ISSN 2564-7784 EISSN 2564-7040

Indexed in Web of Science

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Formerly Gaziantep Medical Journal

VOLUME 23 ISSUE 4 DECEMBER 2017

eurjther.com

European Journal of Therapeutics

OFFICIAL JOURNAL OF GAZİANTEP UNIVERSITY FACULTY OF MEDICINE

Gaziantep Üniversitesi Tıp Fakültesi adına sahibi ve Sorumlu Yazı İşleri Müdürü/Owner on behalf of Gaziantep University School of Medicine and Responsible Manager: Mehmet Murat Sucu • Yayın türü/Publication Type: Uluslararası Süreli Yayın/International Periodical • Basım yeri Printed at: Matsis Matbaa Hizmetleri San. ve Tic.Ltd.Şti, Tevfikbey Mah., Dr. Ali Demir Cad. No: 51, 34290 Sefaköy, Turkey (+90 212 624 21 11) • Basım tarihi/Printing Date: Aralık 2017/December 2017 • Gaziantep Üniversitesi Tıp Fakültesi tarafından yayınlanmaktadır/Published by Gaziantep University School of Medicine, Üniversite Cad, 27310 Şehitkamil, Gaziantep, Turkey (+90 342 360 60 60/77751)

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

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

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Editorial

Dear colleagues,

In order increase the international visibility of our content, we have started to provide our authors with English translation service, free of charge, as of March 2017.

Currently, our journal is indexed by Web of Science-Emerging Sources Citation Index and TUBITAK ULAKBIM TR Index and thus our journal meets “International articles except SCI Expanded” and “National Article” criteria for associate professor applications in Turkey.

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We are expecting your ongoing contributions in the year 2018.

Best regards.

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European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.163

Review / Derleme

Use of botulinum toxin in urology: a literature review

Ürolojide botulinum toksin uygulamaları: literatür derlemesi

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ABSTRACT

Botulinum neurotoxin (BoNT) is currently preferred as a minimally invasive treatment for lower urinary tract pathologies. Although BoNT injections have become widespread globally for the past 5 years, today, the urological use of BoNT Type A (BoNT-A) is only licensed for the treatment of neurogenic detrusor overactivity and overactive bladder. Despite the relative evidence for the use of BoNT-A in benign prostatic enlargement, there is no high-level evidence data for the use in detrusor sphincter dyssynergia, interstitial cystitis/bladder pain syndrome, and chronic pelvic pain. In this comprehensive review, we mention the mechanism of action and efficacy of BoNT in various urological disorders, present the reliability, and evaluate the literature data supporting its use.

Keywords: Botulinum toxin, neurogenic detrusor overactivity, overactive bladder, detrusor sphincter dyssynergia, benign prostatic enlargement, interstitial cystitis

ÖZ

Botulinum nörotoksini (BoNT), günümüzde alt üriner sistem patolojilerinin tedavisinde minimal invaziv bir tedavi yöntemi olarak tercih edilmektedir. Son 5 yıllık süreçte BoNT uygulamaları tüm dünyada yaygınlaşsa da, günümüzde BoNT Tip A (BoNT-A)' nın ürolojik uygulamaları, sadece nörojenik detrusor aşırı aktivitesi ve aşırı aktif mesanede lisanslıdır. BoNT-A'nın benign prostat hiperplazisinde uygulamalarına ilişkin kanıt düzeyleri nispeten yüksek olmasına rağmen, detrusor sfinkter dissinerjisinde, interstisyel sistit / mesane ağrı sendromunda ve kronik pelvik ağrı sendromunda kullanımına ait kanıt düzeyleri yüksek data yoktur. Bu kapsamlı derlemede, BoNT' nin etki mekanizmasının ortaya konulması, farklı ürolojik uygulamalarda etkinliğinin ve güvenilirliğinin değerlendirilmesi, ve bunları destekleyen literatür verilerinin sunulması amaçlanmıştır.

