loss and the Chavda classification (p=0.042) (Table 3).

Discussion

The neurovascular anatomical structures in CPA vary widely. These structural changes can cause several symptoms according to their relationship within surroundings. Vascular compression of the seventh and eighth cranial nerves in the CPA may lead to hearing loss, tinnitus, vertigo, dizziness, imbalance and hemifacial spasm.

There were many studies which aimed to investigate the effects of vascular compression on the CNVIII. We studied the relation between hearing loss and the AICA loop extension/contact to the CNVIII in tinnitus. Ultimately, a relationship was found between HF hearing loss and tinnitus, and the extension and contact types of AICA in the IAC. The Type A contact (n=100) and Type I (n=52) & Type II (n=45) extensions were the most frequent ones in right IAC. According to these, not the extension position but the type of the contact seemed to be affecting only the perception of tinnitus in the right ear. On the other hand, the left IAC imaging revealed that the Type I extension (n=70) and Type A contact (n=96) were the most common anatomic variations. But when compared to the right side findings, extension type was found to be related to both tinnitus and HF hearing loss in the left ear. Correspondingly, Di Stadio et al. (16) reported that direct contact between the vascular loop and the particular nerve could be the causal explanation of the symptoms arising and that also Type A (the most common) localization could bring out the nerve impingements. In our study, as we included the patients only with the tinnitus symptom, we revealed that Type A contact was the common anatomical variation almost in all patients for both sides. Similarly, in a meta-analysis of Chadha and Weiner (17), it was suggested that the patients with pulsatile

Table 2. Comparison of tinnitus in each ear with the extension type and contact type of AICA

	Right sided tinnitus n (%)			p value
	(+)	(-)	Total	
R extention				
Type I	37 (50.7)	15 (41.7)	52 (47.7)	
Type II	30 (41.1)	15 (41.7)	45 (41.3)	0.372
Type III	6 (8.2)	6 (16.7)	12 (11)	
R contact				
Type A	66 (90.4)	34 (94.4)	100 (91.7)	
Type B	---	2 (5.6)	2 (1.8)	**0.023***
Type C	7 (9.6)	---	7 (6.4)	
	Left sided tinnitus n(%)			
	(+)	(-)	Total	
L extention				
Type I	58 (69.9)	12 (46.2)	70 (64.2)	
Type II	19 (22.9)	13 (50)	32 (29.4)	0.030*
Type III	6 (7.2)	1 (3.8)	7 (6.4)	
L contact				
Type A	72 (86.7)	24 (92.3)	96 (88.1)	
Type B	2 (2.4)	0 (0)	2 (1.8)	0.641
Type C	9 (10.8)	2 (7.7)	11 (10.1)	

number (% percentage), (+): Means the presence of tinnitus, (-): Means absence of tinnitus,
*p value of chi-square test statistics which are statistically significant (p<0.050)

tinnitus weremore likely to have vascular abnormalities in MRI. In our results altough there was no pulsatile tinnitus complaint among the patients we encountered with the Type A contact and also Type I extension. Even the Type I extension brings along the lowest risk of nerve impengement, this placement can still lead to perception of tinnitus. Also, Yoo et al. (18) supported the idea that there was an association between the unexplained tinnitus and Type I & II extensions in IAC and even the small sized AICA loops in CPA. Nowé et al. (19) revealed that if the vascular compression on the CNVIII in cisternal segment was present, there was a possible relation between the high and low pitch tinnitus and hearing loss as well. McDermott et al. (15) reported that tinnitus was not associated with the presence of the vascular loop, but AICA loops caused unilateral hearing loss once in the IAC when extending more than 50%. Altough the most common extension was not more than 50% in our study, likewise we found correlation between the HF hearing loss and extension of AICA into the IAC. In contrast, there are several studies which support the idea that the finding of tinnitus in AICA loops are incidental or may not always be a pathological finding (11,20-22). de Abreu Junior et al. (23) also stated that there was no direct relationship between MRI findings of AICA and clinical symptoms. In another retrospective study which Li et al. (20) conducted, it was reported that high prevalence of any vascular loops could be present in the asymptomatic ear so the ipsilateral symptoms might not be associated with this vascular placement.

Certainly, in our study, laterality of the most frequent type of extension correlated with the side of the HF hearing loss and the side of the tinnitus. Friede has suggested that the outer surface of the cochlear nerve is composed of the nerves that transmit the high pitched sound as they are originated from the basal turn, however the central nerves are originated from the cochlear apex which transmit the low pitched sound, so called tonotopic organization (24). This formation may also explain the HF hearing loss in this study. Nevertheless, tinnitus still can be related with the high prevalence of the Type I extension on the left side and also the HF hearing loss prevelance may also seem to be affecting our results. As all of our subjects had various types and grades of AICA, fibrosis might occur on the nerve structures due to the long standing vascular compression. But concurrently, in our study, almost half of the patients had bilateral symmetrical HF hearing loss which might also lead to tinnitus. Because this is a retrospective study in which all of the participants have AICA variations and tinnitus, we may not put forward very definitive considerations about the subject (25).

Study Limitations

Constitution of a control group from the patients who did not have neither tinnitus nor hearing loss to find a stronger audiological correlation could be the limitation of our study.

Conclusion

This study showed correlation between HF hearing loss, tinnitus and AICA placement. But since the pathophysiology of tinnitus is still unclear and there are multiple factors in the etiology of hearing loss , this relationship must be confirmed with further researches which will be conducted with improved neuroimaging techniques.

Table 3. Comparison of high frequency hearing loss with the left ear AICA extension type

HF	Left ear			Total	p value
	Type I	Type II	Type III		
Normal threshold levels	13 (18.6)	7 (21.9)	3 (42.9)	23 (21.1)	
Right sided asymmetrical HL	7 (10)	7 (21.9)	1 (14.3)	15 (13.8)	**0.042**
Left sided asymmetrical HL	12 (17.1)	2 (6.3)	3 (42.9)	17 (15.6)	
Bilateral symmetrical HL	38 (54.3)	16 (50)	---	54 (49.5)	

number (% percentage), HF: High frequency, HL: Hearing loss, *p value of chi-square test statistics which are statistically significant (p<0.050). *p value of chi-square test statistics which are statistically significant (p<0.050)

Ethics

Ethics Committee Approval: Near East University Scientific Research Ethics Committee (date: 26.11.2020/number: 1195).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: E.T.Y., Y.K., Concept: E.T.Y., Design: E.T.Y., Data Collection or Processing: E.T.Y., Y.K., Analysis or Interpretation: E.T.Y., Y.K., Literature Search: E.T.Y., Writing: E.T.Y.

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Original Article

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Cancer Patients' Knowledge of Exercise in Cancer: A Cross-sectional Study

Kanser Hastalarının Kanserde Egzersiz Bilgisi: Kesitsel Çalışma

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ABSTRACT

Objective: Exercise is effective in reducing the risk of cancer, and treatment side effects. However, our empirical observations indicate that patients diagnosed with cancer have poor knowledge of exercise in cancer. This study aimed to evaluate cancer patients' knowledge of exercise in cancer.

Methods: After a review of the literature, the researchers developed a questionnaire aimed at evaluating knowledge of exercise in cancer. The study included patients with a history of cancer aged ≥18 years. The participants were asked to respond to each item in the electronic survey by selecting "I had no idea", "I have heard of it", or "I know very well".

Results: The study included a total of 125 participants with a history of cancer (75 females, 60%; 50 males, 40%), and their mean age was 52.05±11.50 years. We determined the validity and reliability of the questionnaire before analyzing participants' knowledge of exercise in cancer. Bartlett's test of sphericity and the Kaiser-Meyer-Olkin measure indicated that the data were appropriate for factor analysis ($p<0.001$). Factor analysis confirmed the structural validity of the questionnaire. Cronbach's alpha was calculated as 0.963, implying reliable internal consistency. Subsequently, we analyzed participants' answers to the questionnaire and observed that the response rate of "I know very well" ranged between 3.2% and 14.4% for different items.

Conclusion: We prepared and validated a tool for the measurement of knowledge exercise in cancer. Accordingly, we conclude that cancer patients have inadequate knowledge of exercise in cancer.

ÖZ

Amaç: Egzersizin kanser riskini ve kanser tedavilerinin yan etkisini azaltmakta faydalı olduğu bilinmektedir. Ancak, kanser tanısı almış bireylerin kanserde egzersiz konusundaki bilgilerinin düşük olduğu ampirik gözlemlerimiz arasındadır. Bu çalışma ile kanser hastalarının kanserde egzersiz konusundaki bilgilerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Araştırmacılar tarafından literatür taraması yapılarak kanserde egzersiz bilgisini değerlendirmeyi amaçlayan bir anket formu (ölçüm aracı) oluşturulmuştur. Özgeçmişinde kanser tanısı bulunup 18 yaş üzeri olan hastalar çalışmaya dahil edilmiştir. Araştırmacılar tarafından hazırlanan ölçüm aracındaki her bir maddeye, elektronik anket aracılığı ile "hiçbir fikrim yok", "duymuştum" ya da "çok iyi biliyorum" yanıtlarından birisinin verilmesi istenmiştir.

Bulgular: Çalışmaya özgeçmişinde kanser tanısı olan 125 birey katılmıştır. Çalışmaya katılan bireylerin %60'ının (n=75) kadın, %40'ının (n=50) erkek olduğu ve katılımcıların yaş ortalamalarının 52,05±11,50 yıl olduğu saptanmıştır. Çalışmaya katılan bireylerin bilgi düzeyini değerlendirmeden önce araştırmacılar tarafından hazırlanan ölçüm aracının geçerlilik ve güvenirlilik analizleri yapılmıştır. Kaiser-Meyer-Olkin ölçüm değeri ve Bartlett küresellik test sonuçlarına göre ölçüm aracının faktör analizi yapmaya uygun olduğu belirlenmiştir ($p<0,001$). Faktör analizi sonucunda ölçüm aracının yapı geçerliliğinin sağlandığı gösterilmiştir. Cronbach alfa kat sayısı 0,963 olarak hesaplanan ölçüm aracının güvenilir olduğu saptanmıştır. Ölçüm aracının geçerlilik ve güvenirlilik sağladığı gösterildikten sonra ölçüm aracına verilen cevaplar incelendiğinde

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The developed questionnaire can contribute to assess and improve knowledge of exercise among cancer patients.

Keywords: Cancer, exercise, knowledge

ölçüm aracındaki maddelere "çok iyi biliyorum" cevabının verilme oranının %3,2 ile %14,4 arasında değiştiği gösterilmiştir.

Sonuç: Araştırmacılar tarafından hazırlanıp geçerliliği ve güvenilirliği sağlanmış olan bu ölçüm aracına verilen cevaplar göz önüne alındığında kanser hastaların kanserde egzersiz bilgisi düzeyleri düşük bulunmuştur. Hazırlanan bu ölçüm aracı, kanser hastaların kanserde egzersiz bilgi düzeylerinin değerlendirilmesine, eksikliklerin saptanmasına ve bu doğrultuda bilgi düzeylerinin artırılmasına katkıda bulunulabilir.

Anahtar Sözcükler: Kanser, egzersiz, bilgi

Introduction

Cancer is a leading cause of morbidity and mortality around the world. World Health Organization (WHO) data indicated that 18.1 million people were diagnosed as having cancer in 2018, 30-50% of which were preventable (1). Accordingly, WHO invited all member states to pursue high-level efforts to encourage measures such as healthy eating, increased physical activity, reduced alcohol and cigarette consumption, and vaccination. A 2020 report by WHO indicated that the world was likely to see a 60% increase in cancer cases over the next 20 years if current trends continued (2).

Significant progress was made in exercise and oncology research within the last two decades (3). Regular exercise has been shown to reduce the incidence of many types of cancer, especially breast and colorectal cancers (4). Again, exercise has been associated with a substantial decline in recurrence and mortality in many types of cancer (5). Physical activity reduces life-long endogenous estrogen exposure and increases sex hormone-binding globulin levels (6). Reduced estrogen and increased physical activity help to achieve long-term energy balance and to reduce central adiposity. Decreased estrogen, adiposity, and glucose and increased insulin sensitivity contribute to the improvement of metabolic profile (6). Exercise decreases insulin-like growth factor-1, which is known to increase cancer cell division in breast, prostate, lung, and colorectal cancers, and PGE2, which stimulates cell proliferation in colon cancer (7). Moreover, exercise mediates the reduction of C-reactive protein, improves circulating granulocyte ratio and monocyte function, and contributes to immune function by increasing the cytotoxic activity of natural killer cells and thymidine uptake by lymphocytes (8,9). These physiological contributions translate into reduced cancer recurrence and mortality.

Cancer treatment is associated with weight loss, decreased muscle mass, loss of physical function, and decreased quality of life. Decreased aerobic capacity, fatigue, and depressive symptoms are common during cancer treatment (5). Exercise is a safe and cost-effective tool to prevent or alleviate numerous secondary complications associated with cancer treatment, and to improve quality of life for cancer survivors (10). The most common side effect of cancer treatment is fatigue (4). Loss of muscle mass, anemia, increased cytokine levels, depression, and anxiety cause fatigue. Regular exercise improves physical function and increases aerobic capacity and muscle and bone masses, and is also associated with improved immune function and psychosocial well-being, all of which help to reduce fatigue symptoms (4). Aerobic exercises increase cardiopulmonary capacity, increase hemoglobin concentration, accelerate angiogenesis, increase capillary surface area and improve the oxidative capacity of muscles and adenosine triphosphate resynthesis, contributing to the regulation of physiological functions (11). Resistance exercises increase muscle glucose uptake by increasing muscle and bone masses and thus help to correct hyperinsulinemia and to improve insulin sensitivity (11). In addition, regular exercise improves pain, nausea, vomiting, diarrhea, and insomnia (4). Given these benefits, exercise is a prominent component of cancer rehabilitation (5).

Unfortunately, research has shown that doctors, nurses and other health professionals do not routinely inform patients about exercise programs, which results in poor patient knowledge and limited participation in exercise (12). This study aimed to evaluate cancer patients' knowledge of exercise in cancer.

Methods

This study was granted ethical approval by the local ethics committee (date: 05/03/2021 decision no: 700).

Sample: We invited cancer patients who were members of relevant Turkish non-governmental organizations. The study included patients with a history of cancer who were aged ≥18 years on a voluntary basis. One hundred twenty five participants diagnosed as having cancer (regardless of cancer type) were included in the study. Participants completed the questionnaire prepared by the researchers online (Google Forms).

Measurement Tool: After reviewing the literature (13), the researchers developed a 25-item questionnaire aimed at evaluating knowledge of exercise in cancer. The participants were asked to respond to each item in the electronic survey by selecting "I have no idea", "I have heard of it", or "I know very well".

A pilot study was conducted with healthy individuals to confirm the clarity and utility of the questionnaire, followed by the main study conducted with the target population, i.e., patients diagnosed as having cancer. The sample size was calculated as five participants per item, that is 125 participants.

Statistical Analysis

Sociodemographic data were analyzed using descriptive statistics and frequencies. The validity and reliability of the questionnaire, prepared in line with the literature, were confirmed using SPSS version 23. The suitability of the measurement tool for factor analysis was analyzed with Kaiser-Meyer-Olkin and the Barlett sphericity tests. Cronbach's alpha coefficient was used to evaluate the reliability of the measurement tool. The results were presented as frequencies, percentages, and mean ± standard deviation.

Results

There was a total of 125 participants (75 females, 60%; 50 males, 40%). The mean age was 52.05±11.50 years. Among the participants, 65.6% had completed primary education, 19.2% secondary education, and 15.2% post-secondary education and above. Of the participants 54.4% were in active treatment, 38.4% completed treatment and were on follow-up, and 7.2% received a new diagnosis but were not started treatment.

Cancer diagnoses included breast cancer (41.6%), colorectal cancer (10.4%), stomach cancer (9.6%), female genital system cancer (8.8%), male genital system cancer (6.4%), lung cancer (6.4%), and other (16.8%). The mean time since cancer diagnosis was 49.50±1.89 months.

We determined the validity and reliability of the Knowledge of Exercise in Cancer Questionnaire before analyzing participants' knowledge of exercise in cancer. Kaiser-Meyer-Olkin test (0.877) and Bartlett test of sphericity (3034.55, $p<0.001$) verified the questionnaire's adequacy for factor analysis. The suitability of the items for performing a factor analysis was tested using an anti-image correlation matrix (minimum 0.812 and maximum 0.930). Factor loadings of the items were between 0.504 and 0.857. These results confirmed the structural validity of the questionnaire. The scree test for the plot of eigenvalues showed the questionnaire to be unidimensional with an eigenvalue greater than 1.0. The eigenvalue of the single factor structure was 13.363, and the variance ratio was 53.45%. Cronbach's alpha was calculated as 0.963, implying reliable internal consistency. None of the items if deleted would increase Cronbach's alpha more than 5%. These results indicated excellent reliability. According to results concerning the significance of the difference between the upper and lower 27% of the total scores, all t-values were positive and significant ($p<0.05$). Table 1 presents the results of our study, and responses to each item are indicated as percentages (%).

We analyzed participants' responses to the Knowledge of Exercise in Cancer Questionnaire and observed that the response rate of "I know very well" ranged between 3.2 and 14.4% for different items. This finding suggested that cancer patients had inadequate knowledge of exercise in cancer.

Discussion

We found that the questionnaire prepared in this study was valid and reliable in determining cancer patients' knowledge of exercise in cancer, and our results suggested that cancer patients' knowledge of exercise in cancer needed improvement.

As part of cancer treatment, exercise reduces treatment-related side effects, improves psychosocial status (14), and reduces risk of recurrence and mortality through various mechanisms (5). Due to increasing patients' life expectancy and quality of life, exercise should be a routine part of cancer treatment and rehabilitation. The first step to integrating exercise into daily life is to develop knowledge of exercise (15). Studies have shown that according to the planned behavior theory, exercise adherence is primarily associated with intention (15,16). To create an intention for physical activity, one must increase patients' knowledge of exercise. After setting a positive intention, subsequent steps include creating a positive attitude and establishing and maintaining exercise behavior (15,16). To achieve progress when following these steps, it is necessary to determine patients' knowledge of exercise and to fill any gaps.

Exercise should be integrated into cancer care early on (17). Knowledge of exercise is the first of many factors that influence exercise adherence during cancer treatment. Ormel et al. (18) reported that predictors of adherence to exercise interventions during cancer treatment included the location of exercise facilities, history of exercising, motivation for exercise, and exercise limitations, and that predictors of adherence after treatment included less extensive surgery, low alcohol consumption, history of exercising, family support, feedback by medical staff, and knowledge and skills of exercise. Rogers et al. (19) demonstrated that most women with breast cancer did not have knowledge of exercise in cancer treatment. The majority of the participants had not been previously informed by their physicians, and most noted that the exercise intervention was more beneficial than harmful (especially in terms of reducing fatigue and improving quality of life). Moreover, half of the participants requested that training and guidance be provided about exercise programs by educated medical staff. Similarly, one study divided 26 patients with breast cancer into two groups: standard treatment, and standard treatment + exercise intervention (8 sessions of aerobic exercise, and at-home strength training) (20). The intervention group had significantly higher exercise levels after the intervention compared to the control group ($p=0.003$). In our study, the response rate of "I know very well" ranged between 3.2% and 14.4% for items concerning exercise knowledge. This finding is consistent with the literature. Assessing the relevant predisposing factors and increasing patients' knowledge of exercise as a first step to introducing exercise to cancer care are important to improve the overall well-being of patients.

A review of the literature revealed a few studies on the reasons behind the lack of exercise knowledge among cancer patients. For instance, Nadler et al. (12) surveyed 120 oncology care providers and found that 80% were not aware of any exercise guidelines. Moreover, oncology care providers had insufficient knowledge on when, how, and which patients to refer to exercise programs. Oncology care providers' barriers to providing information on exercise included poor knowledge, lack of time, and safety concerns. Most participating oncology care providers stated that

Table 1. Answers to the knowledge of exercise in cancer questionnaire

	I have no idea (%)	I have heard of it (%)	I know very well (%)
1. Individuals diagnosed as having cancer should practice moderate aerobic physical activity for at least 150 minutes per week, or alternatively 75 minutes of high-intensity exercise.	62.4	28.8	8.8
2. Individuals diagnosed as having cancer should perform strength training exercises 2-3 days per week.	61.6	32	6.4
3. Individuals diagnosed as having cancer should perform stretching exercises to improve muscle flexibility.	63.2	28.8	8
4. Not all patients diagnosed with cancer need to undergo testing before starting exercise.	72	24.8	3.2
5. Testing is not required before light exercises, including walking, stretching, and low-weight strength training.	70.4	20.8	8.8
6. Some testing may be required before starting moderate-to-high or high-intensity exercise programs.	69.6	20	10.4
7. Morbidly obese patients diagnosed as having cancer may require additional medical assessment before starting an exercise program for safety.	64	24	12
8. Patients who have received hormone therapy or whose cancer has spread to bones (bone metastasis) or who have developed cardiac insufficiency due to treatment side effects need to undergo medical assessment before starting exercise programs.	66.4	24.8	8.8
9. In some types of cancer, the arm-forearm area, calf-thigh area, or muscle strength must be evaluated before starting an exercise program.	71.2	18.4	10.4
10. Patients undergoing surgery to treat cancer should return to exercise as soon as the wound heals, and patients receiving other non-surgical treatments should return to exercise as early as possible.	72.8	20	7.2
11. Patients with excessive fatigue, anemia, or unstable gait/dizziness (ataxia) should take a break from/stop exercising.	68	24	8
12. Patients with ostomies (where the intestine is rerouted to a stoma) must avoid sports where they may receive blows (football, basketball, taekwondo, etc.).	68.8	18.4	12.8
13. Patients who have received hormone therapy or whose cancer has spread to bones (bone metastasis) are at risk of bone fracture during exercise.	68	19.2	12.8
14. There is a risk of infection during exercise while receiving chemo-/radiotherapy or when the immune system is compromised.	68.8	18.4	12.8
15. Patients diagnosed as having cancer with swollen arms or legs (lymphedema) should refrain from exercising arms/forearms or calves/thighs.	69.6	20.8	9.6
16. Patients with ostomies (where the intestine is rerouted to a stoma) should stop exercising if they develop a hernia during exercise, or ostomy-related infections.	72.8	16	11.2
17. Not all patients diagnosed as having cancer need to exercise under supervision.	80	11.2	8.8
18. Patients whose cancer has spread to bones (bone metastasis) or who have developed cardiac insufficiency due to treatment side effects must exercise under supervision.	72.8	13.6	13.6
19. Patients with swollen arms or legs (lymphedema) can prevent this complication by wearing tight-fitting clothing.	73.6	20	6.4
20. Weights should be increased gradually during strength exercises.	72.8	15.2	12
21. If a patient who does strength exercises takes a 2-week break from exercise and wants to go back to exercising, they should do so starting with lighter weights.	72	13.6	14.4
22. Patients with ostomies (where the intestine is rerouted to a stoma) should refrain from increasing abdominal pressure by performing the Valsalva maneuver (forceful attempted exhalation against a closed airway) during strength exercises.	73.6	18.4	8
23. Patients who underwent major surgery for prostate cancer (radical prostatectomy) should exercise their pelvic floor muscles.	80	11.2	8.8
24. In cancer patients who have received a bone marrow transplant, high-intensity exercise can negatively affect the immune system.	73.6	14.4	12
25. Patients with inflammation of nerve endings (peripheral neuropathy) should ride bicycles instead of walking.	77.6	11.2	11.2

it would be beneficial to organize training sessions to increase their knowledge on the subject, and to have an exercise specialist in the clinical team (12). A different survey of 66 patients with cancer and 18 oncologists investigated awareness on the need for structured exercise programs during and after cancer treatment (21). This study found that patients would prefer to meet with an exercise specialist to arrange an exercise program while taking into account their medical and exercise history. On the other hand, oncologists noted that they did not have enough time to provide information about exercise in their outpatient clinics (21). These studies suggest that an important factor limiting patients' knowledge of exercise is the insufficient knowledge and time of doctors and other medical personnel that are involved in their treatment.

A report titled "Moving guidelines into action" by Tomasone et al. (10) discussed basic barriers to exercising among cancer patients, and potential solutions. The report indicated that knowledge gaps on both the patient's and the physician's side, and lack of awareness and provider knowledge presented barriers to exercise. Accordingly, they argued that it was imperative to raise awareness on exercise in cancer and the relevant guidelines among physicians and other medical staff by scheduling discussions, and also among patients via training classes, developing various patient education resources (e.g. brochures, promotional videos, etc.), and creating a patient manual (10). This report emphasized the importance of including exercise recommendations or prescriptions as part of cancer treatment and that it was crucial to increase patient awareness and facilitate access to local exercise programs (including creating a database of existing programs) and establish a process for referral to these programs (10).

The current consensus is that physical activity and exercise should be an integral and continuous part of cancer care, both during and after treatment. Strong evidence suggests that physical activity and exercise should be encouraged among patients of all types of cancer (including advanced-stage cancers) before, during, and after receiving cancer treatment (22). The American College of Sports Medicine recommends avoiding sedentariness as much as possible during cancer treatment, and to practice aerobic exercise (including walking, biking, swimming, and dancing) 150 minutes per week, progressive resistance exercises for 20-30 minutes 2-3 days a week, and flexibility exercises most days of the week (23). Therefore, it is urgent to improve knowledge in order to increase patient well-being. On the other hand, there is a need for a measurement tool that measures knowledge of exercises in cancer and what to do in any potential adverse event during exercise (17). Statistical assessment indicated that the Knowledge of Exercise in Cancer Questionnaire was appropriate for factor analysis (Kaiser-Meyer-Olkin test 0.877, Bartlett's sphericity test 3034.55), and subsequent analyses demonstrated the questionnaire to be structurally valid. The questionnaire had excellent reliability (Cronbach's alpha 0.963). In reference to our results and the literature, we believe that this tool can also be used in different sample groups to measure knowledge of exercise in cancer among cancer patients.

Conclusion

We conclude that cancer patients have inadequate knowledge of exercise in cancer. We confirmed the reliability and validity of the Knowledge of Exercise in Cancer Questionnaire. The developed questionnaire can contribute to assess and improve knowledge of exercise and to create awareness among cancer patients in the clinical setting.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (number: 700/date: 05.03.2021).

Informed Consent: The patients were informed about the questionnaire and their consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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Original Article

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Foot Care Applications of Patients with Tinea Pedis Diagnosis and Affecting Factors

Tinea Pedis Tanısı Alan Hastaların Ayak Bakımı Uygulamaları ve Etkileyen

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ABSTRACT

Objective: The aim of this study is to determine the adequacy of foot care practices and the influencing factors of patients diagnosed with tinea pedis.

Methods: Participants are 187 patients who were examined in a dermatology outpatient clinic in a state hospital in Anatolia between January 10 and April 15, 2021 and were diagnosed with tinea pedis. The research was carried out by applying a face-to-face questionnaire to the participants.

Results: Exploratory factor analysis was performed on the scale used in the study. The total foot scale mean score of the group was found to be 39.31±7.98. The average age is 40.370±0.693, and that of men is 37.313±1.018. The majority are university graduates (69.1%), health insurance is obtained by the social security institution (41.0%). Employees working as civil servants more (32.4%), equal to the income and expenses of the majority (46.9%) and 67%; I smoke 6 cigarettes. Those with chronic diseases are 21.8%. 17% of them regularly use medication.

Conclusion: It was determined that the foot care witchcraft scores of women, those living in the city, those who have the habit of wiping/washing the inside of their shoes, daily airing and changing daily socks were found to be higher. It may be suggested to the society; training on foot hygiene, the use of shoes and socks, foot

ÖZ

Amaç: Bu çalışmanın amacı tinea pedis tanısı alan hastaların ayak bakımı uygulamalarının yeterliliğinin ve etki eden faktörlerin belirlenmesidir.

Yöntemler: Katılımcılar, 10 Ocak-15 Nisan 2021 tarihleri arasında Anadolu'da bir devlet hastanesinde dermatoloji polikliniğinde muayene olan ve tinea pedis tanısı alan 187 hastadır. Araştırma, katılımcılara yüz yüze yöntemi ile anket uygulanarak gerçekleştirildi.

Bulgular: Araştırmada kullanılan ölçeğe doğrulayıcı faktör analizi yapıldı. Grubun ayak bakım ölçeği toplam puan ortalaması 39,31±7,98 olarak tespit edildi. Katılımcılardan kadınların yaş ortalaması 40,370±0,693, erkeklerin 37,313±1,018'dir. Çoğunluk üniversite mezunu (%69,1), sağlık güvencesi sosyal güvenlik kurumu tarafından sağlamaktadır (%41,0). Memur olarak çalışanlar daha fazla (%32,4), çoğunluğun (%46,9) geliri giderine eşit ve %67,6'sı sigara kullanmamaktadır. Kronik hastalığa sahip olanlar %21,8'dir. Bunlardan %17'si düzenli ilaç kullanmaktadır.

Sonuç: Kadınların, kentte yaşayanların, ayakkabısının içini silme/yıkama, günlük havalandırma ve günlük çorap değiştirme alışkanlığı olanların ayak bakımı davranışı puanlarının daha yüksek olduğu tespit edilmiştir. Topluma; ayak hijyeni, ayakkabı ve çorap kullanımı, ayak bakımı ve önemi hakkında eğitim verilmesi, eğitimlerde kırsalda yaşayanları ve erkek popülasyonu kapsayacak şekilde düzenlenmesi önerilebilir.

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care and its importance, it may be suggested to organize it in a way that includes the residents and the male population.

Keywords: Foot care, nursing, tinea pedis

Anahtar Sözcükler: Ayak bakımı, hemşirelik, tinea pedis

Introduction

Tinea pedis (TP) is a fungal infection that can be caused by different types of fungi and can be seen on the soles of the feet, between the toes, and on nails (1). Foot hygiene and moisture are two very important factors in fungal infections of foot (2, 3). Common areas such as showers, bathrooms, pools, and shared use of shoes, socks, and personal care products affect the transmission of infection. Inadequate foot hygiene, wrong choice of shoes, inadequate hygiene of shoe and socks also facilitate the formation of fungus (4,5). According to the literature, the correct application of foot care, being educated on this subject, the level of education (5,6), gender (7), the shoes used (8) affect the formation of fungus. Living in the countryside (6), using closed shoes (7), and the presence of some chronic diseases (5) increase the occurrence of infection. The incidence of TP has been reported to be between 15% and 46% in studies in the literature (7,9-11). Although imidazole, allylamine and benzylamine groups and other antimycotic agents can be used in the medical treatment of TP, especially emphasizing the importance of foot care and hygiene will increase the success of the treatment (1).

Foot care is an application that can be learned and taught. There are many studies showing that foot care training is very effective and positive results are achieved especially in diabetic individuals (11-14). Training on the adequacy of foot care practices (5,6,8) and the use of correct socks and shoes and ensuring their cleanliness (5,7,8) have positive contributions to the foot health of the individual (5,6,11). It is explained that the socio-cultural level of the individuals, depending on the education level (5) and the place they live in, affects the foot care and foot health (6).