Anahtar kelimeler: Botulinum nörotoksin, nörojenik detrusor aşırı aktivitesi, aşırı aktif mesane, detrusor sfinkter dissinerjisi, benign prostat hiperplazisi, interstisyel sistit

INTRODUCTION

Botulinum neurotoxin (BoNT), a protein produced by *Clostridium botulinum*, an anaerobic gram-positive bacterium, is a potent neurotoxin. Clinical manifestations are caused by infection through contaminants (particularly canned food prepared at home), meat, sausage, and gastrointestinal tract infection or gastrointestinal colonization in infants with open bruises (1). After discovering that food poisoning in the nineteenth century was usually caused by homemade sausages, this toxin was named as "Botulinum toxin" after the Latin term "Botulus" meaning sausage (2).

Toward the mid-1900s, BoNT Type A (BoNT-A) was injected in a hyperactive muscle, and it blocked the motor nerve stimulation by inhibiting acetylcholine release from the presynaptic end thus causing paralysis (3, 4). These developments inspired the use of BoNT in the treatment of various other diseases resulting in an increasing number of studies exploring the effectiveness of this treatment method. In 1973, Scott (5, 6) published a study of the effects of BoNT on rectus lateralis in monkeys, and in 1981, he reported the first administration of the toxin on human subjects by treating patients with strabismus. Following the Food and Drug Administration (FDA) approval of the use of BoNT-A in the treatment of eye disorders in 1989, the use of BoNT for initial treatment was successfully implemented for strabismus, benign essential blepharospasm, and hemifacial spasm (7).

Botulinum neurotoxin was subsequently used in a wide range of indications, including urological pathologies. The use of BoNT injections on the external urinary sphincter in patients with detrusor sphincter dyssynergia (DSD) who had spinal cord injury (SCI) was first diagnosed by Dykstra (8) in 1988. The use of BoNT-A by Schurch et al. (9) in the same group of patients accelerated the work in this area and opened the way for further developments.

Currently, BoNT can be used in urological pathologies, such as overactive bladder (OAB), neurogenic detrusor overactivity (NDO), interstitial cystitis (IC)/bladder pain syndrome (BPS), DSD,

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Received/Geliş Tarihi: 21.07.2017 • **Accepted/Kabul Tarihi:** 20.09.2017

benign prostatic hyperplasia (BPH), and chronic pelvic pain (CPP; Table 1). However, the FDA approval of BoNT treatment for only OAB and NDO has been obtained from these pathologies (10-12). In this comprehensive review, we mention the mechanism of action and efficacy of BoNT in various urological disorders, present its reliability, and evaluate the literature data supporting its use.

CLINICAL AND RESEARCH CONSEQUENCES

Types of Botulinum Toxin

Botulinum neurotoxin is a neurotoxin secreted by *Clostridium botulinum*, which is a gram-positive, anaerobic, spore-forming, rod-shaped bacterium. Immunologically, 7 active subtypes of A, B, C, D, E, F, and G have been identified. Today, the most commonly used subtypes are BoNT-A and Type B. Numerous comparative studies have demonstrated that Type A is more potent and long-acting than Type B (10-14).

The commercial forms containing BoNT-A used in clinical practice are onabotulinumtoxin A (Botox®; Allergan, Dublin, Ireland), abobotulinumtoxin A (Dysport®; Ipsen-Biotech, Paris, France), incobotulinum toxin A (Xeomin®; Merz Pharmaceuticals, Frankfurt, Germany). The dose equivalency of Botox® and Dysport®, the 2 preparations used in our country, is approximately 1 to 3-5 (15, 16).

Mechanism of Action

Acetylcholine is one of the most important molecules in neural transmissions. Various fusion proteins [Synaptosomal-associated protein 25 (SNAP-25), vesicle-associated membrane protein (VAMP), and Syntaxin) are involved in the release of acetylcholine molecules into the presynaptic domain. Although the different subtypes of botulinum toxin are structurally the same, they differ with regard to serological and antigenic properties. This is because the presynaptic site binds to different fusion proteins. The toxin affects nerves presynaptically by inhibiting the release of acetylcholine at cholinergic nerve endings (17).