There are many studies conducted with diabetic patients who apply foot care correctly (11-14). The general conclusion drawn from the studies is that the rate of foot lesions decreases significantly in individuals who apply foot care correctly (15). However, although the necessity of foot care and hygiene in patients with TP is explained (1-10), no study evaluating foot care behaviors for these patients has been found in the literature. Therefore, in this study, it was aimed to determine the adequacy of foot care practices and the affecting factors of patients with TP.

Methods

This was a descriptive and correlational research.

Research Hypotheses

H1: Patients with TP have different foot care application scores according to their socio-demographic features (age, gender, place of residence, education level, occupation, income level)

H2: Patients with TP have different foot care application scores according to their health-related features (Smoking, chronic disease and drug use).

H3: Patients with TP have different foot care application scores according to their foot hygiene habits (wiping/washing shoes, airing shoes, changing socks).

Location and Characteristics of the Research

The research was conducted in a state hospital in Anatolia.

The Universe of the Research

The population of the study consisted of patients who were admitted to the dermatology outpatient clinic of the hospital where the study was conducted.

Sample of the Research

All patients who were diagnosed as having TP and who were admitted to the dermatology outpatient clinic without selecting a sample and meeting the inclusion criteria were included in the study. Sample calculation was made in accordance with studies of unknown population. The frequency of occurrence of 20% was used by taking the average of 0.05 margin of error, 90% confidence interval and the value range (7,9-11) given in the literature. The sample calculation was made on a web page (16), and it was calculated that the number should be at least 172. A sample of 187 patients who were admitted to the dermatology outpatient clinic of the hospital, were diagnosed as having TP, agreed to participate in the study, and met the inclusion criteria were included in the study.

Inclusion Criteria for Participants in the Study

Being between the ages of 18-65

Having been diagnosed as having TP

Not experiencing clouding of consciousness

Agreeing to participate in the research

Not having a problem with reading and understanding Turkish

Exclusion Criteria for Participants in the Study:

Being unable to care for oneself/needing someone else's help for care

Foot wound/presence of diabetic foot

Data Collection Technique and Tools

The data were collected face to face by the researcher in the outpatient clinic. Written consent was obtained from the patient before the data were collected. After the diagnosis of TP was made for the patient who came for the outpatient clinic examination, the data were collected with the data collection form in the time period suitable for the patients. Data were collected with a patient information form and a foot care behavior scale.

Patient Data Form

The patient data form was created by the researchers based on the literature (1-8). The form includes 16 items questioning age, gender, income level, education, smoking, use of socks and shoes, chronic disease and drug use.

Foot Self Care Observation Guide

Borges and Ostwald (2008) developed the "Foot Self Care Observation Guide" and this guide was converted into a 16-item scale in line with the American Diabetes Association criteria. The scale was adapted into Turkish by Kırbiçer and Enç (2011). The Turkish version (Foot Care Behavior Scale-FCBS) is a five-point Likert-type scale consisting of 15 items (1= Never, 2= Sometimes, 3= Sometimes, 4= Often, 5= Always). The Cronbach alpha coefficient is 0.83. The lowest possible score on the scale is 15; the highest score is 75. The scale has no sub-dimensions and cut-off points.

Data Collection

Data were collected through face-to-face interviews with the patient in the dermatology outpatient clinic between January 2021 and April 2021.

Variables of the Study

Dependent variables: Scale total score.

Independent variables: Age, gender, place of residence, education, occupation, income, presence of chronic disease, drug use, smoking status, practice of cleaning shoes, ventilation of shoes, changing socks

Ethical Aspect of Research:

- Permission for the research was obtained from the Ethics Committee of the Faculty of Health Sciences of Necmettin Erbakan University (date: 06.01.2021/meeting: 6/decision: 4).
- Written informed consent was obtained from the participant along with the data collection form.
- Permission for use was obtained from the scale owners.
- The research was performed in accordance with the Declaration of Helsinki
- This research was prepared, applied and reported according to the Observational Research Reporting Criteria (STROBE) (17).

Limitations of the Research

The limitation of the study was that the patients wanted to stay in the outpatient clinic as short as possible, since the study was conducted during the Coronavirus disease-19 pandemic.

Statistical Evaluation of Data

The statistical analyses were made using the Statistical Package for Social Sciences (SPSS, IBM, v. 22) and SPSS AMOS 22 program. In descriptive statistics; number, percentage, chi-square test and arithmetic mean were used, while Kruskal Wallis and Mann-Whitney U tests were used for relation-seeking statistics. A single factor confirmatory factor analysis (CFA) was performed for the scale used. All results were evaluated at the 0.05 significance level.

Results

Test of the Scale Used in the Research

In order to test the validity of the scales used, a single factor CFA was performed for the FCBS. Since the fit values produced by the measurement models created to test the validity of the scales were not within acceptable limits, the modifications suggested by the program were made and four statements (2,12,13,14) were removed from the scales. Since the values of X2/df=2.092, GFI =0.915, CFI =0.957, RMSEA =0.076 were within acceptable limits, the structures of the scales used in the study were verified. The factor loadings of the scales and the Cronbach-alpha coefficients for their reliability are shown in Table 1. According to the results in Table 1, the fact that the factor loads are at least 0.50 and higher than this value indicates that each statement has loads that can explain the foot care behavior structure (18). Likewise, the Cronbach Alpha coefficient for the reliability of the FCBS was obtained as 0.752 and it was concluded that the scale was reliable.

The mean age of the women was 40,370±0.693, and the mean age of the men was 37.313±1.018. Majority of them were university graduates (69.1%) and health insurance was provided by the social security institution in 41.0% of them. Employees as civil servants constituted 32.4% of the participants, the income of the majority (46.9%) was equal to their expenses, and 67.6% of them did not smoke. Those with chronic diseases constituted 21.8% of the participants. Of them 17% used regular medication. The total mean score of the FCBS was 39.31±7.98 (minimum:18-maximum:54).

Of the participants 67.9% (127) were females and 32.1% were males (60), Most of them were living in the city center (70.7%), had the habit of wiping/washing the inside of their shoes (59.6%), aired their shoes (79.6%) and changed their socks daily (87.2%) (Table 2).

According to the analyzes made, FCBS scores were similar according to educational status, health insurance, occupation, income level, smoking status, having a chronic disease and using regular medication ($p>0.05$). In addition, gender, place of residence, foot washing, foot ventilation and socks changing habits made a difference in FCBS score ($p<0.05$). Foot care score was found to be 40.370±0.693 in women and it was 37.316±1.018 in men, and the difference was statistically significant ($p=0.008$). Accordingly, FCBS scores of males were lower than female individuals. The FCBS scores of the people living in the province, district and village were 39.406±0.702, 40.428±1.171 and 34.846±1.947, respectively. The FCBS scores of the people living in the province and the district are similar ($p<0.05$), but higher than those living in the village. The difference is significant ($p=0.049$). The FCSB score was higher in

Table 1. Foot care behavior scale factor loads and cronbach-alpha coefficients

Questions	Factor loads	Item reliability	Overall scale reliability
I control the temperature of the water I wash my feet in (ABO1)	0.537	0.373	0.752
I use moisturizing cream for my feet (ABO3)	0.580	0.312	
I do not apply cream between the toes (ABO4)	0.516	0.390	
I cut my toenails straight (ABO5)	0.736	0.408	
I check my nails for thickening, ingrownness and length (ABO6)	0.767	0.585	
I check the skin for peeling, fungus and clawing due to moisture between the fingers (ABO7)	0.777	0.650	
I check the bottom of my feet for calluses, redness, blisters or open sores (ABO8)	0.649	0.657	
I check the inside of the shoes for foreign objects such as nails, dust, stones (ABO9)	0.519	0.545	
I don't go anywhere barefoot (eg: at home, on the street, on the beach) (ABO10)	0.670	0.328	
I wear shoes that fit my feet perfectly, suitable for width, height and height (ABO11)	0.602	0.455	
I do not use sharp tools (razor, scissors, etc.) while doing my foot care (ABO15)	0.525	0.320	

the group who wiped/washed their shoes regularly (40.571±0.703 and 37.473±0.967) and the difference was significant (p:0.026). The FCBS score of those who had the habit of airing their shoes regularly was 40.00±0.608 and it was 36.184±1.527 in those who did not, and the difference was significant (p:0.031). The FCBS scores were 40.067±0.580 in individuals who changed their socks regularly, and 34,208±1.987 in those who did not have the habit of changing their socks regularly. The group that changed their socks regularly had a higher score and the difference was significant (p:0.007) (Table 3).

Table 2. Descriptive statistics

		Frequency	Percentage (%)
Gender	Female	127	67.9
	Male	60	32.1
	Total	187	100
Living place	Province	133	70.7
	District	42	22.3
	Village	13	6.9
	Total	188	100.0
Wiping/washing the inside of the shoe	Yes	112	59.6
	No	76	40.4
	Total	188	100.0
Airing the shoes	Yes	149	79.6
	No	38	20.4
	Total	187	100.0
Changing socks	Yes	164	87.2
	No	24	12.8
	Total	188	100.0

Discussion

No study was found in which foot care behavior was evaluated in individuals with TP. However, in a study evaluating the relationship between diabetes and foot care, it was reported that foot care was generally inadequate and the rate of those with TP was 53.4% (19). It is stated that foot care is evaluated within the scope of self-management in diabetic patients and that care is not sufficient (12-14). It was reported in a study that the foot care score was 49.02±10.25 in diabetic patients (11). In another study, foot care scores of diabetic adults were reported as 43.16±5.70 (20). In our study, the FCBS total score of our group was lower than the diabetic patients (39.31±7.98). With these results, it can be concluded that foot care behavior is effective in the development of TP.

One of the factors thought to be effective in the development of TP is gender. In a study conducted with 420 participants, the relationship between the shoes used and TP was examined and it was stated that the probability of TP occurrence increased in male gender [odds ratio (OR): 1.80, p<0.01] (8). In another study, it was reported that 61.7% of 399 participants diagnosed as having nail fungus were male, and the incidence of TP was higher, especially in males (21). The result of the study in which patients with TP and eczema were evaluated showed that while the rate of TP was 80% in men, it was 45% in women (22). Similarly, in a study in which 2,574 people were evaluated in a rural area in Turkey, it was stated that the incidence of fungal infections of the hands and feet was higher in men than in women (male OR: 1, female OR: 0.39), and it was stated that the difference was significant (p=0.000) (23). In this study, women's FCBS score was found to be higher which supported the literature. It can be thought that women are more sensitive to foot care than men.

In a study conducted with farmers in rural areas, the knowledge level of the participants about TP was questioned and it was

Table 3. Difference analysis according to descriptive variables

		N	Mean	Std. error	Median	Min	Max	P
Gender *	Female	127	40.370	0.693	40	18	54	-2.664
	Male	60	37.316	1.018	37	18	51	**0.008**
Living place**	Province	133	39.406	0.702	39	18	54	5.892
	District	42	40.428	1.171	40	18	51	**0.049**
	Village	13	34.846	1.947	35	24	46	
Education status**	Literate	3	27.333	3.179	27	21	31	
	Primary education	31	39.193	1.349	39	23	53	6.801
	secondary education	24	38.666	1.622	39	18	51	0.079
	University	130	39.746	0.701	40	18	54	
Health insurance**	No	27	39.592	1.556	39	19	53	
	Emekli sandigi	54	39.481	0.840	39	19	51	
	Bagkur	15	36.533	1.973	36	18	46	5.297
	SSK	77	40.129	1.005	40	21	54	0.381
	Special insurance	8	34.750	3.989	35	18	45	
	Green card	7	39.285	2.327	39	33	50	
Occupation**	Housewife	27	38.296	1.359	38	26	53	
	Retired	12	41.916	1.311	42	30	48	
	Employee	13	34.538	2.615	34	22	46	7.582
	Self-employed	14	35.785	2.431	36	18	47	0.108
	Officer	61	39.836	1.012	40	18	54	
	Not working	12	37.166	1.841	37	24	45	
	Other	49	41.408	1.163	41	19	51	
Income status**	Income less than expenses	62	38.532	1.057	38	18	51	0.510
	Income equals expense	88	39.988	0.723	40	19	51	0.775
	Income more than expenses	37	39.000	1.643	39	18	54	
Smoking**	Yes	52	37.653	1.209	38	18	51	2.719
	No	127	40.063	0.688	40	18	54	0.257
	Quit smoking	9	38.444	1.780	38	31	45	
Wiping/washing shoes*	Yes	112	40.571	0.703	41	18	54	-2.222
	No	76	37.473	0.967	37	18	51	**0.026**
Airing foot*	Yes	149	40.100	0.608	40	18	54	-2.162
	No	38	36.184	1.572	36	18	50	**0.031**
Changing socks**	Yes	164	40.067	0.580	40	19	54	-2.688
	No	24	34.208	1.987	34	18	46	**0.007**
Having a chronic disease*	Yes	41	38.658	1.160	39	18	50	-0.761
	No	147	39.503	0.671	39	18	54	0.447
Regular medication*	Yes	32	38.843	1.289	39	26	50	-0.627
	No	156	39.416	0.651	39	18	54	0.531

*Mann-Whitney U test
**Kruskal-Wallis test

stated that their knowledge was insufficient in 62% (6). Taking care of foot hygiene and having knowledge about it are important to prevent the development of TP (1,58). The structure of the shoes used and the cleanliness of the inside are an important factor in the development of the infection. For this reason, it is necessary for individuals to choose shoes correctly and to have sufficient interior cleaning (7). As the level of awareness of individuals about foot care, shoe and stocking preference and use increases, the incidence of TP decreases, and their awareness of the transmission routes of the infection increases (5). In this

study, the FCBS score of the people living in the village was found to be lower than those living in the city center and town. It can be thought that the people living in the village do not have enough awareness about foot care.

Foot hygiene habits include hygiene of shoes, feet and socks. In addition, it includes proper foot care (4,5). Keeping the feet dry and clean is an important factor in preventing the formation of fungal infections. While the feet of swimming pool workers are constantly wet and because they work in a humid and hot environment with a high risk of contamination, the incidence of TP is 15 times higher than in normal individuals (3), while it is stated that wearing closed shoes in military personnel increases this risk by four times (7). Leather, ventilable and cleanable shoes are recommended to be preferred. In a study conducted with 420 patients, the humidity of the inside of the shoes and the internal temperature were explained as factors that increased the risk, and it was stated that this risk increased even more for men (8). The inside of the shoes, which prevent the foot from airing, keep the foot warm and sweaty, is a suitable environment for the development of microorganisms. Because both fungi and bacteria can cause infection in TP (10). Wearing boots that limit the ventilation of the feet, preference of synthetic leather shoes, and high indoor temperature (8) and sweating feature of the shoes are shown as risk factors due to causing humidity and high internal temperature ($p<0.05$) (8,9). In addition, it is emphasized that it is important to evaluate individuals with undiagnosed "hidden TP" symptoms such as bromodosis in addition to diagnosed TP (9).

When TP is diagnosed, an infection caused by microorganisms is mentioned. Before diagnosis, these microorganisms can identify themselves with odor on the feet/in the shoes (9). Microorganisms can create a living space in shoes as in many places. In the study examining the microorganisms in 50 pairs of shoes used daily, it was stated that 15 different fungal species were isolated in the shoes. Among the isolated species, there are also those known to cause TP. It is recommended to wash/wipe/disinfect the inside of the shoes so that the infection due to the microorganisms found in shoes does not develop/spread/contaminate in question (24). Since the humidity and temperature in the shoes are also factors that support the growth of microorganisms, keeping the inside of the shoes dry is important for the prevention of fungal infections (25). In order to ensure dryness, it is recommended to ventilate the shoes daily, to use the same shoes most frequently every other day, and to dry them in the sun when not in use. Not only shoes, but also the hygiene of socks, correct selection of socks and correct use of socks are also important factors. Preferring cotton socks, washing and changing them daily, and wearing them after the socks are completely dry are important topics (26). In this study, the FCBS score of those who have the habit of wiping/washing their shoes, airing and changing their socks daily was found to be higher. It can concluded said that those who care about foot care have a high awareness of the correct use of shoes and socks.

Training given to patients with health problems in their feet can produce solutions to the patient's problems (27). While it is easier for the patient to learn, develop and adapt to the situation with the education given (28,29), desired behavioral changes can be gained with self-care training and individuals can become able to apply the foot care training given (30-32) and increase their quality of life (33). While the foot care score was 49.02±10.25 in diabetic patients, it increased to 62.09±7.38 after foot care training (11). For this reason, it is recommended to establish and implement foot care protocols and to provide training accordingly (34). In order to improve the foot care behaviors of individuals, starting from the groups with low awareness, providing education will increase the awareness of the individuals about the importance of foot care and positively affect the foot care behavior.

Conclusion

It was determined that there was a relationship between the FCBS score of the patients with TP and the socio-demographic characteristics such as gender and place of residence, foot hygiene habits such as wiping/washing the inside of the shoes, airing the shoes and changing the socks daily. It was determined that women, those living in the city, those who had the habit of wiping/washing the inside of their shoes, daily airing and changing socks daily had better foot care behaviors/higher scores. The presence of smoking, chronic disease and routine drug use did not affect the foot care score.

Ethics

Ethics Committee Approval: Necmettin Erbakan University Health Sciences Scientific Research Ethics Committee (date: 06.01.2021/number: 4).

Informed Consent: Permission for use was obtained from the scale owners.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: R.B., İ.Ö., İ.Ö.Ö., Design: R.B., Y.A., İ.Ö.Ö., Data Collection or Processing: M.D., İ.Ö.Ö., İ.Ö., Analysis or Interpretation: Y.A., Literature Search: R.B., M.D., İ.Ö.Ö., Writing: R.B., M.D.

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Original Article

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Being a Student and Faculty Member in the Faculty of Medicine During Pandemic: An Evaluation of Distance Education

Pandemide Tıp Fakültesinde Öğrenci ve Öğretim Üyesi Olmak: Bir Uzaktan Eğitim Değerlendirmesi

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ABSTRACT

Objective: We aimed to reveal the opinions of students and faculty members about the educational process in the distance education provided in a medical school during the pandemic period, the problems they encounter and their relationship with digital literacy levels.

Methods: The design of the study is cross-sectional. An online survey including demographic information, positive and negative aspects of distance education, opinions about the process, and digital literacy scale was administered to 1st, 2nd, 3rd, 4th and 5th year medical students and faculty members. A p-value of <0.05 was considered significant in the data analysis.

Results: A total of 513 individuals (52.9%) responded to the questionnaires. The mean digital literacy score was 3.42±0.84 for students and 3.57±0.82 for faculty members. For faculty members, age (B=-0.041, t=-2.72 p=0.009) and having no previous distance education experience (B=-0.813, t=-2.32 p=0.025), and for students, female gender (B=-0.287, t=-3.65 p<0.001) and having no previous distance education experience (B=-0.343, t=-2.53 p=0.011).

Conclusion: Distance education, which gained speed with the pandemic, will continue to exist in education in the coming years. Although the digital literacy scores of students and faculty members in the medical faculty are above average, advanced digital literacy will enable better and accurate use of digital technologies and a more effective and efficient education.

ÖZ

Amaç: Pandemi sürecinde bir tıp fakültesinde verilen uzaktan eğitimde öğrenci ve öğretim üyelerinin eğitim süreci ile ilgili düşüncelerini, karşılaştıkları problemleri ve dijital okuryazarlık düzeyleri ile ilişkisini ortaya koymayı amaçladık.

Yöntemler: Araştırmanın tasarımı kesitselidir. Tıp fakültesinde eğitim gören 1., 2., 3., 4., 5. sınıf tıp öğrencileri ile eğitim veren öğretim üyelerine demografik bilgiler, uzaktan eğitimin olumlu ve olumsuz yönleri, süreçle ilgili düşünceleri ve dijital okuryazarlık ölçeğini içeren çevrimiçi anket uygulanmıştır. Veri analizinde p<0,05 anlamlı kabul edilmiştir.

Bulgular: Anketlere 513 kişi (%52,9) yanıt vermiştir. Dijital okuryazarlık puanı ortalaması öğrencilerin 3,42±0,84 ve öğretim üyelerinin 3,57±0,82'dir. Öğretim üyeleri için yaş (B=-0,041, t=-2,72 p=0,009) ve daha önceden uzaktan eğitim tecrübesi olmamak (B=-0,813, t=-2,32 p=0,025) ve öğrencilerde ise kadın cinsiyet (B=-0,287, t=-3,65 p<0,001) ve önceden uzaktan eğitim tecrübesi olmamak (B=-0,343, t=-2,53 p=0,011) dijital okuryazarlık ölçek puanını negatif etkileyen değişkenler olarak saptanmıştır.

Sonuç: Pandemi ile birlikte hız kazanan uzaktan eğitimin önümüzdeki yıllarda da eğitim öğretimde varlığı devam edecektir. Her ne kadar tıp fakültesindeki öğrenciler ve öğretim üyelerinin dijital okuryazarlık puanları ortalamanın üstünde olsa da gelişmiş dijital okuryazarlık sayesinde dijital teknolojilerin daha iyi ve doğru kullanılması, eğitimin daha etkili ve verimli olması sağlanacaktır.

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Anahtar Sözcükler: COVID-19, tıp eğitimi, dijital okuryazarlık ölçeği, çevrimiçi öğrenme, koronavirüs pandemisi

Introduction

The Coronavirus disease-19 (COVID-19) outbreak that started in Wuhan, China rapidly turned into a worldwide pandemic in 2020 (1). The obligatory closure experienced in all areas of society has also affected educational institutions (2). In case of continuing face-to-face education, many countries had to take some measures in this area, since the spread of the virus might increase in young individuals, thus in the entire society (3). Schools were closed in more than 190 countries around the world in April, and more than 90% of the world's student population was affected (4). During this period, educators in all countries quickly found solutions to many challenges (5). The Council of Higher Education in Turkey interrupted education on March 16 due to the pandemic. One week later, it was restarted with distance and open education in digital environment in order not to interrupt the education and training (6,7).

Medical education has been affected by the pandemic all over the world with its practices, skills curriculum, and intensive theoretical content. Due to the nature of the disease, traditional training methods have been replaced by online live video conferencing modalities (3). COVID-19 has revealed an urgent need for many institutions to rapidly implement alternative training and assessment strategies (8).

During the pandemic period, distance education, which involves almost the whole of the education world with its advantages such as accessibility, reduction in costs, remote access, and student-centered learning, has brought some difficulties. Major difficulties in students and their educators include the lack of face-to-face communication, lack of online education experience, reduced course concentration, as well as lack of technological infrastructure, inability to provide practical training, technophobia, and time management (9,10). The three basic components of a feasible, efficient and effective distance education process are teacher, student, and the tools and equipment that provide access between the two (11). Another component that complements these components is digital literacy. Although the concept of digital literacy has many definitions, its basis is related to the use of digital technologies such as computers, tablets, smartphones, and smartboards. It includes various concepts such as being digitally literate, accessing accurate information using digital technologies, and at the same time, ability to use it safely, analyzing and synthesizing information, sharing, and communicating (12,13). Concepts such as digital competence and digital literacy have come to the fore more in this period (14).

In our country, the experiences of students and faculty members with the aspects of higher education in the pandemic such as technological infrastructure, communication skills, and digital literacy have been demonstrated by some studies (14). Our study is different from other studies. We aimed to identify the thoughts and problems experienced at the beginning of distance education, which was rapidly integrated into medical education due to the pandemic, from the perspective of both students and faculty members. In this study, we aimed to determine the positive and negative aspects of distance education carried out in the medical faculty in terms of students and teaching faculty members and to reveal their relationship with the digital literacy level.

Methods

The study was a cross-sectional study and was conducted in the medical faculty of a public university in İstanbul between 30 July and 30 August 2020. The universe of the study consisted of 1st, 2nd, 3rd, 4th, and 5th year medical students and faculty members. The 6th year students of the faculty of medicine were not included in the study because they did not receive distance education and continued their internship at the hospital. The study included 181 first-year medical students, 165 second-year students, 141 third-year students, 215 fourth-year students, 121 fifth-year students, and 146 faculty members. The sample was not selected, and aiming to reach the whole universe (969), 513 individuals (52.9%) were reached. Three faculty members who stated that they did not provide distance education during the pandemic period were not included in the analysis.

The study data were collected with two separate questionnaires created for faculty members and students. The questionnaire prepared for faculty members consisted of 3 parts. The first part included questions about the socio-demographic characteristics of the participants (age, gender, unit, working years as a faculty member), the second part included questions about distance education (distance education experience, status of receiving training about distance education, status of providing distance education during the pandemic period, frequency of live online courses, devices used for distance education, positive and negative aspects of distance education) and 5-point Likert-type proposals about the distance education process, and the third part included the digital literacy scale (DLS). The student questionnaire also consisted of 3 parts, and unlike the faculty member questionnaire, it questioned the socio-demographic characteristics of age, gender, year of education during the pandemic period, residency during the pandemic period. Other parts of the questionnaire were prepared in the same way used in the faculty member's questionnaire. The data were collected through a web-based survey. The questionnaires were delivered to faculty members and students via chat applications.

The DLS used in the questionnaires was developed by Ng (12) in 2012. This 5-point Likert type scale consists of 17 questions aimed at revealing the technical, cognitive and social/emotional dimensions of digital literacy as well as attitudes of students and faculty members towards using information and communication

technologies for learning. The scale, which was adapted to Turkish by Üstündağ et al. (13) in 2017, is a 5-point Likert type scale consisting of 10 questions. As the score obtained from the scale increases, the level of digital literacy increases. The Cronbach's Alpha coefficient of the scale was found to be 0.86.

The approval for the study was obtained from the Clinical Research Ethics Committee of Göztepe Training and Research Hospital with the decision number of 2020/0504 and date of 24.06.2020.

Statistical Analysis

The data were analyzed using SPSS 22.0 software. In the analysis, the chi-square test was used to examine the level of correlation between variables, as well as descriptive statistics (frequency, mean, standard deviation, minimum, maximum) were used. Student's t-test and One-Way ANOVA test were used to compare the mean scores of the DLS. In order to test the relationship between the dependent variable (digital literacy levels of students and faculty members) and some independent variables which might predict DL, such as age, gender, having distance education experience and being educated on the subject, a multivariate linear regression model was applied one by one and an entry method was used in the model. A p-value <0.05 was considered as statistically significant.

Results

The mean age of the students was 21.26±1.86 (18-29) years, and of whom, 42.4% (195) were male and 69.8% (321) stated that they lived in a metropolitan city during the pandemic period, 15.4% (71) in the province, 12.0% (55) in the district, and 2.8% (13) in the village. The mean age of the faculty members was 47.36±7.68 (35-69) years, and of whom, 46% (23) were male. According to the sciences they studied, 28% (14) were working in basic sciences, 44% (22) in internal sciences, and 28% (14) in surgical sciences (Table 1). The mean duration of employment as a faculty member was 10.88±9.91 (1-43) years.

Before the pandemic period, 9.1% (42) of the students and 12% (6) of the faculty members had had distance education experience. Of the faculty members, 44% (22) had received training on distance education. Of the students, 88.5% stated that they received live online lessons every day during the pandemic period, while 10% (5) of the faculty members provided live online lessons every day (Table 1).

Table 1. Distribution of participants by some characteristics and answers to distance education

		Student		Faculty member	
		n	%	n	%
Gender	Female	265	57.6	23	46.0
	Male	195	42.4	27	54.0
Department	Internal medicine departments	-	-	22	44.0
	Surgical sciences departments	-	-	14	28.0
	Basic medical sciences departments	-	-	14	28.0
Year	1st	133	28.9	-	-
	2nd	99	21.5	-	-
	3rd	82	17.8	-	-
	4th	89	19.3	-	-
	5th	57	12.4	-	-
Frequency of live lessons	Everyday	407	88.5	5	10.0
	Every other day	27	5.9	13	26.0
	Once a week	15	3.3	19	38.0
	Once a month	11	2.4	13	26.0
Pre-pandemic distance education experience	Yes	42	9.1	6	12.0
	No	418	90.9	44	88.0
Frequency of receiving/providing lessons online	Every day	407	88.5	5	10.0
	Every other day	27	5.9	13	26.0
	Once a week	15	3.3	19	38.0
	Once a month	11	2.4	13	26.0
Tool used for distance education	Computer	345	75.0	50	100.0
	Smartphone	263	57.2	3	6.0
	Tablet	83	18.0	1	2.0

It was determined that the rate of evaluating distance education as flexible, easy to use, and accessible was higher among faculty members (p=0.028 χ^2=4,856, p=0.001 χ^2=10,422, p<0.001 χ^2=18,394, respectively). Unlike the faculty members, 70.7% of the students evaluated the more comfortable student participation as a positive aspect (p=0.016, χ^2=5,848) (Table 2).

As the negative aspect of distance education, 78% (39) of the faculty members stated difficulty in communicating (p<0.001, χ^2=14,186). On the other hand, it was determined that the students mostly stated inadequate internet access and not having as many equipment/materials as in the school environment as the negative aspects of distance education (p=0.001, χ^2=10,921, p<0.001, χ^2=15,050, respectively). Of the students, 61.7% (284) stated the stress and workload of working from home as another negative aspects of distance education (Table 2).

In the evaluations of students and faculty members regarding the whole distance education process, it was determined that 32.2% of the students evaluated distance education as sufficient for theoretical courses (p=0.009, χ^2=9.534). It was determined that 30.2% of the students did not think that the pandemic period offered new opportunities in education (p=0.003, χ^2=11,314) (Table 3).

The mean DLS score of the students participated in the study was 3.42±0.84 (1-5), and it was 3.57±0.82 (1.8-5) in faculty members (p>0.05). It was determined that the students and faculty members with previous distance education experience had a higher digital literacy score than those without experience (t=2.45 p=0.014, t=2.22 p=0.031, respectively) (Table 4).

The correlation between the age of the faculty members, the time they worked as a faculty member, and their digital literacy score was analyzed and no significant correlation was found (r=-0.277, p=0.052, r=-0.067 p=0.642, respectively).

Multiple linear regression analysis was performed to find out factors affecting the digital literacy score. The model included the variables of age, gender, previous distance education experience, and receiving a training on distance education for the faculty members. Table 5 shows the results of the multiple linear regression multivariate analysis.

Discussion

In this study, we aimed to determine the problems faced by students and faculty members as well as their digital literacy levels during the distance education process which started with the pandemic announcement. More than 90% of the students and faculty members did not have a previous experience with distance education before the pandemic. While distance education has some positive aspects such as being flexible and accessible, easy to use, and comfortable for students to participate in, difficulties in communication and not having enough equipment and materials compared to those provided in the school environment are evaluated as its negative aspects. Most of the participants stated that distance education was not as effective as face-to-

Table 2. Positive and negative aspects of distance education

Positive aspects	Student		Faculty member		p
	n	%	n	%	
Being flexible	192	41.7	29	58.0	**0.028**
High variety of resources	29	6.3	6	12.0	0.130
Ease of use	160	34.8	29	58.0	**0.001**
Ability to personalize student learning	75	16.3	5	10.0	0.244
Applicable variety of methods	57	12.4	11	22.0	0.058
Being accessible	169	36.7	34	68.0	**<0.001**
Easy participation for the student	238	51.7	24	48.0	0.615
Comfortable participation for the student	325	70.7	27	54.0	**0.016**
Negative aspects					
Lack of knowledge/experience in distance education	178	38.7	18	36.0	0.710
Owned technological equipment, lack of infrastructure	122	26.5	8	16.0	0.105
Technological equipment owned by the faculty member/ student, lack of infrastructure	176	38.3	27	54.0	**0.031**
Inadequate internet access	126	27.4	3	6.0	**0.001**
Inadequate internet access of the student/faculty member	106	23.0	24	48.0	**<0.001**
Difficulty in communicating	230	50.0	39	78.0	**<0.001**
Inadequate digital literacy	74	16.1	3	6.0	0.058
Inadequate digital literacy of the student/faculty member	84	18.3	5	10.0	0.144
Not having as many tools/materials as in the school environment	303	65.9	19	38.0	**<0.001**

face education, giving practice-based lessons remotely was not enough, and that the lessons given in this process should be made up with face-to-face education. It was determined that while having previous distance education experience affected the level of digital literacy in both students and faculty members, gender in students and age in faculty members also affected digital literacy levels.

Approximately 90% of the students and faculty members participated in the study did not have distance education experience before the pandemic period. Due to the sudden transition to distance education instead of face-to-face education with the pandemic, those who do not have experience are likely to face more problems in this process. Similarly, a study on the barriers to online learning found that students who previously received online courses faced less problems compared to those who did not (15).

It was determined that the faculty members' evaluation of the positive aspects of distance education as flexible (58%), easy to use (58%), and accessible (68%) was highly positive compared to the students. In a qualitative study conducted on students and faculty members of medical and dental faculties, online learning was a flexible and accessible learning/teaching resource and facilitated some of the administrative work of faculty members, according to the participants (10). Two-thirds (70.7%) of the students stated that the distance education was more comfortable, which was the positive aspect compared to

Table 3. Opinions about the distance education process

		Disagree		Neutral		Agree		p
		n	%	n	%	n	%	
I think the distance education process is well-planned.	**Student**	82	17.8	102	22.2	276	60.0	0.346
	Faculty member	6	12.0	15	30.0	29	58.0	
I have difficulty while following/teaching the lessons due to the distance education system.	**Student**	176	38.3	70	15.2	214	46.5	**0.001**
	Faculty member	32	64.0	8	16.0	10	20.0	
I think the distance education lessons are as effective as face-to-face education.	**Student**	295	64.1	86	18.7	79	17.2	0.825
	Faculty member	34	68.0	9	18.0	7	14.0	
I think the distance education should continue with face-to-face education even after the pandemic process is over.	**Student**	252	54.8	73	15.9	135	29.3	0.181
	Faculty member	23	46.0	13	26.0	14	28.0	
I think it is sufficient to provide theoretical lessons remotely.	**Student**	215	46.7	97	21.1	148	32.2	**0.009**
	Faculty member	23	46.0	19	38.0	8	16.0	
I think it is not enough to provide practical lessons remotely.	**Student**	25	5.4	21	4.6	414	90.0	0.060
	Faculty member	7	14.0	2	4.0	41	82.0	
I think it would be beneficial to make up face-to-face training for the lessons and practices provided in this period.	**Student**	63	13.7	73	15.9	324	70.4	0.626
	Faculty member	5	10.0	10	20.0	35	70.0	
I am worried about my personal information falling into the hands of third parties.	**Student**	170	37.0	125	27.2	165	35.9	0.191
	Faculty member	12	24.0	16	32.0	22	44.0	
I think not having face-to-face education with faculty members/students will create problems/deficiencies in future trainings.	**Student**	56	12.2	98	21.3	306	66.5	0.391
	Faculty member	4	8.0	8	16.0	38	76.0	
I think the pandemic period offers new opportunities in education.	**Student**	139	30.2	137	29.8	184	40.0	**0.003**
	Faculty member	5	10.0	24	48.0	21	42.0	
I think the use of distance education increases my motivation for lessons.	**Student**	293	63.7	100	21.7	67	14.6	0.167
	Faculty member	30	60.0	16	32.0	4	8.0	
I think it is easier to follow/teach with distance education than with traditional methods.	**Student**	218	47.4	90	19.6	152	33.0	**0.049**
	Faculty member	15	30.0	15	30.0	20	40.0	

Table 4. Distribution of digital literacy scores by some characteristics of participants

		Mean ± (SD)	p
Duty	Student	3.42±0.84	0.242
	Faculty member	3.57±0.82	
Gender/student	Male	3.59±0.85	**<0.001**
	Female	3.30±0.82	
Gender/faculty member	Male	3.67±0.82	0.442
	Female	3.49±0.82	
Working unit/faculty member	Basic sciences	3.80±0.69	**0.005**
	Internal sciences	3.16±0.74	
	Surgical sciences	3.98±0.79	
Distance education experience/student	Yes	3.73±0.88	**0.014**
	No	3.39±0.83	
Distance education experience/faculty member	Yes	4.25±0.66	**0.031**
	No	3.48±0.80	
Receiving training on providing distance education in faculty members	Yes	3.67±0.81	0.466
	No	3.50±0.83	

SD: Standard deviation

the faculty members. In another study conducted on university students, online education was considered comfortable (67.7%), similar to that in this study (15). The fact that the vast majority of university students attend training in their own homes and in their rooms near their families, which are more comfortable environments, instead of the ongoing education life with friends or in the dormitory away from their families alone may be a factor in this evaluation. In addition, the fact that the time they spend coming to the university for education due to reasons such as transportation and traffic is added to their personal time is also a possible factor in this result.

Difficulty in communication was the negative aspect of distance education, which was stated more by the faculty members than the students. Difficulties in communicating face to face, which are more on the agenda with distance education, have been emphasized in many studies (9,15,16). A study including 1,056 students showed that the major obstacle to online learning was the lack of communication and there was a strong correlation between the effectiveness of learning and communication (15). Communication is one of the keys that can pave the way for effective, intriguing, in-depth learning and evidence-based rational learning in long and intense medical education. Integrating the educational skills of faculty members, such as creating a positive educational environment, creating assessment tools based on interactive teaching methods, coaching, knowledge, and competence, effective communication and preparing presentations, and using audio-visual training tools into the distance education system may help overcome communication problems that may occur in distance education.

Of the students, 65.9% stated that they could not have as many tools and materials as in the school environment as a higher rate of negativity than the faculty members. Although the distance education started for students with the pandemic announcement, most of the faculty members continued to work at the hospital and to provide distance education from the faculty. Additionally, the students' lack of access to materials such as models used in laboratory and practical courses, deprivation of bedside training might lead to learning difficulties. On the other hand, two-thirds of the faculty members stated that they had difficulties in adapting their medical education practices to distance education. The benefit of using different virtual learning platforms and simulation applications in practical training has been shown in various studies as a solution to these problems (17,18). Of the faculty members, 82% cannot perform measurement-evaluation suitable for distance education. Written and oral assessments have been replaced by online exams and homework. At this point, providing educational measurement assessments for faculty members, which include new skills and techniques for distance education evaluations, may help to close the gap for this issue (19).

According to 61.7% of the students, working from home caused stress and extra workload. In the process of developing online education to replace the bedside training of the fourth-year, fifth-year, and sixth-year medical students at the University of Auckland, difficulties of working from home for students and faculty members were attributed to having other people at home as well as having their children at home due to the closed schools (20).

In our study, about half of the students stated that it was easier to follow the lesson with traditional methods. A similar

Table 5. Factors affecting digital literacy score of participants

Variables	B	p	95% CI
Faculty member gender (r: female)	-0.278	0.250	-0.758-0.203
Faculty member age	-0.041	**0.009**	-0.072-0.011
Faculty member distance education experience (r: no)	-0.813	**0.025**	-1.519-0.108
Receiving training on distance education	0.036	0.873	-0.418-0.491
Student gender (r: female)	-0.287	**<0.001**	-0.442-0.133
Student age	-0.004	0.858	-0.045-0.037
Student distance education experience (r: no)	-0.343	**0.011**	-0.608-0.077

CI: Confidence interval

result was found in another study conducted in a faculty of medicine. Half of the students stated that they had difficulties while following the lesson with distance education and that traditional education was better (16). Additionally, another study reported that students who had not previously received distance education thought that they would learn worse with distance education (15). Most of the students in our study had no previous distance education experience. This may cause them to approach distance education with prejudice. The fact that physician candidates in the first three years and the fourth-year and fifth-year medical students studying in hospital clinics are distanced from practical courses, which gradually increase every year, can be considered as the reasons for preferring traditional education. The fact that the vast majority of students did not find practical training to be provided remotely enough also supported this.

Of the students and faculty members, 40% thought that the pandemic offered new opportunities in education. As a result, the use of technology in a fast and innovative way to continue learning in medical education has come to the fore. It is likely that there will be a transformative and exciting change in education as a result of the integration of new technologies in medical education (21).

With the distance education, it is important to use digital technologies in the educational life more effectively and correctly. At the digital literacy level, the prevalence and usage experience of technology are effective rather than age (12). In our study, there was no difference between the digital literacy scores of the students and faculty members. With the 21st century, the use of technology has become widespread in our country and all over the world, and more than 60% of the world population has internet access (22). The digital literacy scores of the students and faculty members with previous distance education experience were higher than those without experience. This shows the contribution of these individuals' familiarity with technology and their experiences to digital literacy (12). The added value of digital literacy to the personal development of individuals will return as an effective, fast, efficient, and easy educational process in the distance education. Plans should be made to increase the digital literacy of both students and faculty members for access to accurate and reliable information, analysis and synthesis of information, sharing and effective use of information, and practical training should be provided.

Study Limitations

The strength of our study was that it was conducted in the period when the distance education process was just beginning and in a way to include both students and faculty members. However, the time interval to collect data was the period when education was interrupted. The students and faculty members were asked to respond to questions about the period of distance education before the interruption, and they may have had difficulty in remembering due to the period of approximately two months that passed. Due to the pandemic, data were collected electronically and there were difficulties in reaching students and faculty members. The percentage of responding to web-based questionnaires was generally lower than other questionnaire methods such as mail and telephone, and may affect the sociodemographic characteristics of the participants. Those who answered web-based questionnaires were more interested in the subject, had time to answer the questionnaire, had a computer or a smartphone which they could use to answer e-surveys, and had internet access. Our results should be interpreted taking into consideration that those who did not have a computer or a smartphone and whose economic conditions were not favorable did not respond the questionnaire and that age, gender, and being a student might have an effect on digital literacy. Individuals must actively use digital technologies to respond to a web-based questionnaire. This suggested that the digital literacy scores of those who responded to the questionnaire were higher than those who did not. In addition, the study was a single center cross-sectional study. Each institution uses different educational systems and methods in the distance education process. The sociodemographic characteristics of the students and faculty members within the institutions may differ. For this reason, the results cannot be generalized to the whole education system and higher education institutions.

Conclusion

The distance education process, which was introduced to continue education in the COVID-19 pandemic, affected medical faculties in different ways. For both students and faculty members, the courses in the distance education process were not as effective as in face-to-face education. In addition, during this period, most of the students and faculty members had difficulties in communicating, had problems with internet access, and could not have as many tools/materials as in the school environment. They stated that theoretical and practical trainings were not sufficiently provided remotely and that compensatory trainings should be provided after the pandemic. All these show that medical education can not continue with distance education, especially due to practical and bedside trainings. In the ongoing process, institutions should review their planning and accordingly organize their curriculum to eliminate the deficiencies and malfunctions in education. Digital literacy needs to be developed for a better, effective, and correct use of digital technologies.

Ethics

Ethics Committee Approval: İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (date: 12.08.2020/ number: 2020/0504).

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: H.İ., I.M., Design: H.İ., Data Collection or Processing: H.İ., M.K., H.H.M., I.M., Analysis or Interpretation: H.İ., M.K., I.M., Literature Search: H.İ., M.K., H.H.M., Writing: H.İ., M.K., I.M.

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Original Article

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Determination of Total Protein and Free Amino Acid Content of *Artemisia Abrotanum L.* in the Blooming and Pre-Blooming Period

Artemisia abrotanum L. Bitkisinin Çiçekleme ve Çiçeklenme Öncesi Dönemdeki Toplam Protein ve Serbest Amino Asit İçeriğinin Belirlenmesi

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ABSTRACT

Objective: The aim of this study is to determine the total protein and free amino acid content of *Artemisia abrotanum L.* in two different periods, the pre-blooming and blooming periods.

Methods: The Dumas and Kjeldahl methods were applied comparatively to determine the total protein amount. In addition, after the sample was extracted with water:methanol (80:20) containing 0.1% formic acid, free amino acids were determined in liquid chromatography-mass spectrometer.

Results: By using the Dumas method, the % nitrogen content was found to be 2.10 and 2.20, in the pre-blooming and blooming period samples. The results obtained by applying the Kjeldahl method are 2.16 and 2.25, respectively. The total protein content was calculated from the nitrogen content of the plant by using a nitrogen conversion factor of 6.25. The total free amino acid content in the pre-blooming and blooming period was found to 453.41 and 606.18 mg/100 g dried plant respectively.

Conclusion: Since the total protein and free amino acid content of *Artemisia abrotanum L.* is higher during the blooming period, it should be preferred to be harvested during this period.

Keywords: *Artemisia abrotanum*, Kjeldahl method, Dumas method, protein, free amino acid, LC-MS/MS

ÖZ

Amaç: Bu çalışmanın amacı *Artemisia abrotanum L.* bitkisinin çiçeklenme öncesi ve çiçeklenme dönemi olmak üzere iki farklı dönemde toplam protein ve serbest amino asit içeriğinin belirlenmesidir.

Yöntemler: Toplam protein miktarının belirlenmesinde Dumas ve Kjeldahl metodu karşılaştırmalı olarak uygulanmıştır. Ayrıca numune %0,1 formik asit içeren su:metanol (80:20) ile ekstrakte edildikten sonra serbest amino asitler sıvı kromatografisi-kütle spektrometresi de tayin edilmiştir.

Bulgular: Çiçeklenme öncesi ve çiçeklenme dönemi numunelerde Dumas metodu kullanılarak % azot miktarı sırası ile 2,10 ve 2,20 olarak bulunmuştur. Kjeldahl metodu uygulayarak elde edilen sonuçlar ise sırası ile 2,16 ve 2,25'tir. Toplam protein içeriği 6,25 azot dönüşüm faktörü kullanılarak % azot miktarından hesaplanmıştır. Çiçeklenme öncesi ve çiçeklenme dönemindeki toplam serbest amino asit içeriği ise sırasıyla 453,41 ve 606,18 mg/100 g kurutulmuş bitki olarak bulunmuştur.

Sonuç: *Artemisia abrotanum L.* bitkisinin toplam protein ve serbest amino asit içeriği çiçeklenme döneminde daha yüksek olduğu için bu dönemde hasat edilmesi tercih edilmelidir.

Anahtar Sözcükler: *Artemisia abrotanum*, Kjeldahl metot, Dumas metot, protein, serbest amino asit, LC-MS/MS

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Introduction

One of the largest and widely distributed members of the *Asteraceae* family is the *Artemisia* genus. It has more than 500 species distributed throughout Europe, Asia, and North America (1). The ethanol extracts of fresh young flower leaves of *Artemisia abrotanum* L. have been used in particular in homeophatic treatment. In traditional medicine, the leaves of the plant are used as a peptic and appetising agent (2). Today, it is mostly used for flavoring and cosmetic purposes (3).

People have to consume proteins for growth, cell reparation, and also for a healthy life. A high protein diet is very popular for its effectiveness for losing weight, preserving muscle mass, and increasing strength. Although generally animal products are preferred for protein intake, recently plant proteins have been recommended to be consumed as an alternative to those proteins. Animal protein presents growing costs and can be dangerous for human health due to causing cardiovascular diseases and others (4).

Determination of protein content in food is based on the nitrogen content analysis done by the Kjeldahl and Dumas methods. In the Kjeldahl method measures the total nitrogen content of a food, which is then used to estimate the crude protein content by applying a conversion factor to the result (5). The Dumas method is an alternative to the Kjeldahl method with some advantages such as only requiring the use of small quantities of dry chemicals (6).

In plants, amino acids have so many functions such as being used both in protein biosynthesis, and for building blocks for several other biosynthesis pathways (7). In the human diet, proteins consist of amino acids linked by peptide bonds, and the amino acids are vital for maintaining the function of all organs. Protein quality is related to amino acids and the amount of nitrogen (8). Each amino acid has a different and important role in the functioning of the organism. The non-essential amino acids alanine, arginine, aspartic acid, cysteine (Cys), glutamic acid, glycine, proline (Pro), serine (Ser), and tyrosine (Tyr) can be synthesized in the human body (9), while the essential amino acids histidine (His), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine (Met), phenylalanine (Phe), threonine (Thr), tryptophan (Trp), and valine (Val) cannot be synthesized. They must be provided in the diet (8,10).

The aim of the study is to evaluate the nutritional value of the pre-blooming and blooming periods of *Artemisia abrotanum L.* by determining the protein and free amino acids amounts. The comparison of Kjeldahl and Dumas will enable the selection of the most appropriate method for the protein determination. The determination of the amino acids of the plant will give information about the protein quality.

Methods

Samples

Artemisia abrotanum L. samples were harvested from Lisinia Nature Project Area near the village of Karakent in Burdur (Turkey). The material collection process was carried out at two different times: pre-blooming and the blooming periods. After harvesting the plants were dried at room temperature for one week in the shade, ground and stored in sealed plastic containers until the analysis time. The herbarium of the plants was done by Prof. Dr. M. Zeki Haznedaroğlu from İzmir Katip Çelebi University.

Chemicals

The free amino acid (Lysine, Cystine, Histidine, Arginine, Aspartic acid, Serine, Threonine, Glutamic acid, Alanine, Glutamine, Pro, Valine, Methionine, Tyrosine, Isoleucine, Leucine, Phenylalanine) analytical standard mixtures were purchased from Sigma-Aldrich. All the other reagents (H_2SO_4, $CuSO_4$, K_2SO_4, NaOH, HC_l) were of analytical grade purity and purchased from Merck. The ultra-pure water was obtained from the water purification system (Human Power I, Human Corporation, KR).

Total Protein by Dumas Method: The elemental analyzer system (2400 Series II, Perkin Elmer, US) was used to determine the nitrogen amount. The dried samples (2-3 mg) were weighed directly into tin capsules by using ultra-micro balance (AD 6000, Perkin Elmer, US) capable of weighing samples to a resolution of 0.1 μg and placed the auto sampler of the instrument. A cystine analytical standard (29.99% C, 5.03% H, 11.66% N, 26.69% S) was used as a reference standard. Each sample was analyzed in three replicates. The instrument parameters were shown in Table 1.

Total Protein by Kjeldahl Method: In addition to the nitrogen determination by the elemental analyzer, the Kjeldahl method was also applied by using a distillation system (Vapodest-50, Gerhardt, DE). The dried samples (≈1.0 g) were digested in 30 mL H_2SO_4 in the presence of the catalyst 1 g of $CuSO_4$ and 10g K_2SO_4, after digestion, NaOH was added followed by steam distillation, and the distillate was collected in 20 mL 4% boric acid. Then, the nitrogen content was determined by using titration with 0.01 N HCl.

Free Amino Acid Profile by UPLC-MS/MS: The dried samples (≈0.5 g) were extracted with 10 mL of 0.1% (v/v) formic acid in water: methanol (80:20) (v/v). The mixture was vortexed for 5 min and then centrifuged at 4,000 rpm at 4 °C for 15 min. The

Table 1. Instrument parameters (Dumas method) for nitrogen detection

Parameters	Value
Combustion temperature	925 °C
Reduction temperature	500 °C
Thermal conductivity detector (TCD) temperature	82.2 °C
Separation column	GC column SS - 2 m 6x5 mm (CHNS)
Carrier gas (helium) purity	99.999%
Combustion gas (oxygen) purity	99.999%
Pneumatic gas (air) purity	99.995%

upper phase obtained after centrifugation was passed through a 0.2 µm PTFE membrane filter and injected to the UPLC-MS/MS (Dionex Ultimate 3,000 - TSQ Fortis, Thermo Fisher Scientific Inc. US) (11).

The chromatographic separation was achieved using a gradient program. The analysis began with 100% mobile phase A and was held 2 min at this composition. After 2 min, the mobile phase A percentage was linearly decreased to 0% in 1.5 minutes. The mobile phase A percentage was held at 0% for 3 min. Then, the gradient was changed to a 100% mobile phase A and re-equilibration time took 0.5 min. The flow rate was 0.4 mL/min and the run time of the analysis was 7 min (12). The other chromatographic and mass spectrometric conditions are shown in Table 2. The MS-MS optimization for each free amino acid was performed by using a single analytical standard in order to determine the ion transitions and collision energies (Table 3). An appropriate amount of dilutions was done from the stock mixed solution to generate the calibration curve. Different calibration points in the range of 0-15 mg/L were established for each free amino acid.

Statistical Analysis

The results were evaluated using the t-test function available in MS Office Excel.

Results and Discussion

The protein content of *Artemisia abrotanum* L. was determined as the amount of the total N by Kjeldahl and Dumas methods. The amount of nitrogen content of the plant was calculated by using a nitrogen conversion factor of 6.25. The results showed that there was no significant difference between the amount of total protein in the pre-blooming and blooming periods of the plant ($p>0.05$) (Table 4). The accuracy of the Dumas method was checked by using cystine and the relative error was found to be 1.66. The precison of both methods was calculated and the RSD results were given in Table 4. In both methods, the results of the N contents of the plants were quite close to each other although the precision was better in the Kjeldahl method ($p>0.05$).

There are not so many studies on the protein content of the Artemisia species. Ochkur et al. (13) determined the N content of *Artemisia abrotanum* L. level, which was grown in Ukraine, as 26.9% by using the Dumas method. In our study, the protein content of the plant was found to be 13.1% and 13.54% in pre-blooming and blooming periods of the plant, respectively by Dumas method.

Table 2. Chromatographic and MS conditions

UPLC	
Mobile phase A	4 mM ammonium formate, 0.1% formic acid (95:5, H_2O: MeOH)
Mobile phase B	4 mM ammonium formate, 0.1% formic acid (95:5, MeOH: H_2O)
Column	HYPERSIL GOLD C18 (50 x 2.1 mm, 1.9 µm)
Column oven temp	40 °C
Injection volume	10 µL
MS/MS	
Ionization type	ESI (Electrospray ionization)
Spray voltage	+3,500 V
Sheath gas	50 Arb
Aux gas	20 Arb
Capillary temp.	270 °C
Vaporizer temp.	50 °C
Detection mode	MRM (multiple reaction monitoring)

MS: Multiple sclerosis

Table 3. Retention time and MRM method parameters of free amino acids using UPLC-MS/MS

Amino acid	RT (min)[a]	Quantification transition (m/z)	Confirmatory transition (m/z)	CE (V)[b]
Lysine	0.74	147.0	84, 130.1	20
Cysteine	0.77	241.3	120, 152	15
Histidine	0.76	156.1	93.1, 110.2	10
Arginine	0.76	175.2	70, 116	15
Aspartic acid	0.78	134.1	88, 116	15
Serine	0.78	106.0	60, 88	15
Threonine	0.78	120.1	56.1, 102.1	15
Glutamic-acid	0.79	148.1	102.1, 130.2	20
Alanine	0.78	90.0	57.1, 71	15
Glutamine	0.74	147.1	84.1, 130.1	15
Proline	0.81	116.1	43.3, 70.1	15
Valine	0.86	118.1	55, 72	20
Methionine	0.94	150.2	104.1, 133.2	15
Tyrosine	1.01	182.2	136.1, 165.1	20
Isoleucine	1.28	132.2	69.2, 86.1	15
Leucine	1.27	132.1	68, 86	15
Phenylalanine	1.99	166.2	103.1, 120	15

[a] RT: Retention time, [b] CE: Collision energies, MRM: Multiple reaction monitoring, UPLC-MS/MS

Pereira et al. (14) and Pérez et al. (15) compared the two methods for the protein analysis in their studies. In both studies, a small difference was found between the values of the two methods. The results of this study supported those results. In another study published in 2001, it was concluded that the Dumas method was superior to the Kjeldahl method in determining the total N concentration of many agricultural samples analyzed in a routine analytical laboratory (6).

In some previous studies, the total amount of protein in the leaves of some plants was 15.00% in *Tribulus terrestris* L., 15.14% in *Zygophyllum simplex* L., 13.20% in *Fagonia cretica* L., 11.15% in *Peganum harmala* L. (16), 8.32% in *Cassia sophera* Linn (17), 17.9% in *Cynodon dactylon*, 29.8% in *Dactylis glomerata*, 18.8% in *Ehrtharta erecta*, 26.5% in *Lolium multiporum*, 16.7% in *Paspalum dilatatum*, and 14.7% in *Pennisetum clandestinum* (18). The amount of nitrogen found in this study was approximately 13%. Total protein content of *Artemisia abrotanum* L. grown in Turkey showed similar values with other plants.

The amino-acids content of *Artemisia abrotanum* L. is given in Table 5. The amino-acids levels were relatively high in the blooming period. When the total amount of the free amino acid concentration was compared, there were significant differences between the pre-blooming period and the blooming period of the plant ($p<0.05$). The total free amino acid concentrations in pre-blooming and blooming periods were 453.41±9.62 and 606.18±8.23, respectively. This result overlapped the knowledge of the usage of the flowers of this plant in homeopathy (2).

The nutritional quality of a protein is evaluated with its content of essential amino acids. "Lys is essential for body nitrogen balance, Val assist in motor coordination, Met + Cys is related to the immune system, and Ile + Leu are the building blocks present in most proteins" (8). Ochkur et al. (13) determined in their study the amino acid content of *Artemisia abrotanum* collected from Ukranie. The lysine concentration in *Artemisia abrotanum* L. collected from Turkey was found to be lower than those collected from Ukranie (7.39 mg/100 g <19.9 mg/100 g). There was information on the N concentration of the plant; therefore, it was impossible to evaluate the lysine and protein contents of the plant. The valine concentration was relatively high (120.44 mg/100 g >36.9 mg/100 g). In this study, the amount of Met + Cys (sulfur amino acids) and Ile + Leu were

Table 4. Amount of total protein in *Artemisia abrotanum* L. by using two different methods

	Pre-blooming period			Blooming period		
	Nitrogen % mean ± SD	RSD	Total protein %	Nitrogen % mean ± SD	RSD	Total protein %
Dumas method	2.10±0.06	3.07	13.10	2.20±0.07	3.22	13.77
Kjeldahl	2.16±0.04	1.94	13.53	2.25±0.01	0.50	14.09

SD: Standard deviation, RSD: Relative standard deviation

Table 5. Amount and type of free amino acids in two different periods of *Artemisia abrotanum* L. Results are expressed as mg of free amino acid per hundred grams of dried samples and standard deviation is given (n=6)

Amino acid	Abb.	Type	*Artemisia abrotanum* L. (mg/100 g ± SD)					
			Pre-bloom period			Bloom period		
Alanine	Ala	Non-essential	43.17	±	2.40	50.72	±	2.21
Arginine	Arg	Non-essential	16.19	±	0.45	20.19	±	0.91
Aspartic_acid	Asp	Non-essential	5.63	±	0.28	7.67	±	0.39
Cystine	Cys	Non-essential	4.42	±	0.18	5.11	±	0.32
Glutamic_acid	Glu	Non-essential	23.90	±	1.02	31.07	±	1.80
Glutamine	Gln	Non-essential	1.58	±	0.19	1.77	±	0.16
Proline	Pro	Non-essential	66.04	±	1.68	111.60	±	5.66
Serine	Ser	Non-essential	35.67	±	1.09	42.91	±	1.75
Tyrosine	Tyr	Non-essential	6.11	±	0.24	8.15	±	0.55
$\Sigma_{\text{non-essentials}}$			202.71±51.84			279.19±61.43		
Histidine	His	Essential	3.91	±	0.38	5.81	±	0.36
Isoleucine	Ile	Essential	43.27	±	0.77	53.33	±	0.79
Leucine	Leu	Essential	37.03	±	1.30	40.30	±	1.46
Lysine	Lys	Essential	4.73	±	0.29	7.39	±	0.31
Methionine	Met	Essential	3.62	±	0.26	4.43	±	0.38
Phenylalanine	Phe	Essential	64.17	±	2.01	75.24	±	1.43
Threonine	Thre	Essential	14.49	±	0.51	20.05	±	0.98
Valine	Val	Essential	79.48	±	1.96	120.44	±	6.06
$\Sigma_{\text{essentials}}$			250.70±48.35			326.99±57.87		

SD: Standard deviation, Abb: Abbreviations

found to be 9.54 and 93.63 mg/100 g and also in the study of Ochkur et al. (13) they were found to be 33.4 and 22.1 mg/100 g, respectively. The other essential amino acid Phe concentration was higher in the Turkish *Artemisia abrotanum* L. (75.24 mg/100 g >32.6 mg/100 g).

In general, for both the essential and non-essential, the amount of each amino acid differs, in some, higher in the Ukranian species, and in some higher in those collected from Turkey. It was observed that the comparison of some medicinal plant free amino acid contents gave similar results (13,16).

Conclusion

It has become important to know more about the structure, growing conditions, and harvest time of *Artemisia abrotanum* L. and similar medical plants with the start of cultivation of these species . In this study, the protein and free amino acid content of the *Artemisia abrotanum* L. were evaluated. The result of the free amino acid content in the plant pre and at blooming period time, showed that the harvesting time of the plant is important. *Artemisia abrotanum* L. should be harvested in blossom time. Both protein determination methods could be used for the evaluation of the protein content of the plant. On the other hand, the Dumas method was easier to apply and gave detailed information about the structure of the plant. Another advantage of this method is its contribution to green chemistry with its low time consumption and chemical usage.

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Ethics

Ethics Committee Approval: Ethics committee approval is not required due to the type of study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: Ö.S., Design: Ö.S., Data Collection or Processing: İ.C., Analysis or Interpretation: İ.C., Ö.S., Literature Search: İ.C., Ö.S., Writing: İ.C.

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Original Article

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Can Dehydroepiandrosterone-Sulphate be a New Diagnostic Parameter in Idiopathic Hypogonadotropic Hypogonadism?

Dehidroepiandrosterone-Sülfat İdiyopatik Hipogonadotropik Hipogonadizmde Yeni Bir Tanı Parametresi Olabilir Mi?

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ABSTRACT

Objective: Dehydroepiandrosterone (DHEA) and its sulfate derivative DHEA-sulfate (DHEA-s) are major androgen hormones which are synthesis from the adrenal origin. The purpose of this study was to investigate DHEA-s levels in male patients with idiopathic hypogonadotropic hypogonadism (IHH) and to determine whether DHEA-s level are a useful marker for diagnosis of IHH.