Table 1. Use of botulinum toxin A in the treatment of urological disorders

Overactive Bladder/Non–Neurogenic Detrusor Overactivity
Neurogenic Detrusor Overactivity
Interstitial Cystitis/Bladder Pain Syndrome
Detrusor Sphincter Dyssynergia
Benign Prostatic Hyperplasia
Chronic Pelvic Pain

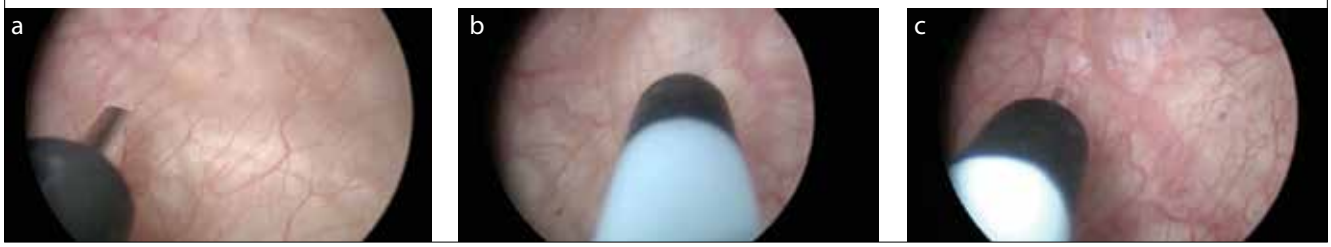
Botulinum toxin reaches the cholinergic nerve terminal, exhibiting typical selectivity when injected into a target tissue. The toxin is then internalized into the structure where it breaks down the rings of an important protein chain that carries acetylcholine from the intracellular domain to the synaptic region. This carrier protein is the soluble N-ethymaleimide-sensitive factor attachment protein receptor (SNARE) protein and is the target of various BoNT serotypes (18). The inhibition of motor neurons following injection of toxin into the bladder inhibits involuntary contractions by reducing acetylcholine release. The significant decrease in phasic contractions, increase in cystometric capacity, and improvement in urinary incontinence (UUI) are due to this mechanism of inhibition in motor neurons. Through sensory neuronal effects, there is also a significant reduction in sensation, degree of compression, nerve receptor, and nerve growth factor levels in the bladder. It has been reported that the frequency of UUI, nocturia, and pollakuria decreases after injection. In these cases, the number of daily pad usage was decreased or complete dryness was achieved, consequently improving the quality of life (10-12, 18, 19).

The attachment of the toxin to the presynaptic membrane is irreversible creating a lasting paralytic effect. It may take up to 24-48 hours for the toxin to take effect. However, after 3-6 months, the axons regenerate leading to the reversal of the effects of denervation (10-12, 18).

Injection Techniques

The procedure can be performed under local, spinal, or general anesthesia. Prior to injection, local anesthesia with intravesical 30 mg 2% lidocaine is administered. After 15-20 minutes, a rigid or flexible cystoscope is inserted into the bladder. BoNT-A 100 IU is diluted with 10 mL saline for OAB and BoNT-A 200 IU is diluted with 20 mL saline for NDO. The bladder is injected with 0.5-1 mL at each point into the base or the bladder walls at a distance of 1-1.5 cm from each point (10-12, 18, 19) (Figure 1). Injection to the bladder dome is not recommended to avoid intestinal injury. The knowledge that BoNT-A also affects the sensory nerves resulted in administering BoNT-A injections into the trigone and suburethral area; consequently, vesicoureteral reflux was not observed after trigonal injections. In a recent meta-analysis com-

Figure 1. a-c. The endoscopic image of the bladder before intradetrusor botulinum toxin injection (a), the endoscopic image of the bladder during intradetrusor botulinum toxin injection (b), the endoscopic image of the bladder after intradetrusor botulinum toxin injection (c)



paring trigonal and extratrigonal injections in patients with NDO and idiopathic detrusor overactivity, there were no significant differences between the 2 methods in terms of side effects and short-term efficacy. The authors reported that patient-related factors and dosing were the major contributors to BoNT-A injections (10-12, 20).

Although the use of a higher concentration of the BoNT ensured improved results, it also causes urinary retention, voiding dysfunction, increased postvoiding residual urine volume (PVR), and requirement of clean intermittent catheterization (CIC). Another important point is the possibility of developing tolerance due to neutralizing agents against BoNT. For individuals with high initial and recurrence doses, the initial dose of BoNT should be as low as possible, since tolerance development is rapid. The efficacy covers a certain period and re-injections are often necessary after an average of 6-9 months (10-12, 18). After BoNT injection, urinary tract infection (UTI) may occur between 3.6% and 44%, PVR levels of up to 100-150 cc (0%-75%) and urinary drainage needed through CIC are reported as high as 43%, as a side effect (21).

Use in Urology

Although BoNT injections have become widespread globally for the past 5 years, today, the urological use of BoNT-A is only licensed for the treatment of NDO and OAB. Despite the relative evidence for the use of BoNT-A in BPH, there is no high level of evidence data for the use of BoNT-A in DSD and IC/BPS (10-12, 18).

1- Overactive Bladder-Non Neurogenic Detrusor Overactivity

Overactive bladder is defined as a syndrome characterized by urinary urgency with or without urgency-associated UUI. It is often associated with pollakuria and nocturia without a diagnosed pathology or infection (10-12). Nearly 12%-17% of the population is affected by this syndrome. Behavioral therapies are recommended as the first-line of treatment, and pharmacological therapy in the form of antimuscarinics and beta-3 agonists are recommended as a second-line of treatment (11, 22). Patients who have been using one or more different antimuscarinic agents for 3 months, often without adequate benefit and/or inability to tolerate the side effects of the drug, are considered as refractory OAB patients (10-12). Onabotulinum toxin A (onaBoNT-A) injections are presented as the standard therapy for the treatment of refractory OAB, according to the European Urology Association (EUA) and American Urology Association guidelines (11, 23).

In a phase 3 study by Nitti et al. (24), 557 patients were treated with 100 IU of onaBoNT-A or placebo. The authors reported a significant decrease in UUI episodes was noted and demonstrated a significant reduction in OAB symptoms compared to the placebo. The urinary retention rate was reported as 5.4%. In another phase 3 trial by Tincello et al. (25) involving 240 female patients with refractory OAB, 200 IU BoNT-A was injected in 122 patients and placebo in 118 patients. The patients were followed-up for 6 months, a significant reduction in urgency and UUI were observed and complete continence was also reported in one-third of cases. The most common adverse effect was UTI (31%), and the rate of patients that required CIC was reported as 16%.

Onem et al. (26) prospectively evaluated 80 patients with resistant OAB in the first multicentric study in Turkey. The mean urinary frequency, UUI episodes, urgency episodes were decreased (all at $p<0.05$), and the bladder capacity was increased both at the third and ninth month postoperatively. There was a 57.1% increase in quality of life scores of the patients, and there was no significant change in the mean PVR and maximum flow rate (Qmax). Three (3.75%) patients had urinary retention and 5 (6.25%) had urinary infection and transient hematuria. It has been reported that re-injection requirement rates were 20% in the third postoperative month and 63% in the ninth postoperative month. In the article published by Leong Randall et al. (27), there was a reduction in the symptoms of approximately 80% of patients after injection, a reduction of 12%-53% in daily urinary frequency, 28%-70% in urgency, 35%-87% in UUI episodes, and an average 45% increase in maximum cystometric capacity (MCC). In addition, the authors noted a decrease of 54%-57% in the Impact Questionnaire-Short Form Score and 38%-64% in the Urogenital Distress Inventory Score.

In a recent review by Mangera et al. (10), there was a 29% decrease in daily frequency, 38% in urgency, and 59% in incontinence episodes with BoNT-A injection (all at $p<0.02$). Urodynamically, an increase of 58% in MCC and a 42% decrease in maximum detrusor pressure (MDP) were reported ($p<0.04$, $p<0.02$, respectively). However, UTI rates (21% vs. 7%, $p<0.01$) and requirement of CIC (12% vs. 0%, $p<0.01$) were increased when compared to the placebo. The EAU guidelines have shown that injection of 100 IU BoNT-A into the bladder wall is superior to placebo in terms of UUI and improvement in quality of life. There is no evidence of decreased efficacy with recurrent injections. However, it is emphasized that patients should be warned about possible urinary system infections and the potential necessity of CIC (11).