Methods: A total of 91 subjects, 31 males with IHH (mean age 19.7±2.6 years) and 60 healthy males (mean age 20.7±2.6 years), were enrolled in this study. The patients with IHH were selected from the subjects who had not yet started treatment for hypogonadism and who had no additional disease, while the healthy control group consisted entirely from individuals admitted to the same hospital outpatient clinic for routine check-ups. Both groups' blood sampling, anthropometric measures, and physical examination were undertaken

Results: Mean DHEA-s level was 133.4±56.5 μg/dL in the IHH group and 433.3±160.3 μg/dL in the control group (p=0.000). The low DHEA-s level in patients with IHH was independent of age, cortisol, and adrenocorticotropic hormone (ACTH) at multivariate logistic regression analysis. The ROC analysis showed that DHEA-s ≤38.2 μg/dL supports a diagnosis of IHH with 100% specificity and 100% sensitivity. DHEA-s was as predictive as total testosterone which is used in the diagnosis of patients with IHH.

ÖZ

Amaç: Dehidroepiandrosteron (DHEA) ve onun sülfat türevi olan DHEA-sülfat (DHEA-s) adrenal kaynaklı majör androjen hormonlardır. Bu çalışmanın amacı, erkek idiyopatik hipogonadotropik hipogonadizmli (İHH) hastalarda DHEA-s düzeylerinin araştırılması ve DHEA düzeyinin İHH tanısında yararlı bir belirteç olup olmadığını belirlemektir.

Yöntemler: Bu çalışmaya 31 İHH'li erkek (ortalama yaş 19,7±2,6 yıl) ve 60 sağlıklı erkek (ortalama yaş 20,7±2,6 yıl) olmak üzere toplam 91 kişi alındı. İHH hasta grubunda yer alan hastalar hipogonadizm için henüz tedavi başlanmamış, yeni tanı konulan ve ek hastalığı olmayan kişilerden, yine sağlıklı grupta polikliniğe rutin kontrol amaçlı başvuran tamamen sağlıklı gönüllülerden seçildi. Her iki grubun da kan örneklemesi, antropometrik ölçümleri ve fiziksel muayenesi yapıldı.

Bulgular: Ortalama DHEA-s düzeyi İHH grubunda 133,4±56,5 μg/dL ve kontrol grubunda 433,3±160,3 μg/dL idi (p=0,000). İHH hastalarında düşük DHEA seviyesi, multivariate logistic regression analizinde yaş, kortizol ve adrenokortikotropik hormondan (ACTH) bağımsızdı. ROC analizi, DHEA-s ≤38,2 μg/dL, %100 spesifite ve %100 sensitivite ile İHH teşhisini desteklediğini göstermiştir. DHEA-s, İHH'li hastaların tanısında kullanılan total testosteron kadar prediktif idi.

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Conclusion: DHEA-s level was significantly lower in the males with IHH compared to controls. Therefore, DHEA-s may be a potential predictive marker for diagnosis of IHH.

Keywords: Dehydroepiandrosterone, dehydroepiandrosterone-sulphate, idiopathic hypogonadotropic hypogonadism

Sonuç: DHEA-s düzeyi İHH'li erkeklerde kontrollere göre anlamlı olarak daha düşüktü. Bu nedenle, DHEA-s, İHH tanısı için potansiyel bir prediktif belirteç olabilir.

Anahtar Sözcükler: Dehidroepiandrosteron, dehidroepiandrosteron-sülfat, idiyopatik hipogonadotropik hipogonadizm

Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is the deficiency of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). These hormones play a major role in the regulation of the male reproductive endocrine system (1). Since LH and FSH are the trophic hormones of the testis, impairment of the secretion of these pituitary gonadotropins results in low androgen levels. The major androgen hormone is the testosterone which is secreted from the testis.

The IHH is a lifelong disease resulting from GnRH neuron dysfunction and deficiency. Clinical findings in patients with IHH include non-occurrence of puberty and virilization, delayed epiphyseal closure, small testes and penis, and azoospermia (2). The prevalence of IHH is approximately 1/10,000 in males (3).

In males, androgens regulate secondary sex characteristics. These sexual characteristics are largely determined by testosterone (gonadal steroids). Adrenal androgens have a minimal effect on the regulation of sex characteristics. The principal adrenal androgens are dehydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione. The zona fasciculata and the zona reticularis of the adrenal cortex produce a significant quantity of DHEA, an androgen precursor, and androstenedione which is considered a weak androgen. These androgen precursors are converted into more powerful androgens outside the adrenal tissue, and androgens become pathological if specific steroidogenic enzymes are defective. The purpose of this study was to investigate whether DHEA-s, a metabolic by product of testosterone, was a useful marker in the diagnosis of IHH.

Methods

A total of 91 subjects, 31 males with IHH and 60 healthy males, were recruited into the study. The patients in the IHH group were selected from recently diagnosed subjects who were not treated for hypogonadism at the Endocrinology Department of the University of Health Sciences Turkey Erzurum Regional Traning and Research Hospital. The healthy control group consisted of subjects who were admitted for routine check-ups at the Internal Medicine Outpatients clinics in the same hospital. The disease was identified as having total testosterone level <229 ng/dL and free testosterone level <5.1 pg/mL due to the absence or deficiency of pituitary gonadotropins. All patients underwent the GnRH test and no FSH and LH response were observed, and also growth hormone deficiency was excluded. Again, hypothalamus and pituitary gland imagings were performed in all patients. Exclusion criteria were chronic illness, panhypopituitarism, hypo and hyperthyroidsm, nephrotic syndrome, steroid use or use of any drug causing hypogonadism. Also, none of the study subjects was a current smoker or alcohol user. All participants gave their written informed consent to participate in the study and the study was approved by the local ethical committee (2018/05/27).

Total testosterone, free testosterone, LH, FSH, adrenocorticotropic hormone (ACTH), cortisol and DHEA-s levels were investigated in the patient and the control groups. Body mass index (BMI) was calculated by the ratio between weight and height squared in kg/m^2. DHEA-s and ACTH levels were analyzed using Siemens Immulite 2000 XPİ (Siemens Healthcare Diagnostics Inc., Munich, Germany) device by solid-phase, competitive chemiluminescent enzyme immunoassay method. LH, FSH, total testosterone, and free testosterone levels were analyzed using Abbott Architect i2000 SR (Abbott Türkiye, İstanbul, Turkey) device and the chemiluminescent microparticle immunoassay method. Ten cubic centiliter venous blood specimens were collected for hormonal analysis from all patients and healthy volunteers from the antecubital vein between 07:30 and 09:00 in the morning after 12-hour fasting. These specimens were centrifuged for 10 min at 4000 rpm using an Electromag M4808 P Centrifuge device. Data were obtained by analyzing blood specimens in appropriate analyzers.

Statistical Analysis

After analysis of the variance, comparisons between groups were done using Student's t-test or Mann-Whitney U test for continuous data. Unless otherwise stated, the results were expressed as mean ± stadart deviation. One-tailed Pearson's correlation test or Spearman correlation test was performed to find out the correlation between various variables. Logistic regression analysis was performed whenever it was appropriate. ROC curve analysis assessed the cut-off DHEA-s level with the best diagnostic accuracy for detecting IHH. $p<0.05$ was considered statistically significant. The statistical analysis was performed using SPSS version 19.0 software program (IBM-SPSS, Chicago, USA).

Results

There wasn't any significant difference between sociodemographic characteristics of the patient and the healthy control groups. The mean ages were 19.7±2.6 years in the patient group and 20.7±2.6 years in the control group (p=0.1). BMI values in the patient and the healthy control groups were 21.9±4.8 kg/m^2 and 25.4±7.8 kg/m^2, respectively (p=0.1). The sociodemographic characteristics of both groups are summarized in Table 1.

The mean DHEA-s values were 133.4±56.5 µg/dL in the IHH group and 433.3 ± 160.3 µg/dL in the control group (p<0.001). The total testosterone levels in the patient and control groups were 28.0±26.3 nmol/L and 568.1±288.0 nmol/L, respectively (p<0.001). In the patient and the control groups, the free testosterone levels were 9.7±14.3 pg/mL and 18.0±9.0 pg/mL, respectively (p=0.006). The FSH levels were 1.6±2.4 mIU/mL and 4.3±5.4 mIU/mL (p<0.001), and the LH levels were 0.7±0.9 mIU/mL and 4.2±2.6 mIU/mL (p<0.001) in the patient and the control groups, respectively. The results are summarized in Table 1.

Table 1. Clinical and biochemical characteristics of the patient and control groups

	IHH	Control	p value
Total number of patients	31	60	
Age (years)	19.7±2.6	20.7±2.6	0.1
Weight (kg)	62.8±16.8	66.1±18.5	0.7
Height (cm)	168±9	162±16	0.2
BMI (kg/m²)	21.9±4.8	25.4±7.8	0.1
DHEA-s (µg/dL)	133.4±56.5	433.3 ± 160.3	0.000*
Total testosterone (nmol/L)	28.0±26.3	568.1±288.0	0.000*
Freetestosterone (pg/mL)	9.7±14.3	18.0±9.0	0.006*
FSH (mIU/mL)	1.6±2.4	4.3±5.4	0.000*
LH (mIU/mL)	0.7±0.9	4.2±2.6	0.000*
ACTH (pg/mL)	23.1±10.4	24.3±13.0	0.7
Cortisol (µg/dL)	13.9±4.1	15.9±5.3	0.7
p<0.05 significantly*			

ACTH: Adrenocorticotrophic hormone, BMI: Body mass index, DHEA-s: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

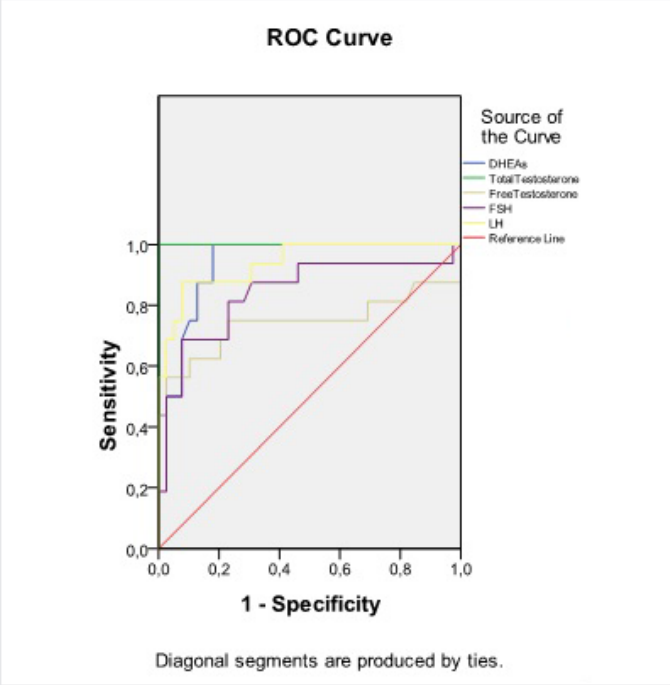

Figure 1. ROC curve

The ACTH levels in the patient and the control groups were 23.1±10.4 pg/mL and 24.3±13.0 pg/mL (p=0.7), and the cortisol levels were 13.9±4.1 µg/dL and 15.9±5.3 µg/dL (p=0.7), respectively (Table 1). At the correlation analysis, the DHEA-s level exhibited the positive correlations with the total testosterone (p=0.02, r=0.411), free testosterone (p=0.01, r=0.412), cortisol (p=0.005, r=0.321), ACTH (p=0.01, r=0.382), LH (p<0.001, r=0.432) and prolactin levels (p=0.01, r=0.295), and BMI (p=0.01, r=0.307). The data obtained are shown in Table 2.

Multiple regression analysis of the DHEA-s level and the other risk factors were performed. Low DHEA-s level was found to be an independent risk factor from age and cortisol and ACTH levels in patients with IHH. The data obtained are shown in Table 3. The ROC curve of DHEA-s level predicting IHH is shown on the Figure 1. The AUC of the DHEA-s was 0.95 (p<0.001). The cut-off point of DHEA-s level was ≤38.2 µg/dL (sensitivity: 100%; specificity 100%).

Discussion

In the present study, it was be detected that the DHEA-s level in males with IHH was much lower than the healthy subjects.

Table 2. The correlation relationship between DHEA-s and other factors

	r (correlation coeffcient)	p
Height (cm)	0.107	0.4
Weight (kg)	0.219	0.08
Age(years)	0.190	0.08
BMI (kg/m²)	0.307	0.01*
T. testosterone (nmol/L)	0.411	0.02*
F. testosterone (pg/mL)	0.412	0.01*
Cortisol (µg/dL)	0.321	0.005*
ACTH (pg/mL)	0.382	0.01*
FSH (mIU/mL)	0.05	0.6
LH (mIU/mL)	0.432	0.000*
Prolactin (ng/mL)	0.295	0.01*

ACTH: Adrenocorticotrophic hormone, BMI: Body mass index, DHEA-s: Dehydroepiandrosterone sulfate, FSH: Follicle stimulating hormone, LH: Luteinizing hormone

Table 3. Multivariate regression values

Variables	DHEA-s	
	β	p
Age (years)	0.8	0.4
ACTH (pg/mL)	1	0.2
Cortisol (µg/dL)	0.8	0.1

ACTH: Adrenocorticotrophic hormone, DHEA-s: Dehydroepiandrosterone sulfate

The DHEA-s level was determined in patients on the basis diagnostic phases. The DHEA-s level was found lower in the patients. This is one of the first studies to show that the DHEA-s is an easily identifiable marker that can be used in the diagnosis of IHH. We found out that the DHEA-s level ≤38.2 µg/dL predicted the diagnosis of IHH with 100% sensitivity and 100% specificity.

Puberty is a process that begins prenatally and ends in adulthood with the autoregulation of all hormonal secretions. This continuity is based on the equilibrium between neurohormones (GnRH), neurotransmitters (biogenic amines), pituitary gonadotropin (FSH, LH) secretion, and final organ reaction (testis or ovarium) (4). Normal pubertal development involves the release of GnRH from the hypothalamus and activation of the hypothalamic-pituitary-gonadal (HPG) axis, followed by activation in the hypothalamic-pituitary-adrenal axis. This enables the individual to achieve full sexual maturity. Testosterone release in males begins with the effect of GnRH and subsequently of LH and FSH after the onset of pubertal development. As pubertal development continues, adrenal androgens are secreted from the adrenal gland under the effect of ACTH. Adrenarche is referred to the developmental changes concluding with the increased androgen secretion from the adrenal glands (5).

The DHEA and its sulfate conjugate (DHEA-s) are the major steroids secreted from the adrenal glands (6). DHEA-s is the adrenal androgen most present in the circulation. It is regarded as a marker of the onset of adrenarche, and also plays a role in the pubertal development (7). Androgens and estrogens are synthesized from DHEA. DHEA forms from a series of metabolic pathways using cholesterol as a substrate. In the final stage, androgens are synthesized from DHEA with the effect of 17,20-lyase (8,9).

The DHEA, a metabolic by-product in the biosynthesis of the male sex hormone testosterone, follows a circadian rhythm that peaks in the mornings. In contrast, DHEA-s has a relatively stable concentration throughout the day, and it is used as a useful biomarker of adrenal androgen secretion and DHEA. DHEA-s is released from the zona reticularis of the adrenal cortex as a response to ACTH. Production reaches a peak in young adulthood and then decreases by 2-4% a year (10,11).

Since the patient group enrolled in this study had testosterone deficiency due to IHH, and since both the patient group and the control group consisted of young males, we did not determine the age-dependent decrease in the DHEA-s levels. This study investigated the practicability and effectiveness of measuring DHEA-s levels in the diagnosis of patients with IHH characterized by the absence or deficiency of pubertal development.

Previous studies in the literature have investigated the DHEA and DHEA-s levels in panhypopituitarism and pubertal disorders. Differing opinions have been reported on the subject. Giton et al. (12) reported significantly lower DHEA-s level in the patients diagnosed as having IHH and panhypopituitarism compared to the control group. Cohen et al. (13). investigated the levels of adrenal androgens such as DHEA, DHEA-s, and androstenedione in 90 patients with delayed puberty. The DHEA-s level was low in all patients and the authors reported that the DHEA-s level was able to identify 89% of patients with hypogonadotropic hypogonadism. They concluded that measurement of serum DHEA-s levels could be a considerable assistance in the early diagnosis of conditions that might lead to delayed puberty (13). In our study, we also showed that low-level DHEA could identify IHH with 100% sensitivity and 100% specificity.

Rohayem et al. (14) investigated the usefulness of gonadal activity, growth axis activation, and adrenarche markers due to the limited specificity and sensitivity of diagnostic parameters indistinguishing between the constitutional delay of growth and puberty (CDGP) and IHH, and the difficulty in establishing the diagnosis. Seventy four subjects with delayed puberty were enrolled, 24 with hypogonadotropic hypogonadism, 22 classified as pre-pubertal CDGP (PP-CDGP) and 28 with early-pubertal CDGP (EP-CDGP). The LH, FSH, testosterone, inhibin B, and the Anti-Mullerian hormone levels of all patients were investigated. In addition, insulin-like growth factor (IGF)-1, IGFBP3, INSL3, and DHEA-s levels were also investigated in 9 patients in the IHH group, 8 in the PP-CDGP group and all patients in the EP-CDGP group. DHEA-s level was assessed as a marker of adrenarche, and no significant difference was determined between the three groups.

Conclusion

Although we observed no significant difference between the IHH and the control groups in terms of ACTH and cortisol levels in this study, we determined a significant difference in terms of DHEA-s levels. In conclusion, we think that DHEA-s level is as practicable and predictable marker of total testosterone levels in the diagnosis of patients with IHH.

Ethics

Ethics Committee Approval: The study was approved by the local ethical committee (2018/05/27).

Informed Consent: All participants gave their written informed consent to participate in the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: K.Ç., H.K., M.B., A.Ç., Ş.C.A., Design: K.Ç., A.Ç., Ş.C.A., Data Collection or Processing: K.Ç., H.K., M.B., A.Ç., Ş.C.A., Analysis or Interpretation: K.Ç., H.K., M.B., A.Ç., Ş.C.A., Literature Search: K.Ç., H.K., M.B., Writing: K.Ç., M.B.

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

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Original Article

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The Effects of Surgical Timing on Treatment Outcomes in Carpal Tunnel Syndrome

Karpal Tünel Sendromunda Cerrahi Zamanlamanın Tedavi Sonuçları Üzerine Etkisi

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ABSTRACT

Objective: The purpose of this study is to assess and compare outcomes of two different timing surgery for moderately carpal tunnel syndrome (CTS).

Methods: Eighty-eight patients who underwent early and late due to CTS were evaluated retrospectively. Patients with early surgery and late surgery were divided into two groups. Preoperative and postoperative visual analog scale (VAS) score and postoperative Boston Carpal Tunnel Questionnaire (BCTQ) scores of both groups were compared.

Results: Preoperative and postoperative VAS scores were compared, there was a significant decrease in both groups. When BCTQ results of both groups were compared, the results of patients who underwent early surgery were statistically better.

Conclusion: In conclusion, we think that early surgery is better clinically in patients with moderately CTS.

Keywords: Carpal tunnel syndrome, surgical timing, median nerve

ÖZ

Amaç: Bu çalışmanın amacı, orta derece karpal tünel sendromunda (KTS) iki farklı cerrahi zamanlamanın sonuçlarını değerlendirmek ve karşılaştırmaktır.

Yöntemler: KTS nedeniyle erken ve geç dönemde ameliyat edilen 88 hasta retrospektif olarak değerlendirildi. Erken cerrahi ve geç cerrahi geçiren hastalar iki gruba ayrıldı. Her iki grubun ameliyat öncesi ve sonrası görsel analog skala (VAS) skoru ve ameliyat sonrası Boston Karpal Tünel Anketi (BCTQ) skorları karşılaştırıldı.

Bulgular: Ameliyat öncesi ve sonrası VAS skorları karşılaştırıldığında, her iki grupta da anlamlı düşüş vardı. Her iki grubun BCTQ sonuçları karşılaştırıldığında, erken cerrahi uygulanan hastaların sonuçları istatistiksel olarak daha iyiydi.

Sonuç: Sonuç olarak orta derece KTS'li hastalarda erken cerrahinin klinik olarak daha iyi olduğunu düşünüyoruz.

Anahtar Sözcükler: Karpal tünel sendrom, cerrahi zamanlama, medyan sinir

Introduction

Carpal tunnel syndrome (CTS) occurs when the median nerve is under pressure within the carpal tunnel in the wrist and is the most common entrapment neuropathy (1). In its early stage, the most common symptoms include tingling, pain, and numbness in the median nerve dermatome. In advanced stages, in addition to numbness and pain, loss of strength and atrophy may develop in the muscles innervated by the median nerve (2-4).

In CTS treatment, conservative treatments are applied in the early stages, while surgery takes priority in the middle and

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advanced stages (5,6). Conservative treatment consists of steroid injections, physical therapy, medication and splinting. Patients who continue to experience symptoms after physical therapy are treated surgically. In surgical treatment, the flexor retinaculum can be released with open, mini-open, or arthroscopic methods (7,8). Delayed surgical treatment of CTS may lead to exacerbation of symptoms, permanent paresthesia, and atrophy in the thenar region. These consequences reduce the chance of success after surgery (9).The literature recommends conservative treatment in mild and moderate CTS, and surgical treatment in moderate to severe CTS (10,11). Here, the confusing part is whether the appropriate treatment of moderate CTS is conservative or conservative treatment.

Our study aims to evaluate the effect of surgical timing on the results by comparing the clinical and functional outcomes of patients with moderate CTS who underwent surgical treatment in the early and late stages.

Methods

This retrospective study was performed in our clinic after it was approved by the local institutional review board from Ethics Committee Department (2021/03). The preoperative and postoperative clinical and functional outcomes of patients, who were diagnosed as having CTS and underwent treatment between 2015-2019, were reviewed from our hospital's database archives.

All patients were diagnosed as having CTS with clinical symptoms and examination. All of them underwent electrodiagnostic studies (EDX) (nerve and motor conduction studies). Patients who had moderate CTS according to a neurophysiological grading scale for CTS on EDX (12) (Table 1) were included in the current study. We recommended conservative treatment in all patients who had moderate CTS. Conservative treatment was performed in patients who accepted surgery, while conservative treatment was applied in patients who did not accept conservative treatment. Night splint, oral and topical NSAIDs, and lifestyle modifications were recommended in conservative treatment. Patients who received conservative treatment were reevaluated at least 6 months later, and among these patients, those who accepted conservative treatment underwent operation. Group 1 consisted of 40 patients who accepted conservative treatment at initial admission, and Group 2 consisted of 33 patients whose complaints did not resolve after conservative treatment and who accepted surgery at least six months later. EDX was not re-administered to these patients. Fifteen patients who were absent from follow up during conservative treatment or who did not accept conservative treatment were excluded from the study. When these patients were contacted, they stated that their complaints continued, but they did not plan to undergo surgery.

Table 1. A neurophysiological grading scale for carpal tunnel syndrome

Grade 0	Normal
Grade 1	Very mild CTS; demonstrable only with the most sensitive tests
Grade 2	Mild CTS; sensory nerve conduction velocity slow on finger or wrist measurement; normal terminal motor latency
Grade 3	Moderate CTS; sensory potential preserved with motor slowing; distal motor latency to APB <6.5 milliseconds
Grade 4	Severe CTS; sensory potentials absent but motor responses preserved; distal motor latency to APB <6.5 milliseconds
Grade 5	Very severe CTS; terminal latency to APB >6.5 milliseconds
Grade 6	Extremely severe CTS; sensory and motor potentials effectively not recordable

CTS: Carpal tunnel syndrome

Patients who underwent revision CTS and patients with peripheral neuropathy, history of trauma, and pregnant women were excluded from the study.

Clinical Evaluation

Clinical outcomes in both groups were assessed by a specialist who did not participate in surgical procedures. In the preoperative period and 6-month after surgery, visual analogue scale (VAS) and postoperative Boston Carpal Tunnel Questionnaire (BCTQ) scores of both groups were collected and compared.

The BCTQ is a scoring system developed by Levine et al. (13) for the standardization of patients with CTS. It consists of a total of 19 questions, including 11 questions for symptom severity and 8 questions for evaluating functional capacity. Questions are scored on a scale ranging from 1 to 5 and overall score is calculated by dividing the sum of scores by the number of questions. Sezgin et al. (14) conducted the Turkish adaptation of the scale, which was used in our study.

Surgical Technique

All operations were performed by the same surgeon. A vertical line was drawn proximally from the radial side of the fourth finger. After the thumb was placed in maximum abduction, a transverse line was drawn from the ulnar side. A longitudinal incision was made from the intersection of the two lines. After subcutaneous infiltration, the palmar aponeurosis was incised. After partial incision of the transverse carpal ligament, the median nerve was accessed. The median nerve was preserved and the carpal ligament was proximally and distally incised. After making sure the transverse ligament was completely incised, the tourniquet was deflated. Skin closure was made after ensuring bleeding control.

Postoperative Care and Rehabilitation

Active range of motion exercises were permitted after the surgery. Load-bearing exercises were permitted as much as the patient could tolerate.

Statistical Analysis

All analyses were performed using SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk,

NY: IBM Corp.). Continuous variables were expressed as median (minimum-maximum) and mean ± standard deviation values. The results were reported within a 95% confidence interval. Normality distribution of continuous data was assessed with Shapiro-Wilk test, skewness, and kurtosis. Mann-Whitney U test and Independent samples t-test were used for comparisons between two groups. P<0.05 was considered statistically significant.

Results

Age, gender, and affected sides were determined in both groups. Mean age was 51.9±6.6 years in Group 1 and it was 52.3±6.8 years in Group 2. Group 1 consisted of 33 female patients and 7 male patients, and 30 of the operated wrists were right wrists and 10 were left wrists. Group 2 consisted of 27 female patients and 6 male patients; 24 right wrists and 9 left wrists were operated.

Postoperative VAS and BCTQ symptom severity scale and functional status scores are presented in Table 2. Group 1 was found to be statistically superior to Group 2 in terms of BCTQ scores (p<0.05). A significant decrease in postoperative VAS score compared to preoperative VAS score was observed in both groups (p<0.05). Improvement in VAS score was statistically significant in Group 1 compared to Group 2 (p<0.05).

Discussion

CTS is surgically treated by many different surgical branches in clinical practice. These patients are also treated with conservative methods by many non-surgical branches. These multidisciplinary treatment processes lead to differences in clinical applications and uncertainty about the timing of surgery, especially in moderate CTS. It is known that when compressive forces on the median nerve persist, it may lead to irreversible fibrotic changes in the nerve. The pathological changes in the median nerve in CTS cannot be explained by neuropraxia, axonotmesis, and neurotmesis in normal nerve damage. The notion that rapid alleviation of symptoms after surgery in CTS is due to the elimination of local ischemia on the median nerve has gained prominence (15). Studies on the efficacy of conservative treatment and conservative treatment in CTS demonstrated that both treatment methods yielded good outcomes (16-18). Delayed treatment and prolonged compression may lead to end organ atrophy and conservative treatment may not achieve the expected benefit. A previous study found that patients with moderate CTS who underwent surgery in the early term had better functional outcomes than those who underwent surgery in the late period (19). The results of our study also indicate that early conservative treatment provide better clinical outcomes.

Table 2. Clinical outcomes

	Earl surgery Group 1	Delayed surgery Group 2
Preoperative VAS	7.27±1.1	7.24±1.1
Postoperative VAS	2.05±0.9	3.15±1.3
BCTQ SSS	1.97±0.2	2.46±0.3
BCTQ FSS	2.28±0.2	2.61±0.2

VAS:Visual analogue scale, BCTQ: Boston Carpal Tunnel Questionnaire
SSS: Symptom severity score, FSS: Functional status score

Many scoring systems, which vary according conservative treatment to many factors, have been described to evaluate patients with CTS (20,21). However, BCTQ was shown to be a reliable method in the evaluation of patients diagnosed as having CTS, therefore we used BCTQ to evaluate the symptoms and functional status of our patients.

Pourmokhtari et al. (22) compared the 1-year outcomes of patients with moderate CTS who underwent conservative treatment or surgical treatment. They found that the surgical treatment group had significantly less symptoms and that surgical treatment was more successful. As in our study, they demonstrated that surgical treatment was superior to conservative treatment.

Study Limitations

The present study had several limitations, including its small sample size and retrospective design. Postoperative VAS and BCTQ scores were subjectively evaluated. Postoperative EDX studies were not conducted. Patients in Group 2 were not reevaluated with EDX before surgery. None of the delayed patients had a steroid injection which could be a very effective intervention that would avoid surgery in a proportion of patients.

Conclusion

There is no consensus regarding the surgical timing of patients with moderate CTS. The data in our study support that early surgical treatment of moderate CTS provides superior outcomes. We recommend early surgery treatment in patients with moderate CTS, as delayed surgical treatment leads to poor symptomatic and functional outcomes.

Ethics

Ethics Committee Approval: This study was carried out after the approval of Dicle Univercity Medicine Faculty Ethical Committe.

Informed Consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Peer-review: Externally peer reviewed.

Authorship Contributions

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Original Article

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Empathic Tendencies and Attitudes Toward People with Disabilities in Healthy Developing Children and Their Relationship Between Empathic Tendencies of Parents

Normal Gelişim Gösteren Çocukların Empatik Eğilimleri ve Engellilere Yönelik Tutumlarının Ebeveynlerinin Empatik Eğilimleri ile İlişkisi

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ABSTRACT

Objective: This study was conducted to investigate empathic tendencies and attitudes toward people with disabilities in healthy developing children and the relationship between their parents' empathic tendencies.

Methods: Fifty-fourth grade primary school students and their parents were included in this study. KA-SI Empathic Tendency Scale-Child Form (KA-SI), Chedoke-Mcmaster Attitudes Towards Children with Handicaps Scale and Empathetic Tendency Scale (ETS) for parents were used.

Results: When the total scores were considered, there was a moderate correlation between children's empathic tendencies and attitudes towards the disabled ($r=0.594$; $p<0.0001$). Any correlation was not observed among the empathic tendencies of parents and children's empathic tendencies and attitudes towards the disabled ($r=0.263$ and $r=0.270$; $p>0.05$, respectively). Parents with a college degree had a higher level of empathy in their children ($p<0.05$).

Conclusion: In this study, which examined the empathic tendencies of normally developed children and their attitudes towards the disabled and their relationship with the empathic tendencies of their parents, it was concluded that the increase in empathic tendencies of children supported their attitudes towards the disabled in a moderately positive way. The relationship between the level of education of parents and the increase in empathic tendencies of children may indicate the importance of education in this regard. Ensuring the development of children in terms of empathy and

ÖZ

Amaç: Bu araştırma normal gelişim gösteren çocukların empatik eğilimleri ve engellilere yönelik tutumları ile ebeveynlerin empatik eğilimleri arasındaki ilişkinin incelenmesi amacıyla yapılmıştır.

Yöntemler: Çalışmaya ilköğretim 4. sınıfta eğitim gören 50 öğrenci ve ebeveynleri dahil edildi. Çalışmada; KA-SI Empatik Eğilim Ölçeği-Çocuk Formu (KA-SI), çocukların engellilere yönelik tutumlarının değerlendirildiği Chedoke-Mcmaster Engelli Çocuklara Yönelik Tutumlar Ölçeği ve ebeveynlere yönelik Empatik Eğilim Ölçeği (EEÖ) kullanıldı.

Bulgular: Toplam puanlar dikkate alındığında çocukların empatik eğilimleri ile engellilere yönelik tutumları arasında orta düzeyde ilişki bulunmuştur ($r=0,594$; $p<0,0001$). Ebeveynlerin empatik eğilimleri ile çocukların empatik eğilimleri ve engellilere yönelik tutumları arasındaki bağıntı bulunmadı (sırasıyla; $r=0,263$ ve $r=0,270$; $p>0,05$). Üniversite mezunu olan ebeveynlerin çocuklarında empati düzeyinin daha fazla olduğu görüldü ($p<0,05$).

Sonuç: Normal gelişim gösteren çocukların empatik eğilimleri ve engellilere yönelik tutumlarının, ebeveynlerinin empatik eğilimleri ile ilişkisinin incelendiği bu çalışmada çocukların empatik eğilimlerindeki artmanın engellilere yönelik tutumlarını orta düzeyde olumlu yönde desteklediği sonucuna varılmıştır. Ebeveynlerin eğitim düzeyinin artması ile çocukların empatik eğilimlerindeki artış eğitimin bu konudaki önemini işaret edebilir. Çocukların empati ve olumlu tutum açısından gelişimlerinin

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positive attitudes and improving the education levels of parents can support the participation of people with disabilities into life by supporting positive attitudes towards them.

Keywords: Empathic tendency, attitude towards the disabled, social participation, occupational therapy

sağlanması ve ebeveynlerin eğitim düzeylerinin ilerlemesi engelli bireylere karşı tutumları olumlu yönde destekleyerek yaşama katılımlarını destekleyebilir.

Anahtar Sözcükler: Empatik eğilim, engellilere yönelik tutum, toplumsal katılım, ergoterapi

Introduction

Human, who is a social and social being, tends to communicate and interact with the people around him/her. Empathy, which is one of the most basic conditions of establishing a healthy relationship with other people and which is at the base of social skills, is defined as the potential of an individual to understand the other person in human relations (1). It is accepted that empathy skills, the first clues of which date back to infancy, are formed with mechanisms that begin to function at birth and with a biological tendency, and develop in the process as in other developmental areas. In this development, the attitudes of parents, who are the first persons with whom children experience communication, and the environmental factors with which they interact have an important place (2). The empathy skills of the parents in the child's life and the level of these skills are highly related to the development of the children's empathy skills, and it has been stated that if the parents' empathy skills are low, their children's empathy skills are also low (3). As a result of the studies, it has been determined that the ability to empathize prevents communication conflicts and enables the establishment of more positive relationships, increases social sensitivity, adaptation to society, cooperation and other prosocial behaviors, has a reducing effect on aggression and other antisocial behaviors, and increases the academic success of children (4).

Disability is defined as the restriction or inability to fulfill the roles expected from the person, depending on age, gender, social and cultural factors, caused by a disease, accident or loss of function that can occur from birth or may occur during the life process of the person (5,6). Attitudes, on the other hand, are the tendencies that are not observed but assumed to lead to certain behaviors that can be observed (7,8). Attitudes of people with normal development towards disabled people are determinative for disabled people to lead their lives in harmony with society. Negative attitudes create real obstacles for people with disabilities to fulfill their roles and achieve their life goals. For this reason, it is important for social participation and integration to determine the attitudes of individuals with normal development towards the disabled and to change the negative attitudes towards the disabled (7).

It is important for children to develop a positive attitude towards the differences in their environment in the early period, in terms of respecting the differences and developing their empathy skills (9). Children quickly grasp what they experience and see in early childhood, and they also form their own identities, attitudes and perceptions by taking the adults around them as role models (10). Therefore, while adults' awareness of disabled people, knowing their rights and accepting them with their differences, affect social cohesion positively, it can make it easier for the children of these adults to adopt similar social acceptance attitudes (11).

Social participation is expressed as being a part of family and social life, fulfilling roles and responsibilities, and being an active and participatory member of society (12). As a result of the literature research, it has been stated that participation in society is one of the areas where disabled people have the most difficulty and that most of the problems they experience in participation in society are caused by people's negative attitudes. Examining the attitude of the child, who is the most basic part of the society and the most open to change, towards the disabled, within the framework of his/her own empathic tendencies, will enable to make changes at the level of the individual, family and society and to draw a more effective way in intervention programs.

This research was conducted to examine the relationship between the empathic tendencies of normally developing children and their attitudes towards the disabled, and the empathic tendencies of parents. In addition, the relationship between children's attitudes towards the disabled and their empathic tendencies, the relationship between the empathic tendencies and education level of the parents and the children's empathic tendencies and attitudes towards the disabled were also investigated. Thus, it was aimed to understand whether there was a need for the development of these tendencies and attitudes in children and to shed light on the areas of intervention if needed.

Methods

The study was carried out in Tiryaki Hasanpaşa Primary School in Bağcılar district of İstanbul province between February and June 2020. The ethics committee approval required for the study was obtained from the Bezmialem Vakıf University Non-Interventional Clinical Research Ethics Committee with the decision number 01/20. Fifty children, who were 4th grade primary school students and who were not diagnosed as having any developmental disorder, and their parents, who were most interested in their development since birth, were included in the study. Written consent was obtained from the participants. The data collection tools used in the study are listed below:

Sociodemographic Data Form for Families

This form was developed by the researchers to determine the sociodemographic characteristics of the participants. With this form, demographic data that defined the child and family, educational status of family members, occupation, average monthly income, the neighborhood they lived in, and whether there was a disabled person in the family or in the environment were questioned.

Empathic Tendency Scale (ETS)

It was developed by Dökmen (13) in 1988 to measure the tendency of people to empathize in their daily life. The scale consists of twenty items, and some items also include negative questions in order to prevent individuals' tendency to answer "yes" all the time. In the items in the form, a five-point Likert-type scale is used as "(1) Completely contrary, (2) Quite contrary, (3) Undecided, (4) Quite agreeable, (5) Completely appropriate". Negative questions are items 3, 6, 7, 8, 11, 12, 13 and 15 and are scored reversely. The highest score that can be obtained from the scale is 100 and the lowest score is 20. A high score means that the tendency to empathize is high, and a low score means that the tendency to empathize is low (13).

The Sociodemographic Data Form for Families and EES were sent to the families through their children and they were asked to be filled out by the parents who were most interested in the development of the children since their birth.

KA-SI Empathic Tendency Scale-Child Form (KA-SI)

It was developed by Kaya and Siyez (1) in 2010 to determine the empathy tendency levels of children. It consists of thirteen items. It was shown to be valid and reliable in a study conducted on primary school students in Turkey. The questions in the form are evaluated with a four-point Likert-type scale: "(1) Not at all suitable for me, (2) Somewhat suitable for me, (3) Quite suitable for me, and (4) Completely suitable for me". The scale has two sub-dimensions that measure emotional and cognitive empathy. The lowest score to be obtained from the emotional empathy sub-dimension is 7, the highest score is 28. The lowest score to be obtained from the cognitive empathy sub-dimension is 6 and the highest score is 24. Thus, the total empathic disposition score is the lowest 13 and the highest 52. An increase in the score obtained from the scale indicates that the empathic tendency of the child increases (1).

Chedoke-Mcmaster Attitudes Towards Children with Handicaps Scale (CATCH)

It was developed by Rosenbaum et al. in 1986 to measure the attitudes of primary school children towards their disabled peers. Çiçek and Önel showed that the Turkish version of the scale was valid and reliable in the 9-13 age group. The response style of the scale was arranged in a 5-point structure as "(0) I strongly disagree, (1) I disagree, (2) I am undecided, (3) I agree, (4) I strongly agree". The scale consists of positive and negative statements. Items with negative expressions are scored inversely. A high score in each negative statement indicates that the child's attitude on this issue is negative. The highest score that can be obtained from the scale is 124. Higher scores support positive attitudes towards children with disabilities (14).

The KA-SI Empathic Tendency Scale-Child Form and the Chedoke-Mcmaster Attitudes Towards Children with Handicaps Scale were filled in by the children participating in the study under the supervision of the researcher in the classroom.

Statistical Analysis

For statistical analysis, version 26.0 of the Windows-based SPSS (Statistical Package for the Social Sciences) analysis program was used. Significance level was accepted as $p<0.05$. Mean ± standard deviation was used for the variables determined by measurement, and the percentage value was calculated for the variables determined by counting. Correlation analysis was performed to evaluate the relationships between the variables. Pearson correlation coefficient was calculated in correlation analysis since the data were suitable for normal distribution. The correlation coefficient values between 0.3-0.4 indicate a weak correlation, between 0.4-0.6 moderate, between 0.6-0.7 high, between 0.7-0.75 very high, and >0.75 perfect correlation (15). Independent groups t-test was used to test the difference between the means of the same variables in two different groups, and one-way ANOVA test was used to compare three or more groups.

Results

Fifty normally developing children and their parents were included in our study. Of the children, 58% were girls, 42% were boys, and the mean age was 9.94±0.31 years. Of the parents who completed the ETS, 72% were females and 28% were males. It was observed that the number of children who did not have a disabled person in their family or around was higher than the children who did. The most common education level among parents was primary school graduation (Table 1). The mean, standard deviation and minimum-maximum values of the scales are presented in Table 2.

In general, it was seen that there was a moderate ($r=0.594$; $p<0.0001$) positive correlation between the total scores of the KA-SI, which measured the empathic tendency in children, and the CATCH scales, which evaluated the attitude towards

Table 1. Distribution of children participating in the study by demographic features

		n	%
Gender	Female	29	58
	Male	21	42
Presence of disabled individuals in the family or in the environment	Yes	18	36
	No	32	64
Mother's education status	Illiterate	3	6
	Primary school	20	40
	Middle School	10	20
	High school	7	14
	University	10	20
Father's education status	Primary school	16	32
	Middle School	11	22
	High school	13	26
	University	10	20
Total		50	100
	X ± SD	**Min-Max**	
Age (years)	9.94±0.313	9-11	

n: Number of participants, X: Arithmetic mean, SD: Standard deviation, min: Minimum, max: Maximum

disabled children. The correlation of the "emotional empathy" dimension of the KA-SI scale with the CATCH scale total score (r=0.618; p<0.0001) was higher than the "cognitive empathy" dimension (r=0.475; p<0.0001). The "emotional empathy" dimension of the KA-SI scale showed a stronger correlation with the "avoidance" and "similarity" dimensions compared to the other dimensions of the CATCH scale (r=0.544; p<0.0001 and r=0.517; p<0.0001, respectively) seen. No correlation was found between the "cognitive empathy" dimension of the KA-SI scale and the "pity" and "similarity" dimensions of the CATCH scale (r=0.231; p>0.05 and r=0.163; p>0.05, respectively) (Table 3).

No correlation was found between the ETS, which measured empathic tendency in adults, and the total scores of the KA-SI and CATCH scales (r=0.263; p>0.05 and r=0.270; p>0.05, respectively) (Table 4).

When the children's empathy and attitudes towards the disabled were compared according to their gender, no statistically significant difference was found between boys and girls (p>0.05) (Table 5 and Table 6).

When children's empathic tendencies were compared with reference to the education level of their parents, it was observed that the cognitive and emotional empathy levels of children were higher in families with higher education levels compared to families with lower education levels (Table 7 and Table 8).

When the children's attitudes towards the disabled were compared based on whether there was a disabled person in the family or in the environment, it was observed that there was no significant difference between the groups in terms of both sub-components and total scores (p=0.836) (Table 9).

Table 2. KA-SI, CATCH and ETS values (n=50)

Assessment parameters		X ± SD	Min-max
KA-SI Empathic Tendency Scale for Children (KA-SI)	Cognitive empathy	19.18±3.67	10-24
	Emotional empathy	22.26±3.94	13-28
	Total	41.44±7.05	26-52
Chedoke-Mcmaster Attitudes Towards Children with Handicaps Scale (CATCH)	Interaction and acceptance	28.70±6.63	13-38
	Avoidance	31.82± 6.33	14-40
	Pity	6.10±37.75	0-20
	Sense of affinity	13.14±34.70	4-20
	Total	79.76±14.16	46-105
Empathic Tendency Scale for Adults (ETS)		71.18±8.09	51-88

n: Number of participants, X: Arithmetic mean, SD: Standard deviation, min: Minimum, max: Maximum

Discussion

The main purpose of this study was to examine the relationship between the empathic tendencies of normally developing children and their attitudes towards the disabled, and the empathic tendencies of parents. While there was a moderate correlation between the children's empathic tendencies and their attitudes towards the disabled, it was found that there was no correlation between the empathic tendencies of the parents and the empathic tendencies of the children and their attitudes towards the disabled.

Table 3. Relationship between KA-SI and CATCH subparameters

		1	2	3	4	5	6	7	8
1. KA-SI	r	1	0.709	0.919	0.350*	0.469**	0.231	0.163	0.475**
cognitive empathy	p		0.000	0.000	0.013	0.001	0.107	0.259	0.000
2. KA-SI	r			0.930	0.492**	0.544**	0.064	0.517**	0.618***
emotional empathy	p			0.000	0.000	0.000	0.659	0.000	0.000
3. KA-SI	r				0.458**	0.549**	0.156	0.374	0.594**
total	p				0.001	0.000	0.279	0.007	0.000
4. CATCH	r					0.555	0.082	0.359	0.827
interaction and acceptance	p					0.000	0.572	0.010	0.000
5. CATCH	r						0.188	0.327	0.838
avoidance	p						0.190	0.020	0.000
6. CATCH	r							-0.021	0.384
pity	p							0.883	0.006
7. CATCH	r								0.554
sense of affinity	p								0.000
8. CATCH	r								1
total	p								

p: Significance level, r: Correlation coefficient, p<0.05
*: Weak moderate correlation, **: Moderate correlation, ***: Good correlation

Empathy is a key element of communication, interaction, problem solving, acceptance of differences and tolerance. The dimensions of empathy, acceptance of differences and tolerance may come to the fore in interacting with people with disabilities. High empathic tendency can provide positive support for the attitudes people develop towards each other. As the level of empathy increases, the potential to cause positive changes in one's behavior increases (16). On the contrary, it has been shown that individuals with negative attitudes are less likely to approach other people empathetically (17). When the current literature is examined, it is seen that the number of research reports examining the empathic tendencies of normally developing children and their attitudes towards the disabled is quite limited. A few studies conducted examine attitudes towards mainstreaming students. In one of these studies, it was found that there was a significant relationship between the attitudes of normally developing primary school students towards mainstreaming students and their level of empathic tendency (18). In the study conducted by Armstrong et al. (19) on the interaction of students between the ages of 7 and 16 with disabled people, it was found that high empathic tendency mediated the development of positive attitudes. The results of this study also showed that as the empathy levels of the students increased, their attitudes towards disabled individuals also changed positively. This finding supports the relevant literature in terms of enabling children with high empathy skills to develop a positive attitude towards people with disabilities. When examined in terms of sub-parameters of empathic tendency, children's "cognitive empathy" scores were higher than their "emotional empathy" scores and when examined in terms of the sub-parameters of the attitude towards the disabled, it was observed that the "pity" sub-parameter had the lowest average compared to the other sub-parameters. Emotional empathy forms a basis for the development of empathy in early childhood and is defined as the need to share the same feelings with the other person and help with a feeling of compassion. Cognitive empathy, on the other hand, refers to the ability to understand the experience of another by placing oneself in another's situation, and it is observed in parallel with the increase in brain development in school-age children (20). The fact that the students participating in our study were at primary school

Table 4. The relationship between ETS and KA-SI and CATCH

		1	2	3
1. ETS	r	1	0.263	0.270
	p		0.066	0.058
2. KA-SI total	r			0.594
	p			0.000
3. CATCH total	r			1
	p			

p: Significance level, r: Correlation coefficient, p<0.05

Table 5. Comparison of the KA-SI scores of the children participating in the study by gender

Factor	Group	n	X	SD	t	p
KA-SI cognitive empathy	Female	29	20.00	3.52	1.88	0.066
	Male	21	18.04	3.66		
KA-SI emotional empathy	Female	29	22.75	3.72	1.03	0.309
	Male	21	21.57	4.22		
KA-SI total	Female	29	42.75	6.66	1.55	0.128
	Male	21	39.61	7.31		

Independent Samples t test, p<0.05
n: Number of participants, X: Arithmetic mean, SD: Standard deviation, t: t score, p: Significance level

Table 6. Comparison of the CATCH scores of the children participating in the study by gender

Factor	Group	n	X	SD	t	p
CATCH interaction and acceptance	Female	29	29.06	6.78	0.461	0.647
	Male	21	28.19	6.55		
CATCH avoidance	Female	29	33.06	5.79	1.62	0.112
	Male	21	30.09	6.77		
CATCH pity	Female	29	6.48	3.91	0.851	0.399
	Male	21	5.57	3.59		
CATCH sense of affinity	Female	29	12.75	3.65	-0.931	0.357
	Male	21	13.66	3.21		
CATCH total	Female	29	81.37	14.9	0.957	0.343
	Male	21	77.52	13.7		

Independent Samples t test, p<0.05
n: Number of participants, X: Arithmetic mean, SD: Standard deviation, t: t score, p: Significance level

Table 7. Comparison of the KA-SI scores of the children participating in the study according to the education level of their mothers

Factor	Group	n	X	SD	F	p	Tukey HSD
KA-SI cognitive empathy	1	3	16.00	1.00	5.60	0.001	5>1
	2	20	18.00	3.78			5>2
	3	10	18.10	3.69			5>3
	4	7	20.00	2.51			
	5	10	23.00	0.942			
KA-SI emotional empathy	1	3	21.00	2.00	3.36	0.017	5>2
	2	20	21.35	4.40			5>3
	3	10	20.60	3.77			
	4	7	22.71	2.98			
	5	10	25.80	1.81			
KA-SI total	1	3	37.00	2.64	5.24	0.001	5>1
	2	20	39.35	7.56			5>2
	3	10	38.70	6.81			5>3
	4	7	42.71	3.98			
	5	10	48.80	2.29			

One-Way Anova Test, p<0.05, n: Number of participants, X: Arithmetic mean, SD: Standard deviation, F: F value, p: Significance level
1: Illiterate, 2: Primary School, 3: Middle School, 4: High School, 5: University

Table 8. Comparison of the KA-SI scores of the children participating in the study according to the educational status of their fathers

Factor	Group	n	X	SD	F	p	Tukey HSD
KA-SI cognitive empathy	1	-	-	-	6.32	0.001	
	2	16	18.31	3.59			5 > 2
	3	11	16.90	3.83			5 > 3
	4	13	19.46	3.15			
	5	10	22.70	1.05			
KA-SI emotional empathy	1	-	-	-	3.08	0.036	
	2	16	21.00	4.09			5 > 2
	3	11	21.09	4.72			
	4	13	22.53	3.23			
	5	10	25.20	1.98			
KA-SI total	1	-	-	-	5.27	0.003	
	2	16	39.31	7.17			5 > 2
	3	11	38.00	7.82			5 > 3
	4	13	42.00	5.52			
	5	10	47.90	2.64			

One-Way Anova test, p<0.05, n: Number of participants, X: Arithmetic mean, SD: Standard deviation, F: F value, p: Significance level
1: Illiterate, 2: Primary school, 3: Middle school, 4: High school, 5: University

level and had higher cognitive empathy scores were consistent with the empathy development steps defined in the literature.

The development of empathy in children has some age-related features. The average age of the students participating in the study was found to be about 10 years. It has been shown that children between the ages of 10 and 12 are able to direct their empathy towards people they do not know and start to think about social problems (21). This point in the development of empathy can also change children's attitudes towards people with disabilities.

In this study, a moderate correlation was observed beween the sub-dimensions of "emotional empathy" and "avoidance" and "sense of affinity", which were the sub-parameters of the scale that evaluated the attitude towards the disabled. It is thought that this result is due to the fact that the questions in the dimensions of "avoidance" and "sense of affinity" in the attitude

Table 9. Comparison of the CATCH scores of the children participating in the study according to the presence of a disabled person in the family or in the environment

Factor	Group	n	X	SD	t	p
CATCH interaction and acceptance	Yes	18	27.88	7.52	-0.609	0.547
	No	32	29.15	6.16		
CATCH avoidance	Yes	18	32.16	6.93	0.277	0.784
	No	32	31.62	6.08		
CATCH pity	Yes	18	5.38	3.38	-1.04	0.302
	No	32	6.50	3.97		
CATCH sense of affinity	Yes	18	13.72	3.61	0.873	0.389
	No	32	12.81	3.40		
CATCH total	Yes	18	79.16	16.00	-0.209	0.836
	No	32	80.09	13.27		

Independent Samples t test, p<0.05
n: Number of participants, X: Arithmetic mean, SD: Standard deviation, t: t score, p: Significance level

scale towards the disabled, in accordance with the definition of emotional empathy as stated in the literature, include more emotional expressions and questions about the feelings of the other party (22).

It is natural to expect empathetic parents to better read their children's emotional cues and to be more motivated to be sensitive and understanding under conditions that facilitate their children's empathy development. However, current studies examining the relationship between parents' and their children's empathic tendency are limited. According to Köksal (23), there are individual differences in children's reactions to other people's emotional states, and individual differences can be influenced by the mother, father, and other individuals in the immediate environment that children take as models for themselves. However, in some studies, it has been stated that there is no direct relationship between the empathic skills of children and the empathic skills of their parents. In a meta-analysis by Strayer and Roberts (24), including previous studies, it was stated that although mothers reported significantly higher levels of empathy than fathers, there was no correlation between the empathy of neither mothers' nor fathers' and children's empathy contrary to what was theoretically expected. In this study, no statistically significant relationship was found between the empathic tendencies of the parents and the empathic tendencies of the children and their attitudes towards the disabled. Current studies examining the relationship between children's and their parents' empathic tendencies are rare in the literature. For this reason, we think that our study will support the literature in new researches in this field.

When the empathic tendencies of the children participating in the study were compared according to their genders, it was observed that girls had higher averages in cognitive, emotional and total empathy values compared to boys; this difference was not statistically significant. When the studies examining the differences of empathic tendency on gender in children are examined in the literature, there are studies reporting that empathic tendency is higher in girls than boys. According to the results of Yüksel's (25) research that included children in the fifth grade of primary education, it was stated that the empathy level of female students was higher than that of male students. In another study, which examined the development of empathy according to gender as one of the research aims, and in which the average age of children was 11, it was reported that girls were more empathetic than their male peers, especially in terms of cognitive empathy (26). Kahraman and Akgün (27), who reached similar findings with our study, showed that there was no relationship between gender and empathic skills in their study in which they examined the effect of empathy skills training on empathy skills and problematic behaviors of school-age children.

In our study, when comparing children's attitudes towards the disabled by gender, it was observed that girls had a higher average total attitude score than boys, but this difference was not statistically significant. In Gümüş and Tan's (28) study examining the attitudes of students with special needs towards students with special needs, a significant relationship was found between attitude and gender, and the attitudes of female students towards students with special needs were more positive than male students. However, there are also studies that contradict these findings. The results obtained by Ayral et al. (29) showed that the gender variable of normally developing female and male students was not effective in developing attitudes towards the disabled. We think that the gender variable in our study did not affect the attitude towards the disabled, as female and male students might have similar attitudes as a result of spending most of their days at school and interacting with each other.

In this study, when children's empathic tendencies were compared according to their mothers' educational status, a statistically significant difference was found in favor of university graduates in cognitive, emotional and total empathy levels. In the literature, Çetin and Aytar (30) found that there was a significant difference between the empathy scores according to the mother's educational status in their study examining the empathy levels

of fourth grade primary school students. In Taner Derman's (31) study, it was determined that the empathy levels of children differed significantly according to the education level of the mother. In Köse and Kolburan's (32) study, it was determined that the education level of the mothers did not make a significant difference on the empathy levels of the children.

When the children's empathic tendency scores were compared with the educational status of their parents, a statistically significant difference was found in favor of university graduates in cognitive, emotional and total empathy levels. The results of studies examining similar questions in the literature differ. In the study conducted by Sayın, it was found that the educational status of their fathers caused a significant difference in the empathy level of their children (33). In the study of Derman et al. (34) , a contrasting result emerged and it was stated that the educational status of the father did not show a correlation with the empathic level of the child.

There was no statistically significant difference between the groups in the comparison of the attitudes of the children participating in the study towards the disabled according to the presence of a disabled person in the family or in the environment. Similarly, Gümüş and Tan (28) stated that the attitudes of children with normal development towards the disabled did not show a statistically significant difference according to the presence of disabled people in their families and surroundings. It is thought that the presence of a disabled person in the family or in the environment may not be important enough to determine the attitude of the child, since children may frequently encounter disabled individuals outside of their family and close environment in daily life.

Conclusion

The age-related change in empathy development in children and the demonstration that the scales used have sufficient psychometric properties only in certain age groups may limit the generalization of the findings obtained from the research to children in all age groups.

In order to increase the participation of people with disabilities in society and develop strategies, positively developing the attitude of the child towards people with disabilities, who is the most fundamental part of society and the most open individual to change, can lead to positive changes in society. Children exposed to a particular pattern of behavior are more likely to copy those behaviors. Therefore, it is thought that role models displaying positive behaviors and similarly providing children with hands-on experiences with empathic actions will form a basis for future empathic behaviors. However, it is important to make correct assessments in order to be able to make the necessary interventions. For this reason, apart from the studies examining the attitudes towards inclusive students, there is a need for studies that examine the attitudes of children with normal development and different age groups towards the disabled, with sufficient sample size and which are evaluated with the right measurement tools.

Ethics

Ethics Committee Approval: Bezmialem Vakıf University Non-Interventional Research Ethics Committee (date:07.01.2020/ number: 54022451-050.05.04-).

Informed Consent:

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: R.S., Ş.Ö., Ü.U., Data Collection or Processing: R.S., Analysis or Interpretation: R.S., Ş.Ö., Ü.U., Literature Search: R.S., Ş.Ö., Writing: R.S.

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Original Article

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Influence of Current Adhesive Systems on Color Stability of Resin Composite

Günümüz Adeziv Sistemlerinin Rezin Kompozitin Renk Stabilitesi Üzerindeki Etkisi

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ABSTRACT

Objective: The adhesive systems which have an important place in modern dentistry can affect the color properties of final resin composite restorations. Therefore, the aim of the present study is to evaluate the influence of current adhesive systems on color, color stability and translucency of resin composites.

Methods: Fifty disc-shaped microhybrid resin composite specimens were prepared. Resin composite discs were divided into five groups randomly according to adhesive system including a control group (n=10) (Clearfil Protect Bond, Adper EasyOne, Clearfil QuickBond and Tokuyama BondForce). Color and translucency measurements were performed with a clinical spectrophotometer at baseline, immediately after adhesive system application and after immersion in water for 30 days. For statistical analysis, paired-samples t-test, one-way analysis of variance (ANOVA) and Tukey's post-hoc comparisons were used ($p<0.05$).

Results: The adhesive application significantly changed the color (E*) of the resin composite discs regardless of the adhesive brand. Storage of the resin composite discs in water for 30 days caused significant color changes in the control group. Significant differences were found in color values of the Adper EasyOne and Clearfil Protect Bond groups after aging. All adhesive groups showed significant color changes in Δb values in comparison with the control group, indicating increasing bluing. The translucency of composite discs applied with BondForce and Adper EasyOne adhesives significantly decreased after aging.

ÖZ

Amaç: Modern diş hekimliğinde önemli bir yere sahip olan adeziv sistemler, nihai rezin kompozit restorasyonların renk özelliklerini etkileyebilmektedir. Bu nedenle, bu çalışmanın amacı, günümüz adeziv sistemlerin rezin kompozit materyalinin renk, renk stabilitesi ve translüsensliği üzerindeki etkisini değerlendirmektir.

Yöntemler: Elli adet disk şekilli mikrohibrit rezin kompozit örneği hazırlandı. Rezin kompozit diskler, bir kontrol grubu olmak üzere rastgele olarak adeziv sisteme göre beş gruba ayrıldı (n=10) (Clearfil Protect Bond, Adper EasyOne, Clearfil QuickBond and Tokuyama BondForce). Renk ve translüsentlik ölçümleri, başlangıçta, adeziv sistem uygulamasından hemen sonra ve 30 gün boyunca suya daldırıldıktan sonra klinik spektrofotometre ile gerçekleştirildi. İstatistiksel analiz için eşleştirilmiş örneklemler t-testi, tek yönlü varyans analizi (ANOVA) ve Tukey'in post-hoc karşılaştırmaları kullanıldı ($p<0,05$).

Bulgular: Adeziv uygulaması, adeziv markasından bağımsız olarak rezin kompozit disklerin rengini (E*) anlamlı olarak değiştirdi. Kontrol gubunda, rezin kompozit disklerin 30 gün suda bekletilmesi anlamlı renk değişimine neden oldu. Adper EasyOne ve Clearfil Protect Bond gruplarının yaşlandırma sonrası renk değerlerinde anlamlı farklılıklar bulundu. Tüm adeziv grupları, kontrol grubuyla karşılaştırıldığında Δb değerlerinde anlamlı renk değişiklikleri gösterdi, bu da artan mavileşmeyi gösterir. BondForce ve Adper EasyOne adezivleri uygulanan kompozit disklerin translüsentliği, yaşlandırma sonrasında anlamlı olarak azaldı.

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Conclusion: The adhesive systems may influence the final color of the restoration, however the adhesive systems tested in the study caused clinically acceptable discoloration at baseline and after aging.

Keywords: Resin composite, color stability, adhesive system, translucency

Sonuç: Adeziv sistemler restorasyonun son rengini etkileyebilir, ancak çalışmada test edilen adeziv sistemleri başlangıçta ve yaşlanma sonrasında klinik olarak kabul edilebilir renk değişikliğine neden olmuştur.

Anahtar Sözcükler: Rezin kompozit, renk stabilitesi, adeziv sistem, translüsentlik

Introduction

The appearance of tooth-colored restorations in the aesthetic area is affected by several factors including the color and translucency of restorative materials and the underlying tooth tissues (1). Color matching and color stability have an important role in the short- and long-term success of any aesthetic restoration in dentistry (2,3). Polymeric materials, such as resin composites, become discolored over time when exposed to the intraoral environment (4). It is stated that the reason for change in color of resin restorations is due to changes in chemical structure of the materials and extrinsic staining over time (5,6).

Resin composites are semi-transparent materials. Due to this, color of tissues under it affects color of final restorations. This occurs especially when resin composite is applied in thin layers. Prior to placing resin composite restorations, an adhesive system should be applied to enamel and dentin surfaces in order to provide effective bond strength for resin composite with dental hard tissues. Therefore, the color properties of the adhesive system used for bonding may influence the final color of the restoration. In general, adhesive systems are highly complex mixtures containing polymerization initiators, solvents, hydrophilic monomers and hydrophobic monomers. In addition to these complex chemical contents of adhesive systems, chemical contents of each adhesive brand differ significantly (7). Similar to resin composites, adhesive systems are not full-transparent materials. Polymerization initiators such as camphorquinone play a major role in colorization of adhesive systems both before and after polymerization (8).