2- Neurogenic Detrusor Overactivity

Neurogenic detrusor overactivity is a type of voiding disorder, accompanied by decreased bladder capacity, increased intravesical pressure, and reduced bladder compliance with or without incontinence. The association with vesicoureteral reflux may cause damage to the upper urinary tract. The main goals of treatment are to reduce involuntary contractions of the bladder, partially block the efferent parasympathetic innervation of the bladder, and administer CIC. The treatment method chosen varies for each patient group. Pudendal nerve stimulation or sacral root nerve stimulation in spinal cord injury patients may present great benefit in cases with urgency (10-12, 28). Auto-augmentation enterocystoplasty and ileal conduit are complicated surgical interventions and are considered as the last option. Intravesical capsaicin and resiniferatoxin are currently in the evaluation phase, and research needs to be improved in this regard (18, 29).

The effects of intravesical BoNT-A injections on the detrusor muscle in patient with SCI were first demonstrated in a non-randomized retrospective study by Schurch et al. (30). In this study, NDO patients who were refractory to anticholinergic drugs were evaluated. Patients with low bladder compliance due to organic detrusor muscle changes or fibrosis were excluded from the study. BoNT-A 200-400 IU was injected into the detrusor muscle without

trigon, and all 19 patients were followed up for 9 months with clinical evaluation and urodynamic studies. At 36 weeks, the reflex volume increased from 207 mL to 320 mL, with an increase of 54%, and MCC increased from 286 mL to 458 mL, with an increase of approximately 60% (p=0.007, and p=0.003, respectively). In addition, MDP regressed from 62 cmH_2O to 36 cmH_2O (–41.9%).

Ginsberg et al. (31) published a study including 416 patients (227 patients with multiple sclerosis [MS] and 189 patients with SCI). Overall, 135 of these patients were injected with 200 IU onaBoNT-A, 132 with 300 IU onaBoNT-A, and 149 with placebo. Following the injections, improvement of MCC and MDP in the first involuntary detrusor contraction was higher in the onaBoNT-A group than in the placebo group (p=0.001). Re-injection requirements were noted after 256 days in patients given 200 IU onaBoNT-A, after 254 days in patients given 300 IU onaBoNT-A, and after 92 days in patient given placebo. In addition, CIC was required in 10% of the placebo group, 35% of the 200 IU onaBoNT-A group, and 42% of the 300 IU onaBoNT-A group due to urinary retention. In a study including 71 MS patients, Deffontaines-Rafin et al. (32) reported that UUI disappeared in 46% of the patients, NDO was not observed in urodynamic examinations, half-and-half improvement was achieved in 31% of cases, and a significant change was not detected in 23% of the patients, with the 300 IU onaBoNT-A injections. The mean MBC was increased from 240 cc to 328 cc (p<0.001), and the MDP was decreased from 61 cmH_2O to 36 cmH_2O after injections. They also found that the duration of MS was an important factor influencing treatment success (p=0.015).

In a recent review, a 63% decrease in daily incontinence frequency (p<0.01), 18% decrease in catheterization episodes (p <0.01), 63% increase in MCC, and 42% decrease in MDP were reported with BoNT-A injections (10). In the EAU guideline, it is stated that onaBoNT-A is a successful minimally invasive treatment method for NDO in patients with MS or SCI, where antimuscarinic treatment was ineffective. It has been emphasized that the efficacy of onaBoNT-A is proven by randomized, placebo-controlled studies, with no loss of efficacy in repeated injections (33).

3- Interstitial Cystitis/Bladder Pain Syndrome

Interstitial cystitis/Bladder pain syndrome is defined as a set of symptoms based on the exclusion of infection and other identifiable pathologies, together with symptoms, such as urgency, pollakuria, pain in the bladder or pelvic region, and the sensation of pressure (34). Despite extensive research being conducted presently, there is no definite consensus on the optimal treatment of this clinical presentation. The main goal in the treatment of IC/BPS should be to protect the quality of life at the optimal level and to minimize the severity of symptoms. Although BoNT injections together with hydrodistension is not an FDA-approved treatment for this syndrome, it is commonly used in patients because other treatment steps are not effective and worsen the symptoms (12, 35).