The amount of hydrophilic monomers and solvents have been increased in the content of recent adhesive systems. In this way, these adhesives are better infiltrated into microporosities on enamel and dentin surface (9). The increasing solvent and hydrophilic monomer content increase water absorption of the current adhesive systems (10). There is an inverse proportion between water absorption and color stability of polymeric materials (11). Therefore, the water absorption problem of adhesive systems may influence the color properties of the final resin composite restoration. In previous studies, it was stated that the adhesive brand affected both color matching and color stability of final resin composite restoration (12-14). However, such studies are not yet available in the literature for current adhesive systems that are new to the market and differ in their chemical contents. Thus, the aim of the present study is to investigate the effects of newly introduced adhesive systems on the initial colors and color stability of resin composites. The null hypothesis of the present study is that the initial color and color stability of resin composites are not affected by the adhesive system.

Methods

Study Design

Four adhesive systems (Adper EasyOne, 3M ESPE, St. Paul, MN, USA; Clearfil QuickBond, Kuraray Noritake Dental Inc., Tokyo, Japan; BondForce, Tokuyama Inc., Tokyo; Japan Clearfil Protect Bond, Kuraray Noritake Dental Inc., Tokyo, Japan) were tested. Details of the materials used in the study are shown in Table 1.

Specimen Preparation

Fifty disc-shaped specimens from a microhybrid resin composite (shade A2, Herculite Classic, Kerr Italia, Scafati, Italy) were prepared. Resin composite discs were divided into five groups randomly according to adhesive system (n=10). One group without application of adhesive system served as a control group. The elastic mold, which was used to prepare the resin composite discs, was 8 mm in diameter and 1.25 mm in depth. A transparent polyester strip was placed on a glass slide. The elastic mold was fixed on the transparent polyester strip by using a piece of double-faced adhesive band. The resin composite was condensed into the mold. The top of the elastic mold was covered with another transparent polyester strip and a second glass slide was placed slightly over the composite to achieve flat surface. Polymerization was done on top surface of resin composite from 5 different areas each for 20 s with a LED curing unit (Elipar S10, 3M Espe, St. Paul, MN, USA) with an intensity setting of 1,200 mW/cm^2. The curing light intensity was checked by a radiometer. After the resin composite discs were left in the dark for 24 h to complete the polymerization, both surfaces of the discs were polished with 600-, 800-, 1,200-1,500-grit silicon carbide papers under water cooling. For distinction of the bottom and top sides of specimens, little notches were made with a dental bur on the edge of the bottom side of the composite discs. Final thicknesses of resin composite disks were measured by a digital caliper (1.2±0.1). Resin composite discs were kept in black bottles until color measurements were done.

Color Analysis

A clinical spectrophotometer (VITA Easyshade V, VITA Zahnfabrik, Bad Säckingen, Germany) was used for the color measurement. All the measurements were made from the top sides of the discs. The display of the clinical spectrophotometer shows CIE $L^*a^*b^*$ color system. CIE $L^*a^*b^*$ color system states color space by L^*, a^*, and b^* coordinates. L^* symbolizes the

Table 1. Materials used in the study

Material	Chemical composition	Application technique
Clearfil Protect Bond (Kuraray Noritake Dental Inc., Tokyo, Japan) Primer #8H0073 Bond #8J0069	Primer: MDP, MDPB, HEMA, water, hydrophilic dimethacrylate Bond: MDP, Bis-GMA, HEMA, microfiller, surface-treated sodium fluoride	Apply and leave for 20 sec, air dry gently for 5 s; apply bond and light cure for 10 sec
Adper EasyOne (3M ESPE, St. Paul, MN, USA) #4747900	HEMA, Bis-GMA, methacrylated phosphoric esters, 1,6 hexanediol dimethacrylate, methacrylate, functionalized polyalkenoic acid, silica filler, ethanol, water, initiators, stabilizers	Apply adhesive to tooth surface for a total of 20 s; air-dry the adhesive for 5 s; light cure for 10 s
Clearfil QuickBond (Kuraray Noritake Dental Inc., Tokyo, Japan) #700042	HEMA, Bis-GMA, MDP, Hydrophilic amide monomers, Colloidal silica, Silane, Sodium fluoride, Ethanol, Water	Apply with a rubbing motion then no waiting time after applying; dry for 5 s; light cure for 5 s
BondForce (Tokuyama Inc., Tokyo, Japan) #144	Methacryloyloxyalkyl acid phosphate, HEMA, Bis-GMA, TEGDMA, camphorquinone, purified water, alcohol	Apply adhesive and agitate for 20 s; air-dry gently until there is no water movement, then dry with strong air for 5 s; light-curing for 10s
Herculite Classic (Kerr Italia S.r.L., Scafati, Italy) #5517381	Bis-GMA, TEGDMA, camphorquinone, amine, iron oxide pigments, aluminum borosilicate glass, colloidal silica (SiO2) 79% of filler content	2 mm application max, gently adapt the product and light -cure for 20 s

MDP: 10-methacryloxydecyl dihydrogen phosphate, MDPB: 12-methacryloyloxydodecylpyridinium bromide, HEMA: 2-hydroxyethyl methacrylate, Bis-GMA: Bisphenol-A glycidyldimethacrylate, TEGDMA: Triethyleneglycol dimethacrylate

lightness or black/white character of the color. The coordinates a^* and b^* define the chromatic features of the color. The a^* coordinate symbolizes the red-green axis and b^* coordinate symbolizes the yellow-blue axis.

Baseline color measurements (T_0) were performed in a custom-made light box with D65 illumination (KES 123 Led Bulb 12 W, K2 LED Systems, İstanbul, Turkey). Resin composite discs were placed on a white tile. The instrument was calibrated according to the manufacturer's instructions. Three consecutive measurements were made for each specimen and mean L^*, a^*, and b^* values were calculated (15). Color values (E^*) were calculated with the following formula:

$$E^* = (L^{*2} + a^{*2} + b^{*2})^{1/2}$$

Translucency was evaluated with translucency parameter (TP). Measurements were performed in the light box under D65 illumination with the Easyshade Compact spectrophotometer. Specimens were placed on a white tile. TP was obtained by calculating the color difference between the specimen on the white background and the black background with the following formula (15,16):

$$TP = ((L_B^* - L_W^*)^2 + (a_B^* - a_w^*)^2 + (b_B^* - b_W^*)^2)^{1/2}$$

Subscript B refers to the color coordinates on the black background and subscript W refers to those on the white background. If the material is absolutely opaque, TP value is zero; if the material is totally transparent, TP value is 100. Thus, higher values for the TP value represent greater translucency (16).

Adhesive System Application and Water-Storage Aging Procedures

After baseline color (E_0) and translucency (TP_0) measurements, for second measurements (T_1), adhesive systems application procedures were performed at the bottom surface of each resin composite discs according to respective manufacturer's instruction for each group (Table 1). Then, color (E_1) and translucency (TP_1) measurements were re-performed as in the first measurement from top surface of the resin composite discs. After the second measurements, resin composite discs were kept in distilled water for 30-day in separate dark bottles according to their groups. Distilled water in the dark bottles was changed every week. After aging process, resin composite discs were dried and color (E_2) and transparency (TP_2) measurements were made again (T_2). Color change values (ΔE) of resin composite discs between baseline and immediately after adhesive system application (ΔE_{0-1}) and between baseline and after aging procedure (ΔE_{0-2}) were calculated with the following formula:

$$\Delta\, Eab^*\ (L^*\, a^*\, b^*) = (\ (\Delta\, L^*)\ 2 + (\Delta\, a^*)\ 2 + (\Delta\, b^*)\ 2)\ ½$$

Statistical Analysis

Comparisons of E^*, L^*, a^*, b^*, and TP values among different time intervals (T_0, T_1, T_2) for each adhesive system were performed using paired-samples T-test. The effects of adhesive system on ΔE_{1-0} and ΔE_{2-0} values were analyzed by using one-way analysis of variance (ANOVA). Tukey tests were used for post-hoc comparisons among adhesive systems. All tests were performed by using SPSS 16 package program. Statistical significance was set at p=0.05.

Results

Mean and standard deviation of E^*, L^*, a^*, b^* and TP (translucency) values of adhesive bonded resin composite discs in different adhesive system groups and control group before and after artificially aging were presented in Figure 1. Paired t-test showed that adhesive application significantly changed the color (E^*) of the resin composite discs regardless of adhesive brand.

Storage of the resin composite discs in water for 30 days caused a significant change in color of the discs in the control group. Significant differences were found in the color values of Adper EasyOne and Clearfil Protect Bond groups after aging. On the other hand, there was no significant difference in color values of the discs in Clearfil QuickBond and Tokuyama BondForce groups between after and before aging. The translucency of composite discs applied with BondForce and Adper EasyOne adhesives significantly decreased after aging (Figure 1).

The findings of color changes (ΔE, ΔL, Δa and Δb) according to the adhesive system before and after artificially aging were summarized in Table 2. The application of Adper EasyOne (2.16±0.3) and Clearfil Protect Bond (-2.16±0.3) to the resin composite discs resulted in the highest initial color changes without significant differences. Color changes in Adper EasyOne and Clearfil Protect Bond groups after aging were the highest, however, there was no significant difference among all groups. All adhesive groups showed significant color changes in Δb values in comparison with the control group, indicating increasing bluing (Table 2).

Discussion

Since the resin composite material is semi-translucent, the final color of resin composite restorations is affected by the transparency and thickness of material and background color. The clinical success of aesthetic restorations depends on color

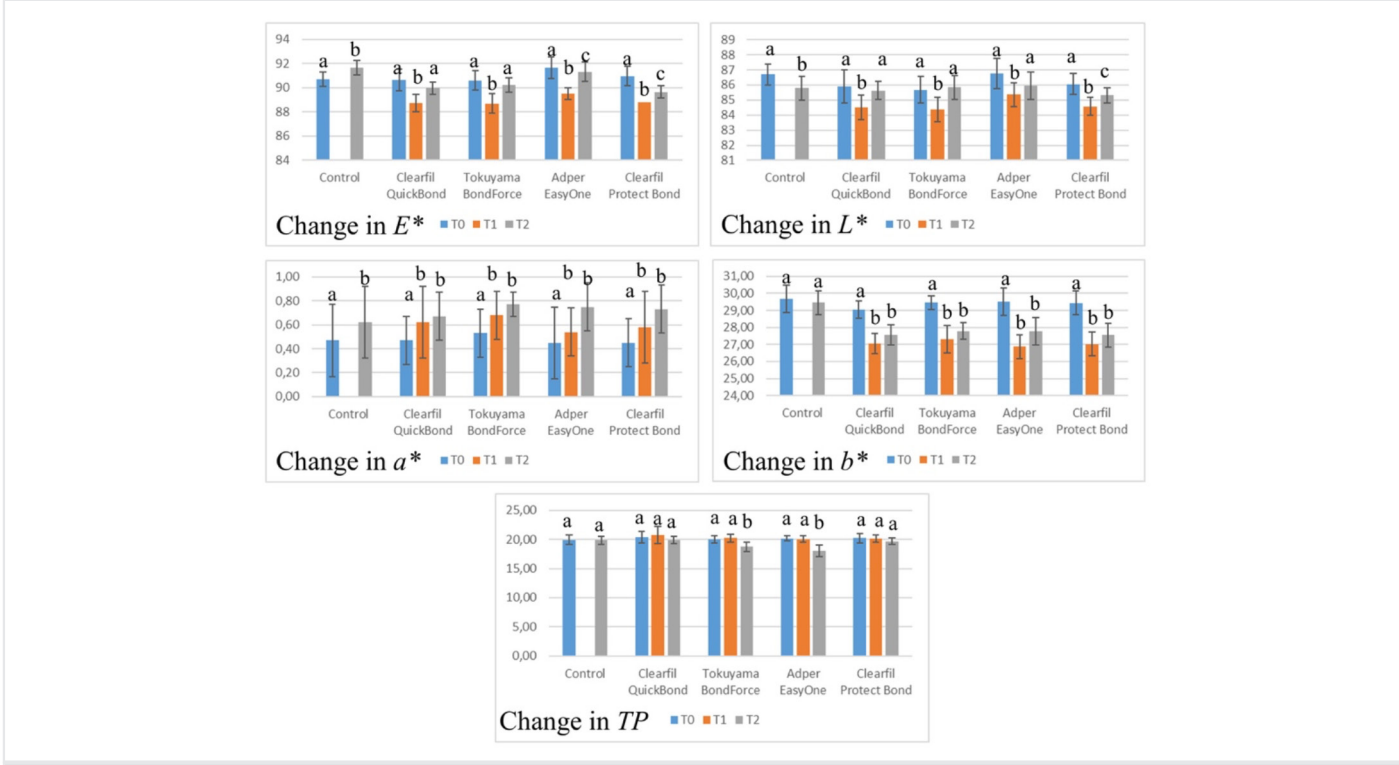

Figure 1. Bar graphs showing E*, L*, a*, b* and TP (translucency) values (means and standard deviations) of resin adhesive bonded resin composite discs according to adhesive brand and artificially aging. T_0: Time of color measurement before adhesive system application; T_1: Time of color measurement after adhesive system application; T_2: time of color measurement after artificial aging. Different superscripts on the bars of same adhesive brand indicate significant differences according to paired t-tests ($p<0.05$)

Table 2. ΔE, ΔL*, Δa* and Δb* values (means and standard deviations) for all test groups

Adhesive system	Before artifical aging Color change				After artifical aging			
	ΔE_{10}	ΔL_{10}	Δa_{10}	Δb_{10}	ΔE_{20}	ΔL_{20}	Δa_{20}	Δb_{20}
Control	-	-	-	-	-0.95±0.8^{a}	-0.92±0.7^{a}	0.72±0.4^{a}	-0.24±1.0^{a}
AEO	-2.16±0.3^{a}	-1.41±0.3^{a}	0.10±0.1^{a}	-2.63±0.3^{bc}	-1.34±1.3^{a}	-0.83±1.2^{a}	-0.74±0.2^{a}	-1.76±0.^{b}
CQB	-1.93±1.0^{a}	-1.38±0.9^{a}	0.15±0.1^{a}	-1.99±0.5^{ac}	-0.71±0.8^{a}	-0.26±0.9^{a}	-1.04±0.3^{a}	-1.47±0.7^{b}
BF	-1.91±0.6^{a}	-1.30±0.5^{a}	0.15±0.1^{a}	-2.14±0.5^{ac}	-0.37±0.6^{a}	0.16±0.7^{a}	-1.03±0.3^{a}	-1.67±0.7^{b}
CPB	-2.16±0.7^{a}	-1.41±0.3^{a}	0.13±0.1^{a}	-2.40±0.5^{ac}	-1.30±0.6^{a}	-0.75±0.7^{a}	-0.84±0.4^{a}	-1.88±1.0^{b}

Different superscripts in the same column indicate significant differences according to Tukey test ($p<0.05$).
AEO: Adper EasyOne, CQB: Clearfil QuickBond, BF: BondForce, CPB: Clearfil protect bond

matching and color stability. As the adhesive system is a material used under resin composite material, it can be considered as a factor affecting the color of resin composite restorations. In particular, the possible influence of the color stability of hydrophilic adhesives on the color of the final resin composite restoration may be significant. Therefore, the effects of three single-bottle one-step self-etch adhesive systems and one two-bottle two-step self-etch adhesive system on the color of resin composite discs that were aged for 30-day by immersing in water and that were not aged were investigated in this study.

Under clinical conditions, there are dental tissues under resin composite and adhesive layer. If clinical conditions were tried to be established in this study, the effects of color and color stability of the adhesive system on the final color of the resin composite discs could not be revealed (12). Therefore, in this study, adhesive systems were applied to the bottom surfaces of composite discs, as in the study of Ritter et al. (13).

Application of adhesive systems on the bottom surface of the resin composite discs significantly changed the initial color values (E^*) of the resin composite discs in all groups. Initial color change (ΔE) values were between 1.91 and 2.16 units. After 30-day storage in water, there were significant differences in color matching in Adper EasyOne and Clearfil Protect Bond groups. The return of discoloration caused by other adhesives over time is a phenomenon that needs to be explained. Color change values (ΔE) of the resin composite discs changed between 1.47 and 1.88 units after aging. In the light of our findings, the null hypothesis, which is that the initial color and color stability of resin composites are not affected by the adhesive system, is rejected.

Considering the relationship between color change and clinical significance, there is no clear consensus in the literature on what extent of color change is visually detectable or acceptable. When the single-step self-etch and the total-etch adhesive systems are evaluated, even in the early stages, they exhibit significant color changes in water, so adhesives may bepossible factors that can affect the color stability of resin composite restorations (12). However, in previous studies, ΔE =1-1.2 and ΔE =2.7-3.7 were specified as perceptible and acceptable color difference threshold values. (12). Alabdulwahhab et al. (14) stated that the color change range of 1.5-2.5 units could be recognized by an experienced clinician. Considering these threshold values, it could be concluded that the adhesives tested in this study caused an initial color change at a clinically acceptable level that could be detected by only experienced clinicians. Since some adhesives also cause perceptible color changes after aging, it can be concluded that color change due to adhesive in resin composite restoration after aging depends on the material. In a different in vitro study in which composite discs were kept in staining agents, it was found that the adhesives applied to the surface as modeling liquid did not affect the initial color and opacity (17).

From a clinical point of view, it may take a long time for adhesives to change color over time as a result of aging with water contact. Because the contact of the adhesive layer and water will be through the dentinal tubules since the other surface is in contact with resin composite. For this reason, in this study, immersion of the adhesive applied resin composite discs directly in water for 30-day can be considered as an accelerated aging process. On the other hand, although it has a narrow surface, the adhesive layer is in direct contact with the oral environment through the resin-composite interface. For this reason, the color stability of the adhesive systems used with composite resin can play an important role in the aesthetic properties of the final restoration in the long term.

Study Limitations

There are some limitations of this study, since the storage conditions of the specimens are different from the oral cavity, it may not fully reflect the change of composite resins and adhesives as much as in clinical studies.

Conclusion

Within the limitations of this study, clinicians should keep in mind that although the effect of dental adhesive application on the initial and post-aging color changes of resin composites is not very perceptible, the color properties of the adhesive system can have some effect on the final resin composite restoration.

Ethics

Ethics Committee Approval: *In vitro* study.

Informed Consent: *In vitro* study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.K.A, Design: M.K.A., Data Collection or Processing: H.G.D., B.K., Analysis or Interpretation: M.K.A., Literature Search: M.K.A., Writing: H.D.B.

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Case Report

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Bezmialem Science 2022;10(5):652-4

Longitudinal Extensive Transverse Myelitis Secondary to Lyme Disease

Lyme Hastalığına Bağlı Gelişen Longitudinal Extensive Transvers Myelit

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ABSTRACT

Transverse myelitis (TM) is a rare disease. It may present as the primary case or it may present as associated with inflammatory diseases following an autoimmune or infectious condition. Lyme disease involves cranial nerve neuropathy, meningitis, and radiculopathy neurologically, while only 4-5% of cases with neuroborreliosis show TM. Here we present a 3-year-old male patient with longitudinal extensive TM (LETM) secondary to Lyme disease.

Keywords: Transvers myelitis, lyme, neuroborreliosis

ÖZ

Transvers myelit (TM) nadir görülen bir hastalıktır. Primer bir olay olarak oluşabildiği gibi; otoimmün, enfeksiyöz veya enfeksiyon sonrası enflamatuvar hastalıklarla da ilişkili olabilir. Lyme hastalığında nörolojik tutulum daha çok kraniyal sinir nöropatileri, menenjit ve radikülopati şeklinde olurken TM nöroborreliosis vakalarının sadece %4-5'inde oluşmaktadır. Bu yazımızda lyme hastalığına bağlı longitudinal extensive TM (LETM) gelişen 3 yaşındaki erkek hastayı sunuyoruz.

Anahtar Sözcükler: Transvers myelit, lyme, nöroborreliosis

Introduction

Transverse myelitis (TM) is an inflammatory disease of the spinal cord that causes sensory and autonomic dysfunction in a few hours or days (1). It may primary or secondary toautoimmune, infectious or postinfectious disorders. Infectious etiologic agents include Herpes simplex type 1 and 2, Varicella zoster, West Nile virus, human immunodeficiency virus (HIV), human T-lymphotropic virus, *Borrelia species*, *Mycoplasma pneumoniae* and *Treponema pallidum*. TM due to *Borrelia species* is very rare (2).

Lyme is a disease caused by Ixodes ticks carrying 3 pathogenic species of Borrelia (*B. burgdorferi*, *B. afzelii* and *B. garinii*). It has a wide range of clinical manifestations. The clinical spectra includes cutaneous, joint, cardiac and neurological symptoms. Neurological manifestations mostly include cranial nerve neuropathy (most common is the 7th cranial nerve), meningitis and radiculopathy (3). However, it may rarely manifest in the form of TM (4,5). Primary infection and neural damage caused by post-infection immunity are responsible for central nervous system involvement (6).

The number of patients with Lyme and TM published in the literature is limited. It is known that a rapid response can be obtained with appropriate antibiotic therapy (2). Early diagnosis is critical in terms of treatment before the disease progresses.

Case Report

A 3-year-old male patient was admitted with weakness in legs and arms. The patient's history revealed that the weakness in both lower extremities started 5 days before, progressed within 3 days and weakness in the upper extremities was added. Physical

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examination revealed that he was conscious, cooperated and oriented. His pupils were isochoric, bilateral light reflexes were positive and eye movements were free in all directions. The fundus examination was normal. During motor examination, flask tetraparesis was detected. Bilateral deep tendon reflexes were normal and bilateral foot sole reflexes were extensor . There were no signs of meningeal irritation or nuchal rigidity. He could not cooperate to the sensory examination. The autonomic examination revealed constipation and urinary retention. No characteristics were detected in his blood tests. In cerebrospinal fluid (CSF) analysis, CSF pressure was normal, protein level was 20 mg/dL, glucose level was 60 mg/dL and direct microscopic examination revealed 40/mm^3 lymphocytes. CSF oligoclonal band was negative and immunglobulin (Ig)G index was normal. Electromyography findings and tests for connective tissue diseases did not show any characteristics of the disease. There were no radiological or biologic findings suggestive of malignancy in our patient.

His cranial magnetic resonance imaging (MRI) was normal while his spinal MRI revealed a longitudinal extensive TM (LETM) on the cervical spinal cord, distal thoracic cord and conus medullaris (Figure 1). Serum serological tests were negative for HIV, Herpes virus, Cytomegalovirus, Toxoplasmosis, Mycoplasma, Chlamydia, Tuberculosis, Brucella, Varicella zoster virus and syphilis. He was negative for Borrelia burgdorferi IgM and positive for Borrelia burgdorferi IgG. Anti-Borrelia antibodies were detected by Western Blotmethod. Ceftriaxone treatment was completed in 7 days and oral amoxicillin treatment was continued for 21 days. Oral low dose steroid treatment was started after intravenous pulse steroid was given for 3 days. During this time the patient received physical therapy. Low-dose steroid treatment was prescribed for the first month and then the dose was gradually reduced and it was terminated one month later. The patient started walking in the second week of steroid treatment, but his arms were still weak. By the end of the first month of treatment he could use his arms fully.

Discussion

TM is a rare disease with rapid onset motor weakness, sensory changes, and bowel or bladder dysfunction (7). Immunopathogenesis is very diverse. There is evidence of perivascular infiltration of monocytes and lymphocytes in the lesions and axonal degeneration (8). The involvement of both gray and white matters with this pathological heterogeneity suggests that TM is a mixed disorder affecting neurons, axons, oligodendrocytes and myelin rather than a pure demyelinating disorder (8).

Idiopathic TM usually occurs as a post-infectious complication which is thought to be caused by the autoimmune process. Of patients 30-60% have a history of respiratory, gastrointestinal or systemic diseases (9). TM may develop due to direct infections or may be secondary to systemic rheumatic diseases (e.g. ankylosing spondylitis, antiphospholipid antibody syndrome, Behçet's disease, mixed connective tissue disease, rheumatoid arthritis, scleroderma, Sjögren syndrome, and systemic lupus erythematosus), paraneoplastic syndromes, post-vaccination reactions or multifocal central nervous system disorders (multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, and neurosarcoidosis) (10-13).

Lyme disease due to *Borrelia species* is presented in three stages as early localized (erythema migrans), early disseminated and late disseminated disease. Clinical symptoms usually begin as erythema migrans and then disseminate to other systems. Arthritis, carditis, cranial nerve neuropathies (mostly 7th cranial nerve), meningitis or radiculopathy are the most common clinical spectra. Most discussions about Lyme disease are related to its nervous system involvement because neuroborreliosis usually causes nonspecific symptoms such as fatigue, headache, impaired cognitive function and memory. These symptoms are not specific for central nervous system infections but can also be seen in many other infectious and inflammatory conditions (14-16). Therefore, especially in pediatric patients, the diagnosis is difficult. TM, on the other hand, is only found in about 4-5% of patients with neuroborreliosis (17). Due to the small number of patients with TM secondary to Lyme disease, TM is not usually considered in the differential diagnosis. However, there are rare case reports in the literature. TM in those reported patients is in the form of LETM. LETM is defined as a type of TM involving three or more vertebra in the spinal cord (18). This relationship is considered important even though the underlying mechanism is unclear (4,19).

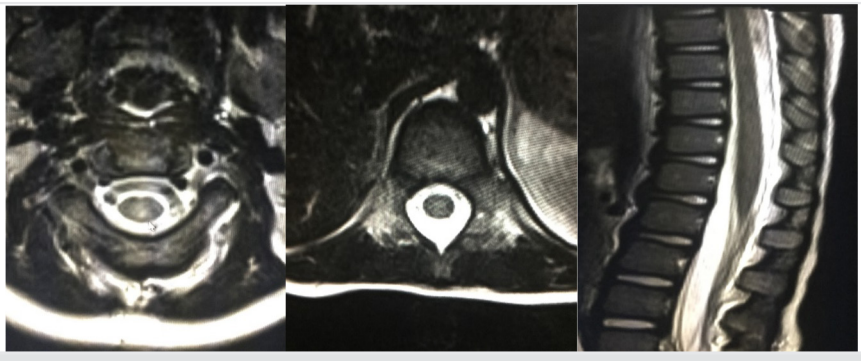

Figure 1. Spinal MRI shows LETM on cervical spinal cord, distal thoracic cord and conus levels
MRI: Magnetic resonance imaging, LETM: Longitudinal extensive transverse myelitis

In our patient, collagen tissue diseases and malignancy were excluded since these tests gave negative results. The clinical data, MRI and CSF findings were not consistent with acute disseminated encephalomyelitis, multiple sclerosis, and neuromyelitis optica spectrum disorder; therefore, these diseases were not considered. Serological tests in serum for infectious etiologies were positive only for Borrelia burgdorferi.

Leukocyte cell count in CSF and Borrelia burgdorferi antibody index in CSF and serum should be evaluated for the diagnosis of neuroborreliosis. However, 30% of patients may have a negative antibody index in CSF. Therefore, a diagnosis of neuroborreliosis can be made with typical clinical symptoms, presence of B. burgdorferi antibodies in serum, positive response in pleocytosis to antibiotic therapy (20,21).

Although our patient did not have a history supportive of Lyme disease, a diagnosis of TM due to neuroborelliosis was made with serum borrelia antibody positivity, confirmatory tests, andclinical response to antibiotherapy and steroid treatment. Control CSF examinations of the patient could not be performed because the family did not give consent.

As a result; due to the absence of features in the tests for autoimmune and demyelinating diseases (CSF oligoclonal band, Ig G index, serum Aquoporin 4 antibody, serum Anti MOG, C3, C4, cANCA, p ANCA etc.), they were not considered in the diagnosis. However, the patient was followed up for these diseases. Even if there is no history of tick bite or erythema migrans; neuroborreliosis should be considered in the differential diagnosis of TM, and if there are strong clinical findings, appropriate treatment should be initiated accordingly.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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Review

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Tobacco: Its Conventional and Modern Dosage Forms in Medication

Tütün: Konvansiyonel ve Modern İlaç Dozaj Şekilleri

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ABSTRACT

Tobacco is one of the most planted products in worldwide and the whole *Nicotiana tabacum L.* plant, its leaves, flowers, seeds or roots, and individual chemical compounds have medicinal uses such as as sedative, diuretic, or expectorant. From the past to the present, tobacco has been used in various dosage forms including oral/transdermal films, sublingual tablets, mouth/nasal spray, and inhaler. In addition, Tobacco is a very valuable plant with uses in medicine and bioengineering applications. In this review, it was aimed to give information about the tobacco plant and its medicinal uses and also the pharmaceutical dosage forms as well as novel delivery systems of nicotine compound of tobacco via comprehensively search method of the literature by using Pubmed, ScienceDirect, ISI Web of Knowledge, and Google Scholar databases for articles published in peer-reviewed journals from mostly 2016 to 2021. It is also aimed to draw attention to the pharmaceutical use of tobacco plant instead of potential harmful uses. In conclusion, there is need to be carried out new studies to enlighten the exact mechanisms of tobacco and its major compound of nicotine on other diseases such as schizophrenia, Parkinson's disease, and prose memory and attention than smoking cessation therapy and evaluate its safety and develop more effective novel pharmaceutical dosage forms.

Keywords: Tobacco, nicotine, pharmaceuticals, dosage forms

ÖZ

Tütün, dünya çapında en çok ekilen ürünlerden biridir ve tüm *Nicotiana tabacum L.* bitkisi, yaprakları, çiçekleri, tohumları veya kökleri ve tek tek kimyasal bileşikleri, yatıştırıcı, idrar söktürücü veya balgam söktürücü gibi tıbbi kullanımlara sahiptir. Geçmişten günümüze tütün, oral/transdermal filmler, dil altı tabletleri, ağız/burun spreyi ve inhaler dahil olmak üzere çeşitli dozaj formlarında kullanılmıştır. Ayrıca tütün, tıp ve biyomühendislik uygulamalarında kullanımları olan çok değerli bir bitkidir. Bu derlemede, Pubmed, ScienceDirect, ISI Web of Knowledge ve Google Scholar veri tabanlarında çoğunlukla 2016-2021 yılları arasındaki hakemli dergilerde yayınlanan makaleler kullanılarak kapsamlı literatür taraması yöntemi ile tütün bitkisi ve tıbbi kullanımları ve ayrıca farmasötik dozaj formları ve tütünün nikotin bileşiğinin yeni salım sistemleri hakkında bilgi verilmesi amaçlanmıştır. Ayrıca tütün bitkisinin potansiyel zararlı kullanımları yerine farmasötik kullanımına dikkat çekilmesi amaçlanmıştır. Sonuç olarak, tütünün ve ana bileşeni olan nikotinin sigara bırakma tedavisinden başka şizofreni, Parkinson hastalığı, Alzheimer hastalığı ve dikkat bozukluğu gibi diğer hastalıklardaki etki mekanizmalarınının aydınlatılmasına, güvenliğinin değerlendirilmesine ve daha etkili yenilikçi farmasötik dozaj şekillerinin geliştirilmesine ihtiyaç vardır.

Anahtar Sözcükler: Tütün, nikotin, farmasötikler, dozaj şekilleri

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Introduction

Tobacco is one of the most planted agricultural products obtained from the leaves of the plants of the genus of Nicotiana of the Solanaceae family (nightshade family). The other known names of tobacco are Tamak, Siah (Marma), Tabaci, and Tabacca. It is economically, agriculturally, and socially a valuable plant (1,2). Tobacco grows all over the world but it is mainly native to tropical and subtropical America (1,2). There are more than 600 tobacco species worldwide and many of them such as *Nicotiana affinis, Nicotiana rustica, Nicotiana Sanderae, Nicotiana alata grandiflora, Nicotiana acuminata, Nicotiana Bigelovii, Nicotiana longiflora, Nicotiana noctiflora, Nicotiana suaveolens, Nicotiana sylvestris*, *Nicotiana Tabacum, Nicotiana wigandioides* are cultivated. However, *Nicotiana tabacum* and *Nicotiana rustica* are the species used for medicinal purposes (3).

The pharmacological activities of tobacco mostly come from the active compound of nicotine found especially in the *Nicotiana tabacum* species (1). *Nicotiana tabacum* is a perennial herbaceous and annual little branched plant. It grows up to 2 meters and has high large green leaves and long white-pinkish flowers (Figure 1). All parts of the plant are sticky because of the yellow-colored exudate containing nicotine (1).

There are many groups of compounds in the tobacco plant, such as alkaloids, essential oils, polyphenols, triterpenes, aromatic substances, fatty alcohols, and phytosterols (4-10). The important secondary metabolites found in some of the parts of tobacco are summarized in Table 1. The alkaloid constituents in tobacco are nicotine, nicoteine, nicotimine, anabasine, anatabine, anatalline, and nornicotine which are found in the leaves of the tobacco plant (3,11). Among these, nicotine is the most active drug, which stimulates the central nervous system and causes addiction like heroin and cocaine. It is present in the moisture of tobacco leaf at different concentrations. Whereas the bright variety leaf contains 2.5% to 3% nicotine, the burley type tobacco contains 3.5% to 4% nicotine and the oriental type contains less than 2% nicotine (12). The chemical structures of the major constituents of nicotine, nicotinic acid and nornicotine of tobacco are given in Figure 2.

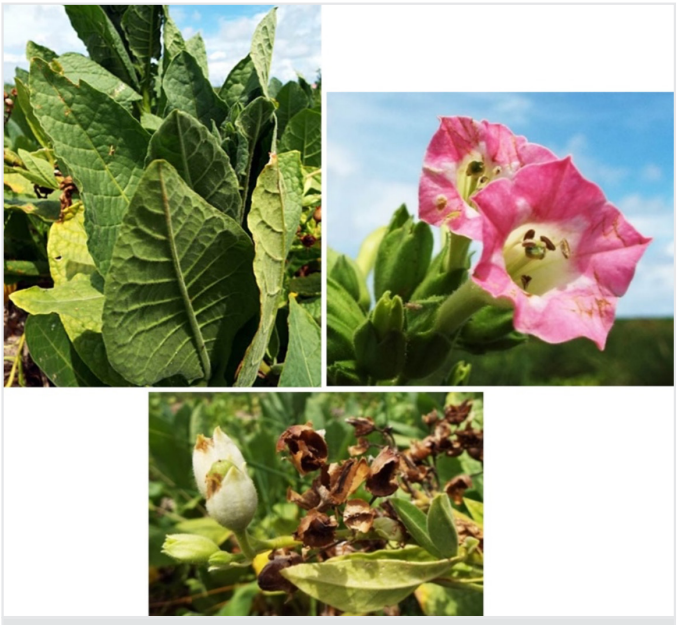

Figure 1. Nicotiana tabacum a) Leaves b) Flowers c) Seeds (https://www.cabi.org/isc/datasheet/36326)

Tobacco is usually used worldwide in cigars and cigarettes, snuff, and pipe, and chewing gums (1,2). In modern times, tobacco is mostly used as a cigarette but there are many pharmacological activities of leaves, flowers, seeds, or roots. Nevertheless, the chemical compounds in cigarettes lead people to have serious cardiovascular or pulmonary diseases and different cancers. By the 20th century, it was presumed that chronic tobacco use was leading to serious health problems based on substance abuse and addiction (1,13). In this review, medicinal uses of the tobacco plant, and conventional and modern pharmaceutical dosage forms of its major compound of nicotine were summarized. It is also aimed to draw attention to the pharmaceutical use of tobacco plant instead of potential harmful uses.

Methods

Comprehensively search method of the literature by using Pubmed, ScienceDirect, ISI Web of Knowledge, and Google Scholar databases for articles published in peer-reviewed journals from mostly 2016 to 2021 and rare and older articles for the history part of tobacco were used. Because the initial search of the study was carried out at the beginning of 2021, the authors decided to search for literature published during the most recent 5 completed years. The search contained either the phrase "Tobacco dosage forms", or the words "nicotine" along with "medication" or "dosage form" in any searchable field (i.e., title, abstract, or keywords). Four hundred sixty seven titles and abstracts were screened and 325 full-text articles were evaluated for assessment. Two hundred seventeen articles were excluded according to the eligibility criteria and remaining108 articles were included. We followed a guideline named PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) when writing the review article (14). The authors decided together to choose the suitable articles based on their title and abstract and shared them equally. The risk of bias in the study was independently assessed by 3 review authors using Cochrane Collaboration's tool (15). These domains were rated: sequence generating, allocation concealment, blinding of outcome assessment, incomplete

Figure 2. The chemical structures of nicotine, nicotinic acid and nornicotine of Tobacco plant (https://pubchem.ncbi.nlm.nih.gov/)

Table 1. The important secondary metabolites found in some of the parts of tobacco (4-10)

Leaves of the tobacco plant	Alkaloids; nicotine, nicoteine, nicotimine, anabasine, anatabine, anatalline, and nornicotine Glucosides, tahacinin, tahacilin and isoquercitrin, 1-quinic, chlorogenic, caffeic, and oxalic acids
Roots	Anatabine and (+) nornicotine
Flowers	Quercetin-3,3´- dimethyl ether, quercetin-3-methyl ether, gibberellins-nicotiana α, β and γ and gibberllins A and A3
Seeds	Cycloartanol, cycloartenol 24-daturadiol, solavetivone, cholesterol, cholest-7- enol, 24-methylenecholesterol, campesterol, stigmasterol, sitosterol, 28- isofucosterol, lanosterol, 31-norlanosterol, lanost-8-enol, obtusifoliol, 31-norcycloartenol, cycloeucalenol, granisterol, citrostadienol, β-amyrin, lupeol, cycloartanol and 24- methylenecycloartanol

outcome data, selective outcome reporting and other sources of bias. Then, the overall risk of bias of each included study was evaluated as either: low (all criteria were of low risk), unclear (at least one criterion was evaluated to be of unclear risk but no criterion of high risk), or high (at least one criterion with high risk of bias).

Medicinal Uses of Tobacco

The whole tobacco plant, its leaves, flowers, seeds or roots, and individual chemical compounds have medicinal uses. It is used medicinally as a sedative, diuretic, expectorant, discutient, sialagogue, and internally only as an emetic when it is the only option. It is also a local irritant on the mucous membrane when chewed, causes sneezing as snuff, and acts as a cathartic when injected into the rectum. Tobacco smoke is good for strangulated hernia and obstinate constipation when injected into the rectum, tobacco leaf rolled into a suppository or in the form of enema of the leaves. It is also beneficial in the treatment of retention of urine, spasmodic urethral stricture, hysterical convulsions and worms, and inflammation of the peritoneum, tympanitis, and tetanus. For the treatment of croup and spasms of the rima glottides, tobacco is formulated as a plaster including snuff and lard and applied to the throat and breast. The leaves of tobacco are beneficial as an ointment for cutaneous diseases and used for obstinate ulcers, painful tremors, and spasms when combined with belladonna or stramonium leaves. In addition, the concentrated juice of tobacco relieves neuralgia. Its other external applications are for poisonous reptiles and insects bites, hysteria, pain, laryngeal spasm, gout, growth of hair, tetanus, ringworm, ulcers, and wounds. However, tobacco causes nausea, vomiting, sweats, drowsiness, and muscular weakness in high doses (16-18). The medicinal uses of tobacco are represented in Figure 3.

The main active compound of tobacco species, nicotine, interacts with nicotinic acetylcholine receptors which are transmembrane ion channels. These receptors are found in the autonomic and central nervous systems and at the neuromuscular junctions. When nicotine act with these receptors, different neurotransmitters are released. Nicotine enhances attention and the ability to concentrate on particular stimuli. So that, nicotine patches have been investigated for the treatment of mild cognitive impairment for a while (19-23).

In addition, nicotine is thought to have analgesic effects and efficacy against obesity (1). However, nicotine has various side effects, especially in the digestive and circulatory systems. It causes palpitation, vascular contraction and arterial degeneration thus increase the risk of heart attack and stroke. When applied externally, it causes poisoning and might be even fatal (17,18,24).

It is shown that tobacco has some antimicrobial properties against various microorganisms. Sesquiterpenoid compounds and their glucosides obtained from tobacco have antibacterial activities (25). Nicotine and zinc complex are found to be more potent than zinc metal against different Gram (+) and Gram (-) bacteria (26). Aqueous and methanol extracts of the leaves of *Nicotiana plumbaginifolia* Viv (wild tobacco) exhibited good antibacterial activity on five human pathogenic bacteria: *Bacillus cereus, Bacillus fusiformis, Salmonella typhimurium Staphylococcus aureus,* and *Pseudomonas aeruginosa* (18). In a study, silver nanoparticles were synthesized using tobacco leaf extract and showed antimicrobial activity against *Pseudomonas aeruginosa*, *Escherichia coli, Pseudomonas vulgaris*, *Bacillus subtilis,* and *Staphylococcus typhi* (27). Tobacco has also antifungal activity due to the isoforms of chitinases and 1,3-glucanases against *Fusarium solani germlings* (28). *Nicotiana tobacum* also has antimicrobial activity against *Mycobacterium tuberculosis* (29). Also, tobacco leaves have antioxidant activity due to the flavonoids and phenolic

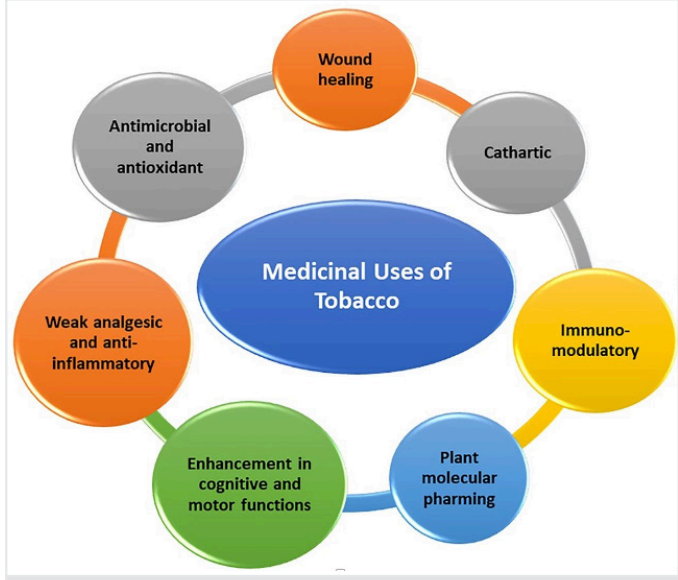

Figure 3. The schematic representation of medicinal uses of Tobacco

compounds contained in the plant (30,31). In a study, it was shown that bioactive extracts of the stem of *Nicotiana tabacum* also had antibacterial activity and antioxidant activity due to the presence of flavonoids in the stem (32). Besides, tobacco plant has antihelmintic activity against *Marshallagia marshalli* due to the alkaloids contained (18,33).

Tobacco plant affects peripheral and central nervous systems. The major compound of tobacco, nicotine, depresses all autonomic ganglia, evokes discharge of catecholamines in low doses, and prevents their release in higher doses. Nicotine stimulates the prejunctional sites in the central nervous system and results in a release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, and growth hormone. It is a weak analgesic in low doses, causes tremors to convulsions at toxic doses, and occasionally induces vomiting. The activation of the sympathomimetic response by nicotine contributes to the activation of chemoreceptors of the aortic and carotid bodies, causing vasoconstriction, tachycardia, and increased blood pressure. It limits the amount of blood reaching internal organs. Also, the activation of parasympathetic ganglia and cholinergic nerve endings by nicotine contributes to the increased tone and motor activity of the bowel (2).

Nicotine has anti-inflammatory effects after exposure following adipose, pulmonary, renal, and hepatic injuries. In recent studies, it has also been shown that tobacco has immunomodulatory effects by decreasing tumor necrosis factor-alfa and interleukin (IL)-1 levels that promote inflammation and increasing IL-6, IL-10, and transforming growth factor-beta levels that reduce inflammation. In addition, nicotine stimulates angiogenesis and wound healing. Thereby, it may have an impact on peripheral nerve regeneration and functional recovery following injuries (2,34,35).

Nicotine affects exocrine glands leading to an initial stimulation of salivary and bronchial secretions and then followed by inhibition. The tobacco plant decreases red blood cell count, hemoglobin level, and platelet count. Also, it causes retarded increase in body weight due to the negative effects of the plant on the normal human metabolism and has anti-nociceptive activity through both central and peripheral nociceptive mechanisms (17).

Although tobacco smoking provokes many fatal diseases, there are some reports that cigarette users have a lower incidence of Parkinson's disease, Alzheimer's disease, and some psychiatric disorders such as schizophrenia, anxiety, and depression (36).

More recently, the tobacco has been used for plant molecular pharming, which is the cell culture and bioengineering application of using plants to produce human therapeutic agents. Tobacco is one of the plants, which has the ability for mass production of pharmaceuticals with less cost than traditional methods due to its short life cycle of 3 months from seed to seeding. Even more, tobacco is the first transgenic plant and usually referrers as the "white mouse" of the plants due to its property of being amicable to genetic modifications for recombinant protein production. In addition, it produces a plenty of biomedically important secondary metabolites such as alkaloids, flavonoids, terpenoids and phenylpropanoids. Firstly, human growth factor was generated with plant-by-plant pharming in tobacco plant. Then, immunoadhesin (DPP4-Fc) protein was obtained from tobacco plant and used against the virus of MERS-CoV infecting lung cells. In addition, many vaccines against malaria, anthrax, hepatitis and influenza were produced in tobacco. Recently, a plant defensin (NaD1), a cationic antimicrobial peptide, was obtained from the flowers of Nicotiana alata and showed good antifungal activity against pathogenic fungi (2,4,37,38).

Despite the medicinal effects of tobacco, it is one of the major public health problems and tobacco smoking is the most common addictive behavior worldwide. Nicotine leads to addiction similar to heroin and cocaine. In addition, tobacco is responsible for more than 3 million deaths a year worldwide. After inhalation of tobacco smoke, nicotine reaches most of the organs in the body too fast. Especially, it increases blood pressure and may cause thrombosis and atherosclerosis in smokers. There are many attempts to stop tobacco smoking worldwide. In nicotine replacement therapy, many other toxic compounds of tobacco smoke such as polycyclic aromatic hydrocarbons and N-nitroso compounds, acrolein, benzene, formaldehyde, ammonia, acetone, acetic acid, and carbon monoxide are separated (3,12,16,39).

Pharmaceutical Dosage Forms of Tobacco

There are many nicotine delivery forms on the market to help quit tobacco smoking. Such forms include chewing gums, sublingual/buccal tablets, capsules, lozenges, oral films, transdermal/mucoadhesive patches, mouth spray, nasal spray, and inhaler (40,41). The aim of stopping smoking is to reduce the death and diseases related to tobacco use. Smokers usually have nicotine withdrawal syndrome after quitting smoking and this condition may be prevented or its effects may be minimized using medicinal nicotine delivery systems. Also, there are many novel nicotine delivery systems in the literature, which have been developed either for nicotine replacement therapy/nicotine vaccination or for medicinal uses of nicotine on the cardiovascular system, the central nervous system diseases, and others (40,42-47). This section reviews conventional and newly developed dosage forms of medicinal nicotine according to their application routes. Also, novel nicotine delivery systems are summarized in Table 2.

Oromucosal Nicotine Delivery Systems

Nicotine replacement therapy can help people to quit smoking by releasing only nicotine, which is found in cigarettes. Medicated chewing gum is an oromucosal dosage form for obtaining systemic drug delivery. The Food and Drug Administration approved the use of nicotine chewing gum as a smoking cessation aid in 1984 and its non-prescription sale in 1995. It is available on the market as either 2 or 4 mg per gum. Nicotine gums release nicotine in a controlled manner but most of the drug is released within the first half an hour. Then, nicotine is absorbed through the buccal mucosa to obtain plasma concentration

Table 2. Novel nicotine delivery systems

Application route	Dosage form/delivery system	Reference
Oromucosal	Medicated chewing gum	(50) (51) (52)
	Lozenge	(54) (64) (65)
	Tablet	(58) (59) (60) (61) (62)
	Oral soluble film	(63)
	Buccal patch	(66)
	Wafer	(67) (71)
	Mouth spray	(72) (73) (74) (75)
	Solid lipid nanoparticles	(76)
	Electrospun nanofibers	(77)
	Microparticles	(70)
Transdermal	Transdermal patch	(79) (82) (83)
	Molecularly imprinted polymers	(92)
	Microneedles	(93)
	Carbon nanotubes	(94) (95)
Nasal	Nasal gel	(101)
	Nasal spray	(101) (104) (105)
	Powder	(103)
Pulmonary	Dry powder inhaler	(107) (108) (109)

levels, which are half of the levels after tobacco smoking. When formulating medicated chewing gums, some excipients are included in the formulation such as gum base, filler, softeners, sweetening agents, flavoring agents, and emulsifiers (45,48-50). The unpleasant taste of nicotine and burning sensation were reduced by adding mint flavor to the gum formulations (51). In another study, the unpleasant taste of nicotine chewing gums was enhanced by using aspartame as sweetener, cherry and eucalyptus as flavoring agents, and sugar as a coating agent. In addition, the chewing gums released 79-83% of nicotine within the first 20 minutes (52). In addition, in some cases, even faster nicotine delivery might be desirable for faster craving relief. In a study, the developed gum formulations released nicotine in the first 10 minutes (53).

Nicotine polacrilex lozenges are over-the-counter nicotine replacement therapy products, which are found as 2 or 4 mg on the market. The nicotine lozenges usually dissolve faster than nicotine polacrilex gums, thereby deliver more nicotine and have more plasma concentrations. However, in a study comparing the safety of 4 mg nicotine lozenges and 4 mg nicotine gums, it was found that the lozenges were similarly well tolerated as the gums and had no worsening effect on the patients with cardiovascular diseases (54).

In order to investigate another usage of nicotine rather than nicotine replacement therapy, patients who received 2-mg nicotine included chewing gum (2 mg/gum) or normal chewing gum and then they were compared in terms of gastrointestinal recovery and prevention of prolonged postoperative ileus after colorectal surgery. It was found that the pain in the first three postoperative days was relieved but there was a need to carry out more studies to reveal the effects of nicotine gum on bowel recovery after surgery (55).

The buccal route has always been the most advantageous route for nicotine administration since the drug can reach the systemic circulation without being degraded by gastrointestinal and hepatic first-pass metabolism (56,57). Sublingual/buccal tablets are other conventional dosage forms designed for nicotine delivery into the oral cavity. In this context, nicotine-β-cyclodextrin complex loaded tablets were prepared. When nicotine-β-cyclodextrin complex dissolved, free nicotine was released from the tablet formulation and penetrated through the oral mucosa (58). In another study, buccal bioadhesive tablets of nicotine were developed. Carbomer and sodium alginate were used as bioadhesive polymers in combination with hydroxypropyl methylcellulose and magnesium carbonate was added into the formulations as a pH-increasing agent. It was observed that these formulations released the drug during 8 h period (59). Indeed, 20% w/w Carbopol and 20% w/w hydroxypropyl cellulose tablets were developed as biphasic buccal adhesive tablets. The bilayer tablets which contained an adhesive controlled release layer and a fast release layer provided an initial burst release of nicotine followed by the controlled release for a period of up to 4 h (60). Moreover, in another study, various biocompatible polysaccharide polymers such as xanthan gum, karaya gum, guar gum, and glycol chitosan were evaluated as mucoadhesive controlled release excipients in mucoadhesive tablet formulations for buccal drug delivery. The strongest adhesion was obtained with glycol chitosan and guar gum was a poor mucoadhesive where xanthan gum and karaya gum had strong mucoadhesive properties (61). Kanjanabat et al. (62) prepared nicotine-magnesium aluminum silicate complex-loaded sodium alginate matrix tablets for buccal delivery. Magnesium aluminum silicate is a mixture of montmorillonite and saponite clays and forms complexes with nicotine via ionic interactions and thus controls nicotine delivery. The results also indicated that sodium alginate

had an important role in enhancing the mucoadhesive properties of the tablets.

Fast-dissolving oral delivery systems are solid dosage forms that dissolve rapidly in the oral cavity (less than 1 min) without drinking or chewing (63). Rather than chewing gums, lozenges and oromucosal tablets or buccal patches offer rapid delivery of nicotine into the mouth and thus provide a faster craving relief (64-66). Du et al. (64,65) compared a product of 2.5 mg nicotine oral soluble film with 2 mg nicotine lozenge and 2 mg nicotine gum, which were available on the market. The results confirmed that nicotine film enabled faster craving relief than the other dosage forms due to the rapid delivery of the full dose of 2.5 mg nicotine in 2 to 3 minutes. Cilurzo et al. (63) developed fast-dissolving films made of low dextrose equivalent maltodextrins loaded with 0.5 mg nicotine and mint or milk as a flavor in the formulation. The developed films disintegrated within 10 s and neither mint nor milk flavor did not affect the tensile properties of the films.

The free base of nicotine is volatile and prone to oxidative degradation (67). There are many studies in the literature to overcome these challenges of nicotine. In a study, tri-layered buccal mucoadhesive nicotine base or polacrilex patch formulations consisting of a thin dry tablet and a bi-layered mucoadhesive film were developed. The trilayered patch formulations enabled rapid initial drug release especially for nicotine base in 30 min and fast-to-slow permeation rates (66). Also, Pongjanyakul et al. (68-70) prepared sodium alginate–magnesium aluminum silicate and chitosan-magnesium aluminum silicate films loaded with nicotine. The films presented mucoadhesive properties and strong potential as buccal nicotine delivery systems. Whereas films are extensively used in buccal drug delivery systems and prepared by a solvent evaporation method, wafers are other drug delivery systems, which are prepared by the freeze-drying method. Hydroxypropyl methylcellulose and sodium alginate film and wafer formulations are prepared to improve nicotine stability. An anionic polymer of sodium alginate forms strong electrostatic interaction with the cationic nature of the mucin and thereby demonstrates mucoadhesive property. Hydroxypropyl methylcellulose also contributes to the design of a controlled nicotine delivery system (67). In the subsequent studies, the physicochemical properties of nicotine-loaded hydroxypropyl methylcellulose and sodium alginate films and wafers were stabilized with magnesium aluminum silicate. The formulations released showed high permeation flux for both porcine and the buccal tissue and enhanced the functional physical properties such as hydration, swelling, and release (71).

For faster nicotine replacement therapy, another nicotine delivery dosage form is mouth spray. There have been studies in the literature, which are evaluating the efficacy of the spray formulations. Nicotine mouth spray was found to be very potent and preferred over the nicotine gum and inhaler. However, some local side effects such as mouth irritation, nausea, and hiccup were seen by mouth spray formulation containing 1 mg nicotine per actuation (72). Kraiczi et al. (73) evaluated the pharmacokinetics of nicotine at three different doses of the mouth spray (4 mg, 2 mg, and 1 mg per actuation) and compared the nicotine uptake from the spray versus nicotine lozenge and gum. Nicotine was absorbed faster for all doses of nicotine of the mouth spray than either lozenge or gum and maximum plasma concentration was reached in a shorter time with the spray. In the clinical studies, Tonnesen et al. (74) demonstrated that 1 mg nicotine mouth spray was efficacious and safe for smoking cessation with a rate of 2.48 compared to placebo regarding abstinence at 1 year. In another clinical study, 1 mg nicotine mouth spray plus nicotine patch showed significant enhancement in prolonged abstinence during 6 months (75).

When nicotine is administered as a solution such as a mouth spray, it is distributed in the mouth by the effect of saliva and mostly swallowed. In order to decrease the adverse effects of nicotine after entering the gastrointestinal tract and obtain a localized delivery in the oral cavity, nicotine may be incorporated into a nanocarrier system. The small size of the dosage form results in fast nicotine release due to the enhanced specific surface area and therefore fast oromucosal absorption. Ding et al. (76) prepared an oromucosal formulation of lipid-drug-conjugates containing solid lipid nanoparticles, which were prepared with Kolliwax® S, and stearic acid as a counter-ion and hydrogenated sunflower oil (HSO) as lipid particle matrix were used. In addition, the high encapsulation efficiency of nicotine, which was a hydrophilic drug, was obtained in the carrier. Thereby, the developed formulation retained nicotine in the oral cavity and enabled fast absorption. In another study, α-lactalbumin/polyethylene oxide electrospun nanofibers containing nicotine were prepared for oromucosal nicotine replacement therapy. Nanofibers released nicotine faster than two relevant marketed formulations of lozenge and sublingual tablet due to their high surface area property (77). Nicotine base can interact with a negatively charged clay, magnesium aluminum silicate, electrostatically and form microparticles. In a study, high molecular weight chitosan was adsorbed to the surfaces of these microparticles and obtained a positive surface charge. Thereby, mucoadhesive properties of the particles were enhanced and nicotine had high oromucosal permeation (70).

Transdermal Nicotine Delivery Systems

The transdermal delivery system carries drugs through the skin into the blood circulation at a predetermined rate. It is accepted as an alternative route to oral and intravenous delivery. The advantages of this route are lower systemic exposure and thus lower systemic targeted delivery, and lower systemic toxicity than oral/oromucosal routes. Nicotine can easily permeate and absorb through the skin, reach blood vessels and then pass the blood-brain barrier when applied topically. Transdermal nicotine delivery systems are mostly used in smoking cessation programs. In this route, nicotine is released from transdermal dosage forms in a sustained manner (78). The amount of nicotine, which is equivalent to that delivered by a single cigarette, is absorbed transdermally in 3-4 h. Also, nicotine absorption may be enhanced by using skin penetration enhancers in novel nanocarrier systems (79-81).

There are available transdermal patches on market, which are releasing nicotine with polymer matrix diffusion (82,83). Nicotine included 15, 30, and 45 mg doses nicotine-patches on the market were evaluated in terms of safety profiles and it was shown that the use of high doses of transdermal nicotine was safe in dependent smokers and could reduce exposure to the other toxicants of tobacco (84). In another study, 21 mg transdermal nicotine patch was examined on the hypertensive smokers and it was found that transdermal nicotine was safe for short-term exposure in mildly hypertensive smokers (42). Moreover, transdermal patches were found to minimize weight gain which was mostly seen in people who successfully quited smoking (85).

In the past, proliposomes of nicotine were prepared and applied in the form of patches. Sustained nicotine release was achieved since proliposomes acted as a release rate controlling dosage form (86). In a study, a transdermal patch was prepared by forming an inclusion complex between nicotine and β-cyclodextrin. Cross-linked polyvinyl alcohol was used as a rate-controlling membrane in the patch and a zero-order controlled release system was obtained (87). In another study, polyethylene membrane was used as a rate-controlling barrier and carbomer was used as the gel reservoir, which provided sustained release of nicotine with an easy application (88). Also, transdermal patches of nicotine were successfully prepared by using the polymers in the concentrations of 4%, 1.4%, 0.5%, and 0.8% of Eudragit® E100, HPMC E5, PEG4000, and PVP K30, respectively (89). In another study, a drug-in-adhesive patch of nicotine was prepared successfully using an ion-pair strategy, enabling a dual release of nicotine which was a promising strategy to regulate drug release profiles from the patch (90). Pichayakorn et al. (91) used a heat-sealing technique for the developed reservoir-type nicotine transdermal patches, which were composed of a concentrated nicotine solution embedded between a backing layer and deproteinized natural rubber as a controlling layer membrane. The transdermal patches were stable under storage in a tightly sealed container at 4 °C or ambient. Molecularly imprinted polymers are one of the carriers that can be used for the controlled transdermal delivery of nicotine. In a study, molecularly imprinted polymers of nicotine were synthesized by a free radical polymerization method using methacrylic acid as the monomer and ethylene glycol dimethacrylate as the cross-linker (92). More recently, Panda et al. (93) prepared nicotine-loaded microneedles using a mold casting method with polyvinylpyrrolidone as the water-soluble polymer. The microneedles presented immediate nicotine release within the first hour and enabled a potential pain-free and minimally invasive treatment option for nicotine replacement therapy.

Indeed, carbon nanotube membranes in the form of a switchable transdermal drug delivery device were developed. These devices enabled programmable delivery rates with minimal skin irritation and no skin barrier disruption (94) and improved smoking cessation treatments (95). In a study, a new computer-operated delivery system for time-controlled pulsatile transdermal delivery of nicotine was evaluated in phase I clinical trial. The device was programmed to deliver two pulses of drug within 16 hours with three delivery rates and was found to be efficient in smoking cessation for an individualized therapy (96). Moreover, Gulati et al. (97) developed a switchable carbon nanotube membrane device for transdermal nicotine delivery that could be programmed to deliver variable doses matching those of nicotine patches (7, 14, and 21 mg/24 h) and nicotine gums (2 mg/4 mg). It could adjust nicotine dosing between craving and withdrawal blood plasma levels for smoking cessation therapy.

Other than nicotine replacement therapy, transdermal nicotine patches were evaluated for the treatments of central system disorders. The patches enabled improvement in diseases such as schizophrenia, Parkinson's disease, and prose memory and attention (43,44,98). In a study, transdermal nicotine delivery (15 mg/16 h) in the patch form was found as effective and safe in acute pain relief after laparoscopic cholecystectomy surgery (99).

Nasal and Pulmonary Nicotine Delivery Systems

The nasal route for nicotine delivery enables faster action via passing to the systemic circulation than other routes of nicotine administration (oral or transdermal) (100). The first nicotine formulation was developed in the form of a gel consisting of a 0.1 mL droplet of 2 mg of nicotine in a 2% aqueous solution and a cellulose derivative was used to increase the viscosity. In order to enhance absorption, decrease nasal irritation with the gels, and increase acceptability, nicotine was formulated as a nasal spray (101). Later, proliposome formulations of nicotine were prepared for intranasal administration to obtain prolonged delivery to the systemic circulation (102). Another nasal formulation, in the form of nicotine-Amberlite resin complex powder was developed thus a combined pulsatile and sustained plasma nicotine profile for smoking cessation was obtained (103). Also, it was shown that nicotine sprays might modestly enhance attention and spatial working memory in schizophrenic patients who were chronic smokers (104). In another study, 3 mg nicotine nasal spray was found to decrease pain during the 5 days after third molar surgery (105).

The pulmonary drug delivery route is the direct access of drug to the target area with lower doses. Drugs are absorbed in a very short time after inhalation. Because the lungs have high permeability and large absorptive surface area (approximately 70-140 m^2) and a good blood supply (106). Wang et al. (107,108) developed nicotine hydrogen tartrate nanoparticles in the form of inhalable micro-aggregates of biodegradable chitosan for pulmonary delivery of nicotine from dry powder inhaler formulations. Nicotine hydrogen tartrate was released from the formulations with a burst release in the first 8 h and then with a prolonged release. More recently, the activity of controlled release nicotine from dry powder inhaler formulations was assessed via the locomotor activity of C57BL/6 mice. The results revealed that the inhaled nanoparticles were a preclinical option for developing novel inhalation formulations as a potential anti-smoking therapeutic (109).

Conclusion

Tobacco is a very important plant that is grown worldwide and has many medicinal uses from the past to the present day despite having many toxic effects on the body when used as a cigar/cigarette or e-cigarette. Various dosage forms were developed and took place on the market of tobacco or its compounds. Besides its medicinal uses as a sedative, diuretic, expectorant, and antimicrobial, tobacco is also used for plant molecular pharming to produce human therapeutic agents, which makes it a much more valuable plant in terms of cell culture and bioengineering applications. Indeed, the major compound of nicotine is mostly used in smoking cessation therapy in a variety of dosage forms for different routes of administration such as oral, sublingual, transdermal, nasal, or inhaler. The recent studies indicate that nicotine is not only used in smoking cessation therapy and also is a potential compound for the treatments of central system disorders such as schizophrenia, Parkinson's disease, and prose memory and attention, and also in acute pain relief after surgeries. In conclusion, there is a need to carry out new studies to enlighten the exact mechanisms of tobacco and its major compound of nicotine on these diseases, evaluate its safety, and develop more effective novel pharmaceutical dosage forms.

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Review

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An Overview of Nanofiber Applications for Development of Phytopharmaceuticals

Fitofarmasötiklerin Geliştirilmesi için Nanolif Uygulamalarına Genel Bir Bakış

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ABSTRACT

Herbal sources contain a variety of bio-actives, which are also called phytochemicals. Many of the herbal bio-actives have therapeutic effects and distinguished chemical properties that allow them favorable candidates for phytomedicines. The history of traditional herbal medicines, which are the precursors of phytopharmaceuticals, dates back to ancient times. Today, many of the officially approved and widely used medicines are produced by isolating active substances from herbal sources. Although traditional pharmaceutical dosage forms such as tablets, capsules, syrups, solutions, decoctions and ointments are still used today, problems related with the absorption, biotransformation and stability of phytochemicals reduces the efficacy, bioavailability and in some cases safety of herbal medicines. Also, conventional pharmaceutical dosage forms are often providing an immediate release of phytoconstituents. Besides the use of advanced drug delivery systems offer advantages to overcome mentioned problems, they also provide extended release with maximum efficacy associated with minimum side effects. Researches on development of herbal formulations by using novel drug delivery systems have gain attention and the use of nanotechnology-based systems have special attention. One of the nano drug carrier systems is nanofibers which have unique properties making them widely used in different treatments such as infections, allergy, rheumatic diseases, inflammatory diseases, cancers, etc. In this study, the use

ÖZ

Bitkisel kaynaklar, fitokimyasallar olarak da adlandırılan çeşitli biyoaktif maddeler içerirler. Bitkisel biyo-aktiflerin çoğu, bitkisel ilaçlar için uygun aday olmalarını sağlayan terapötik etkilere ve kimyasal özelliklere sahiptirler. Fitofarmasötiklerin öncüsü olan geleneksel bitkisel ilaçların tarihi çok eskilere dayanmaktadır. Günümüzde resmi olarak onaylanmış ve yaygın olarak kullanılan ilaçların birçoğu bitkisel kaynaklardan etken maddelerin izole edilmesiyle üretilmektedir. Tabletler, kapsüller, şuruplar, solüsyonlar, dekoksiyonlar ve merhemler gibi geleneksel farmasötik dozaj formları günümüzde hala kullanılmasına rağmen, fitokimyasalların absorpsiyonu, biyotransformasyonu ve stabilitesi ile ilgili problemler, bitkisel ilaçların etkinliğini, biyoyararlanımını ve bazı durumlarda güvenliğini azaltmaktadır. Ayrıca, geleneksel farmasötik dozaj formları genellikle bitkisel bileşiklerin hemen salınmasını sağlar. Gelişmiş ilaç taşıyıcı sistemlerin kullanılması, bahsedilen sorunların üstesinden gelmek için avantajlar sunmanın yanı sıra, minimum yan etkilerle ilişkili maksimum etkinlik ile uzun süreli salım sağlar. Yeni ilaç taşıyıcı sistemler kullanılarak bitkisel formülasyonların geliştirilmesi üzerine yapılan araştırmalar dikkat çekmiş ve nanoteknoloji tabanlı sistemlerin kullanımına ayrıca önem verilmiştir. Nano ilaç taşıyıcı sistemlerden biri de benzersiz özelliklere sahip olan ve bu sayede enfeksiyon, alerji, romatizmal hastalıklar, enflamatuvar hastalıklar, kanser gibi farklı hastalıkların

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of the nanofiber-based carrier systems to deliver herbal bio-actives through various drug application routes is overviewed.

Keywords: Nanofibers, herbal bio-actives, phytopharmaceuticals, drug delivery

tedavisinde yaygın olarak kullanılan nanoliflerdir. Bu çalışmada, çeşitli ilaç uygulama yollarıyla bitkisel biyoaktif maddelerin salınması amacıyla nanolif yapısındaki ilaç taşıyıcı sistemlerin kullanımı değerlendirilmiştir.

Anahtar Sözcükler: Nanolifler, bitkisel biyoaktifler, fitofarmasötikler, ilaç salımı

Introduction

Herbal sources contain a variety of bio-actives, which are also called phytochemicals. Many of the herbal bio-actives have therapeutic effects and distinguished chemical properties that allow them to be favorable candidates for phytomedicines. For example, compared to the synthetic active pharmaceutical ingredient, herbal bio-actives carry a larger number of chiral centers in their structures, which makes them sterically more complex and inflexible molecules. The inflexibility increases the receptor-binding ability of the molecules, which gives them more stereospecific biological activity and makes them favorable for medicinal use. Furthermore, herbal molecules contain a higher amount of oxygen and nitrogen atoms rather than synthetic drug molecules. This makes their ability to make hydrogen bonds with receptors better and as a result, increases the affinity and efficacy of the medicines (1,2).

The history of traditional herbal medicines, which are the precursors of phytopharmaceuticals, dates back to ancient times. The usage of herbal sources as healing remedies goes back to the ancient era in China, India, Egypt, Europe, Latin America, and Africa. Since then, many advances have been made in the field of herbal medicine. From the 15th century till the early 19th century, evolutions in phytomedicine reached their peak. Many books that were written in different languages were published, classification and naming systems were developed, and many important herbal active substances were isolated (1-3). Nowadays, many of the officially approved and widely used medicines are produced by isolating phytochemicals from herbal sources, which were used centuries ago, such as morphine, guaifenesin, and digoxin. In recent years, the importance of phytochemicals in modern drug research and development has increased with the use of molecular docking programs to determine biological target binding affinities and interactions. Moreover, it is indicated that around 50% of the current medicines are made from natural resources and over one-third of all new molecular entities are from natural sources and their byproducts (4,5).

Although traditional pharmaceutical dosage forms such as tablets, capsules, syrups, solutions, decoctions, and ointments are still used today, problems related to the absorption, biotransformation, and stability of phytochemicals reduce the efficacy, bioavailability, and in some cases safety of herbal medicines (6). Conventional pharmaceutical dosage forms are also providing an immediate release of phytoconstituents in general. However, the use of advanced drug delivery systems offers advantages to overcome mentioned problems and they also provide extended release with maximum efficacy associated with minimum side effects. Research on the development of herbal formulations by using novel drug delivery systems and the use of nanotechnology-based systems have gained special attention. One of the nano drug delivery systems is nanofibers, which have unique properties and are widely used in the treatment of different diseases such as infections, allergies, rheumatic diseases, inflammatory diseases and cancer (7). Studies to formulate novel drug delivery systems which use new technologies like nanotechnology are still taking place in many places around the world. Some of the recently developed drug delivery systems are nanogels, nanotubes, nanomicelles, microcapsules, nanoparticles, microemulsions, liposomes, niosomes, transfersomes, phytosomes, nanosuspensions, nanofibers, etc. These systems are used to deliver one or more active pharmaceutical ingredients or phytoconstituent with different new pharmaceutical dosage forms such as transdermal systems, buccal or mucoadhesive systems, oral or ocular systems, etc. (8).

In this review article, the use of the nanofiber-based drug carrier systems to deliver herbal bio-actives through various administration routes will be given with the examples of recent studies.

Nanofibers as Drug Delivery Systems

Nanofibers are structures with a diameter smaller than 1,000 nm. Because of having large surface area, high porosity, and being flexible, they are preferred in many applications including drug research and development, drug delivery, burn and wound healing, and tissue engineering. With 3D printing of electrospun nanofibers, models such as neural, mucosal, blood-brain barrier and tumor tissue models that stimulate physiological and pathological tissues can be produced , which have a huge potential to improve *in vivo* simulated tests in drug development studies (9). Additionally, nanofibers play an important role in the field of regenerative medicine, which can recover important tissues such as heart, blood vessels, nerves, bones, cartilages, tendons, and joints. This is possible with the combination of 3D printing and electrospinning techniques to form biomimicking nanofiber scaffolds and patches loaded with stem cells (9,10).

The unique specifications of nanofibers have made them widely used in treatment of different diseases such as infections, allergy, hypertension, rheumatic diseases, inflammatory autoimmune diseases, diabetes, intracranial aneurism, Alzheimer's, cardiovascular diseases, gastrointestinal diseases, AIDS, and cancers (11,12).

Mechanical properties of nanofibers such as high surface area-to-volume ratio, high porosity, amorphous structure, and flexibility

make them useful materials for designing different drug delivery systems (9).

Nanofibers may enhance drug dissolvability. The bioavailability of drugs is directly related to their solubility and dissolution rate (13). Unfortunately, most of the novel drugs are in a lipophilic character which means that they have low water solubility and as a result low bioavailability. To solve this problem, drugs can be loaded into nanofibers produced from water soluble polymers. Due to their high surface area and porosity, the dissolution rate of the drugs may increase significantly (13,14).

Among all advantages, the adjustable properties of nanofibers may be their most important feature. Nanofibers can be designed by modifying their production parameters for controlling polarity, fibers diameter, porosity and nanofiber mat thickness to fit any drug delivery requirement (12,13).

One more advantage is the high loading capacity of nanofibers and their modifiable release ability (14). Drug release is adjusted depending on drug loading methods. Some of these methods are co-electrospinning of drugs and polymers, surface immobilization of the drug on nanofibers, sheath, co-axial and layer-by-layer nanofibers. The most suitable method must be chosen according to the purpose of the medication because this affects the drug release process (15). For example, while the co-axial electrospinning method is used to release drugs immediately, matrix-type nanofiber, Core-shell nanofiber, and sandwich technologies may be used to produce prolonged-release nanofibers (13).

There are various methods to prepare nanofibers and between them, the electrospinning method is the most favorable nanofiber production technique. The other widely used methods can be given as drawing method, template synthesis, phase separation, self-assembly, etc. (16). Electrospinning is a method of producing nanofibers by exposing polymer solution to electrostatic energy, which stretches the polymer and reaches the nanoscale (17). The electrospinning system consists of 4 main parts: syringe pump, power source, needle, and collector (18). While the solution is slowly pumped from the syringe through the needle, the solution surface is electrically charged because of the high electric field in the needle. Due to this charge, the surface tension force of the solution is overcome and as a result, a filament occurs. This filament continuously spins and stretches till it reaches the collector surface where nanofibers are collected (19). The properties of the formed nanofibers may be affected by many parameters such as voltage, needle tip-to-collector distance, molecular weight of the polymer(s) and the flow rate, viscosity, surface tension, and the conductivity of the solution (20). By adjusting these parameters, the properties of the nanofibers can be easily designed to have any intended purpose (21). Morphology of the fibers can also be controlled by the selection of polymer(s) to make many types of nanofibers. Besides being a cost-effective method, the versatility and flexibility of this process make electrospinning the most favored method to produce nanofibers (19).

Nanofiber-based Herbal Drug Carrier Systems for Different Delivery Routes

Nanofiber drug carrier systems can be used to deliver active pharmaceutical ingredients through various routes such as topical, transdermal, oral, and transmucosal routes. Taking advantage of natural substances for mostly their antimicrobial, antioxidant, anti-inflammatory, and wound healing activities and nanofibers with unique properties, a variety of research took place to investigate nanofibers incorporated with natural substances for drug delivery applications. The schematic representation of nanofiber-based herbal drug carrier systems via various drug delivery routes is given in Figure 1. Herbal drugs incorporated

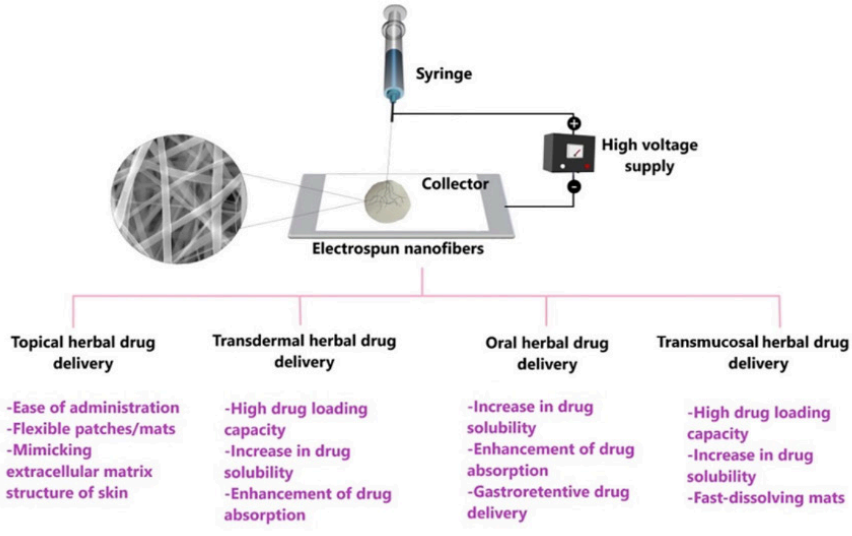

Figure 1. The schematic representation of nanofiber-based herbal drug carrier systems via various drug delivery routes

nanofiber-based carrier systems according to different delivery routes are summarized in this part.

Topical/Transdermal Drug Delivery Route

Topical drug delivery is a local route applied topically to treat skin diseases like bacterial, fungal, and viral infections such as eczema and psoriasis. Transdermal drug delivery differs from topical delivery by being suitable for both local and systemic delivery types. After applying the drug onto the skin, it diffuses through skin layers until reaching blood vessels and joins systemic circulation (22). In the transdermal drug delivery route, the drug does not undergo the first pass metabolism effect of the liver. However, the main challenge of this route is the stratum corneum barrier of the skin. Therefore, nanofiber based drug carrier systems can be used to enhance transdermal drug delivery (23).

Curcumin is a polyphenolic flavonoid that is obtained from the rhizomes of Curcuma longa (turmeric) and has various therapeutic benefits such as anti-inflammatory, antimicrobial, antioxidant, anticancer, antiaging, antidiabetic, and wound healing effects. For this reason, it has been the topic of many recent studies including topical and transdermal delivery (23). Sampath et al. (24) investigated curcumin incorporated poly(lactic-co-glycolic acid) nanofibers to treat squamous carcinoma, which is one of the most deadly skin cancers. *In vitro* release and cell viability studies showed that curcumin incorporated nanofibers had prolonged drug release without initial burst and good anticancer activity against squamous carcinoma cell lines. In another study, curcumin was incorporated into cellulose acetate phthalate electrospun nanofiber transdermal mats by Ravikumar et al. (25). It was shown that the prepared formulations controlled *in vitro* transdermal delivery of curcumin for up to 24 h. Also, Ariamoghaddam et al. (26) evaluated curcumin incorporated gelatin/albumin and PVA nanofibers as transdermal anti-obesity patches. More than 50% of the loaded curcumin was released from the nanofibers after 20 hours and curcumin patches were effective in obesity treatment according to the *in vivo* studies on rats. Tetrahydro curcumin is the major metabolite of curcumin which has similar pharmacological properties with curcumin but is more polar. Ravikumar et al. (27) prepared tetrahydro curcumin into poly(ε-caprolactone)/poly(ethylene glycol) composite electrospun nanofibers and evaluated its *in vitro* drug release properties. It was demonstrated that the prepared nanofibers released the herbal drug according to the Higuchi kinetics model of diffusion mechanism with case II relaxation behavior and anomalous transport for 24 h and it was considered as ideal transdermal patches with the application once daily.

Acne vulgaris is a chronic skin inflammation caused by *Propionibacterium acnes* infection associated with oily skin caused by over release of sebum. Side effects like skin irritation related to drugs used in the treatment of acne vulgaris require advanced pharmaceuticals. In this regard, Tang et al. (28) developed a combination of extracts that incorporated poly(vinyl alcohol)/chitosan nanofibers. *Houttuynia cordata*, *Portulaca oleracea* and *Centella asiatica* extracts were used to inhibit *Propionibacterium acnes*, reduce inflammation, and hydrate the skin, respectively. This combination exhibited good antibacterial activity against *Propionibacterium acnes* and the produced nanofibers showed a rapid efficiency in mild-to-moderate facial acne in a short-term clinical study.

Herbal bio-actives are frequently used for wound or burn healing applications. Propolis is a resinous product collected by honeybees (*Apis mellifera*) from various plant sources, which has antibacterial, antifungal, and antioxidant activities. It was incorporated into poly(lactic acid) nanofibers to enhance its pharmacological activities and bring moisturizing and breathability properties to the wound dressings by Sutjarittangtham et al. (29). While the prepared formulation was able to inhibit *Proteus mirabilis* and *Escherichia coli* at the concentration of 4% (w/v), it was able to suppress *Staphylococcus aureus* and *Staphylococcus epidermidis* at 2% (w/v) concentration. Jin et al. (30) compared efficiencies between polycaprolactone nanofibers loaded with *Indigofera aspalathoides*, *Azadirachta indica*, *Memecylon edule* or *Myristica andamanica* extracts as wound dressings. The results showed that *Memecylon edule* loaded nanofibers exhibited the best metabolic activation in human dermal fibroblasts proliferation assay with the least cytotoxicity. In another study, Sadri et al. (31) found that chitosan/poly(ethylene oxide) nanofibers incorporated with green tea leaf (*Camellia sinensis*) had high potential as a wound dressing. Besides their good antibacterial effect against *Escherichia coli* and *Staphylococcus aureus* strains, these nanofibers have moisturizing, breathable, and highly stable properties, which are suitable for wound healing. Henna (*Lawsonia inermis*) is also one of the herbal drugs which is useful for wound healing due to its antibacterial, antifungal, antioxidant, anti-inflammatory and analgesic activities. In this regard, Yousefi et al. (32) incorporated henna into chitosan/ poly(ethylene oxide) nanofibers to obtain better wound healing results from *Lawsonia inermis* extract. It was demonstrated that henna nanofibers were biocompatible and had good *in vitro* antibacterial activity and accelerated wound healing in *in vivo* studies. Also, Hajilou et al. (33) prepared a wound dressing from *Gamma oryzanol* extract incorporated into poly(ε-caprolactone)/chitosan nanofibers. *Gamma oryzanol* is a crude rice bran oil extraction with antioxidative, antiinflammatory, and antibacterial activities. *In vitro* studies suggested that the prepared dressings had the ability to suppress bacteria, enhance collagen deposition and accelerate wound healing which made it suitable as a wound dressing.

Pineapple (*Ananas comosus*) contains a substance namely bromelain, which has a burn healing effect. Bayat et al. (34) loaded bromelain into chitosan nanofibers and investigated the physicochemical properties and release profile of this delivery system. Chitosan-2% (w/v) bromelain nanofibers were found to be effective in burn injuries with good physicochemical properties and release profile as well as low cytotoxicity. In another study, Motealleh et al. (35) prepared poly(ε-caprolactone)/polystyrene nanofibers loaded with *Chamomilla recutita* (L.) Rauschert extract. Due to the major active substance of chamomile, apigenin, the formulation showed good antibacterial activity against *Staphylococcus aureus* and antifungal activity against

Candida albicans. Moreover, 15% of chamomile-loaded nanofibers reached about 90% of cell proliferation efficiency and gave 10 times better results than unloaded nanofibers. Moreover, *in vivo* studies showed that the nanofibers could treat up to 99±0.5% of wounds in 14-day duration.

Capsaicin is a chemical found in peppers and used as a temporary analgesic for muscle and joint pain. Capsicum extract was loaded into poly(vinyl alcohol) or cellulose acetate nanofibers and *in vitro* drug release, skin permeation, and cytotoxicity characteristics were investigated. Compared to cellulose acetate, poly(vinyl alcohol)-based nanofibers showed better release and skin permeation properties. MTT assay results showed a small decrease in the cell viability via drug loading when compared to blank nanofibers (36).

Blumea balsamifera, or in its other name sambong, was used for centuries in some South-eastern countries as a remedy for different skin diseases such as eczema, beriberi, dermatitis, etc. In a study, Badshah et al. (37) produced electrospun cellulose acetate nanofibers loaded with sambong oil to investigate its wound healing properties. The results confirmed that sambong oil loaded nanofibers had good cell viability and antibacterial activity but inadequate antioxidant properties. Lavender oil majorly contains the compounds linalool and linalyl acetate, which has antibacterial, anti-inflammatory, and antifungal pharmacological effects. Sofi et al. (6) incorporated polyurethane nanofibers with lavender oil and silver nanoparticles. The prepared nanofibers with concentrations of 15% lavender oil and 5% silver nanoparticles exhibited good *in vitro* antibacterial activity against *Escherichia coli* strains. Plai (*Zingiber Cassumunar Roxb.*) has been used extensively as a traditional herbal medicine due to containing antimicrobial, anti-inflammatory, antioxidative and analgesic substances. To improve its efficacy in topical medicines, cosmetics, and skincare products, Tonglairoum et al. (38) prepared Plai oil incorporated poly(vinyl pyrrolidone) nanofibers. *In vitro* release study showed that Plai oil was released from the nanofiber formulations rapidly at first, but then prolonged release was achieved up to 24 hours. In another study, Wongkanya et al. (39) loaded Plai (*Zingiber cassumunar Roxb.*) oil into electrospun poly(lactic acid) nanofibers and examined its properties using (E)-1-(3,4- dimethoxyphenyl) butadiene (DMPBD) as a marker. DMPBD is a compound found in *Zingiber cassumunar Roxb.*, which is exhibiting anti-inflammatory activity. *In vitro* release characteristics and skin penetration and irritation properties were tested. Of DMPBD 80% was released from the nanofibers after 12 hours and 50% of DMPBD permeated through the skin due to the highly lipophilic nature of the substance. Also, Plai oil nanofiber patches did not show any skin irritation.

A food waste, watermelon (*Citrullus lanatus*) peel extract, was formulated as poly(vinyl alcohol) nanofibers to investigate antioxidant and antibacterial effects. The results revealed that watermelon peel extract incorporated nanofibers had better antimicrobial activity against both *Escherichia coli* and *Staphylococcus aureus* strains compared to watermelon peel extract itself. Furthermore, the prepared nanofibers were found to have a 22% enhanced antioxidant activity with a sustained release rate which could reach even 72 hours (40). Also, Lin et al. (41) used green electrospinning to produce poly(ethylene oxide) nanofibers loaded with grape seed extract, which had good antioxidant activity. It was shown that the prepared nanofibers significantly enhanced the proliferation of the skin fibroblasts and protected them against oxidative stress, indicating that they were potential delivery systems to be used in tissue regeneration, wound healing, and cosmetics applications.

Colchicine is a natural substance found in *Colchicum autumnale* and *Gloriosa superba L*. It has cytotoxic effects and can be used efficiently in melanoma, which is the most fatal skin cancer. Morad et al. (42) loaded colchicine into electrospun poly(vinyl alcohol)/chitosan nanofibers to reveal its transdermal performance against melanoma. Both skin permeation and cell viability tests proved the effectiveness of colchicine transdermal nanofiber patches in melanoma management. In another study on the treatment of melanoma, acemannan polysaccharides of aloe vera mediated green synthesized titanium dioxide nanorods loaded resveratrol incorporated poly(vinyl alcohol) nanofibers were produced. By activating apoptosis-promoting caspase enzymes, this formulation exhibited enhanced selective cytotoxicity with fewer side effects (43). Agnes Mary and Giri Dev (44) evaluated the effects of aloe vera loaded nanofibers on the proliferation of human dermal fibroblasts. It was shown that aloe vera nanofibers resulted in a high proliferation rate without any cytotoxic effects. Depending on the results, it was suggested that aloe vera nanofiber scaffolds could be used in skin tissue engineering. In the other study, resveratrol, which was found in grapes and many other plants, was loaded into electrospun poly(vinyl pyrrolidone) and hydroxypropyl-β-cyclodextrin nanofibers to increase its solubility. The results revealed that the nanofiber formulations enhanced water solubility and skin penetration of the drug and exhibited good antioxidant and anti-inflammatory activities (45).

Vitamins are found in many natural nutrients and are used widely as supplementary products. Many studies were carried out to investigate vitamin delivery through the transdermal route to overcome the limitations such as solubility and absorption problems (45-48). Vitamin B12 in poly(ε-caprolactone) based nanofibers, all-trans retinoic acid or vitamin A acid and α-tocopherol or vitamin E in cellulose acetate based nanofibers, ascorbic acid in poly(vinyl alcohol) based nanofibers and folic acid in poly(vinyl alcohol) based nanofibers were investigated for transdermal delivery and all of them showed promising results (49-52).

Oral Drug Delivery Route

Oral route for controlled drug release is usually used to release the drug slowly into the gastrointestinal tract and enable effective drug concentrations for a prolonged period of time (50). Nanofibers are advantageous as oral drug delivery systems due to the properties of improving drug solubility and reducing applied drug dose. Malik et al. (51) evaluated poly(lactic acid) nanofibers loaded with diacerein as a gastroretentive drug delivery system. The results demonstrated that the developed nanofibers exhibited

zero lag time and approximately 61.3% of the herbal drug was released in 30 h, thus facilitating slow drug release with improved drug solubility.

Transmucosal Drug Delivery Route

Transmucosal drug delivery is another systemic and/or local drug application route. All tissues with mucosal membrane are parts of this route, including buccal, ocular, nasal, vaginal, and rectal administrations. The buccal route includes both oromucosal and sublingual applications. Because of the rapid absorption and high bioavailability of drugs in this route, it is commonly used for local and systemic drug delivery and is considered as an alternative to many oral drugs (52). Nanofibers are flexible, mucoadhesive, and stable in oral mucosa depending on the polymer type used in nanofiber production. Due to this, nanofiber-based drug carrier systems are applicable to the buccal cavity either as patches or scaffolds.

Fast dissolving nanofiber formulations composed of poly(vinyl alcohol) and D-a-tocopheryl poly(ethylene glycol) succinate were produced by Nam et al. (53) for oral phloretin delivery against oral cancers. The anticancer activities of phloretin were assessed in oral squamous cell carcinoma cells from the buccal cheek. The antiproliferation efficacy and apoptotic activity of the nanofiber formulations were significantly higher than that of the phloretin solution. Nam et al. (54) also developed poly(vinyl alcohol) and Soluplus based nanofiber mats for the delivery of *Angelica gigas Nakai* extract against oral cancers. The nanofiber formulations showed instant wetting (within 2 seconds) and rapid disintegration (within 3 minutes) properties compared to plain nanofibers, which could be used as a fast-dissolving mat for the treatment of oral cancers.

Tonglairoum et al. (55) developed herbal oil (betel oil or clove oil)-incorporated nanofiber mats with antifungal activity for the prevention and treatment of Candida-associated denture stomatitis. The herbal oils released from the nanofibers rapidly inhibited the growth of Candida species within only a few minutes after contact. Also, George and Varghese (56) formulated *Ocimum sanctum* (Tulsi), which had anti-inflammatory, antimicrobial, antioxidant, and anticancer properties in resorbable poly(vinyl acetate) nanofibers for local periodontal therapy. Then, George et al. (57) evaluated the therapeutic effectiveness of locally delivered electrospun *Ocimum sanctum* nanofibers in patients with periodontitis. *Ocimum sanctum* nanofibers were found to be beneficial in the reduction of interleukin-1β levels, which could be used as an adjuvant in the treatment of periodontitis. In another study, tara extract (*Caesalpinia spinosa*) was loaded into electrospun nanofibers made of poly(ε-caprolactone) and the produced nanofiber membranes indicated a potential of therapeutic application for lesions such as prosthetic stomatitis (58). Moreover, for local drug delivery in bone tissue engineering applications, graphene oxide and zinc-curcumin complex were loaded into coaxial electrospun nanofibers. The shell of the coaxial nanofibers included a blend of carboxymethyl chitosan, poly(vinyl alcohol), and graphene oxide. The prepared nanofibers enhanced the osteogenic performance and had an important antibacterial activity and thus reduced postoperative infections (59). In another study, Zadegan et al. (60) developed silk fibroin nanofibers containing *Urtica dioica L.* (nettle) extract at different concentrations. The prepared nanofibers released nettle in a controlled manner via Fickian diffusion and exhibited osteoblast differentiation in a dose-dependent manner.

Conclusions and Future Perspectives

In conclusion, as a part of nanotechnology, nanofibers have various application alternatives in the medical field, especially promising in drug delivery and regenerative medicine. Due to the high surface area and porosity and also the high drug loading capacity, nanofibers have gained great attention in drug release studies. Although herbal bio-actives have been widely used in various forms of products, most of them have the problems of low stability or water solubility, which can be overcomed by formulating them in nanofiber-based drug carrier systems. For example, resveratrol has increased water solubility in nanofiber formulations, and this enables skin penetration and its activity. Also, extended release can be obtained to enable effective drug concentrations for a prolonged period of time by using nanofibers. This is advantageous especially for oral drug delivery systems in terms of improved drug solubility and reduced applied drug dose in phytopharmaceuticals such as diacerein loaded nanofibers. Although herbal bio-actives including nanofibers have been used mostly in topical/transdermal systems, their use via transmucosal routes such as buccal, ocular, nasal, vaginal, and rectal administrations have increased considerably in recent years. Herbal oils such as clove oil and herbal extracts such as tara extract are widely used via these routes based on the fast-dissolving properties of nanofibers and thus increasing activity. In the light of the previous overviewed studies, nanofibers are promising nanocarriers for the development of phytopharmaceuticals in various drug delivery routes.

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