Giannantoni et al. (36) reported that 200 IU BoNT-A injected into the detrusor muscle in patients with BPS provided significant improvement in pain, urinary frequency, voided volume, and bladder capacity; however, all patients had recurrent basal complaints at the end of the first year. In a randomized controlled trial including 67 patients (56 females, 11 males) by Kuo and Chancellor (37), BoNT-A injections (100 IU and 200 IU) with or without hydrodistension were compared. Only patients treated with hydrodistension + BoNT-A showed improvement in bladder pain visual analog scale (VAS) and MCC. In the postoperative global response assessment at 3 months, the success of hydrodistension + BoNT-A was 80% for 200 IU, 72% for 100 IU, and 48% for patients who underwent only hydrodistension. It has been reported that the effect of BoNT-A lasted 12-24 months. Despite the same efficacy, an increase in the dysuria and PVR were more frequent in patients who received 200 IU BoNT-A. In a double-blind, placebo-controlled, multicentre study, Kuo et al. (38) compared the effects of hydrodistension + 100 IU BoNT-A injections versus hydrodistension + saline injections on 67 patients. On the postoperative eighth week, there was a significant decrease in VAS (–2.6 vs. –0.9, p=0.02) and an increase in MCC (+67.8 vs. –45.4, p=0.020) compared to the placebo group. However, no changes were observed in other urodynamic parameters and subjective symptoms, such as frequency/nocturia.

Although the FDA approval requires extensive patient-populated, placebo-controlled studies, these studies show the efficacy of 100 IU onaBoNT-A in the treatment of IC/BPS. The AUA recommends onaBoNT-A at the fourth step of the IC/BPS treatment by starting at 100 IU (35).

4- Detrusor Sphincter Dyssnergia

Detrusor sphincter dyssnergia is a voiding disorder resulting from spinal lesions between the pontin and sacral voiding centers. DSD causes voiding dysfunction with external sphincter spastic or uncoordinated contraction in patients with MS or SCI during voiding. The treatment is based on the removal of obstruction. Although it is not effective, anticholinergic agents, alpha blockers, and spasmolytic agents are used. In addition, treatment methods, such as CIC, permanent urethral and suprapubic catheters, sphincterotomy, dorsal rhizotomy, are among the modalities performed (10-12, 18, 39).

Dykstra et al. (8) explained that reversible chemical sphincterotomy could be performed with BoNT injections to reduce DSD in SCI patients for the first time. BoNT was injected transurethrally or transperineally into the patients through cystoscopy under electromyographic examination. It was performed to 2/3 different regions of injection sites on the sphincter. Urethral pressure profile and PVR were used as the main parameters to follow the effect of toxin. Eight of 11 patients showed improvement. Urethral pressure profiles decreased by an average of 27 cmH_2O, and PVR decreased by an average of 146 mL. The duration of the efficiency was maintained approximately 50 days, and no side effects were observed. In a double-blind study, Dykstra and Sidi (40) evaluated the efficiency of BoNT injections or saline in the treatment of DSD in 5 male patients with SCI. In 3 patients administered BoNT injections, an average of 30 cmH_2O in the urethral pressure, 122 mL in PVR, and 30 cm H_2O in the bladder pressures decreased after treatment. No improvement was observed in these parameters, in 2 patients injected with saline.

In a prospective study including 24 SCI patients, Schurch et al. (41, 42) compared the efficacy of onedose BoNT injections (100 IU in 1 mL) versus once-monthly BoNT injections for 3 months. In 21 of these patients, maximum urethral pressure, duration of DSD, and urethral pressures were reduced by 48%, 47%, and 20%, respectively. There was a significant reduction in PVR (130 mL). In 8 cases, detrusor hypoactivity and bladder neck dyssynergia completely reduced voiding. No improvement in autonomic dysreflexia was observed. Also, in this study, single injections were observed to have a shorter duration (2-3 months) of efficacy on voiding dysfunction when compared to repeated injections (9-13 months).

Today, BoNT activity in DSD is demonstrated in quadriplegic men who cannot undergo catheterization and in MS patients (8, 18, 39-42). The new and standardized trials should be performed due to lack of protocol data, differences on BoNT doses, and insufficient long-term outcomes.

5- Benign Prostatic Hyperplasia

Benign prostatic hyperplasia is a common condition in older men. The goal of treatment is to reduce BPH-related lower urinary tract symptoms and improve quality of life. Alpha-adrenergic blockers and 5-a reductase inhibitors used in therapy are not always effective and side effects may be seen. Currently, the gold standard surgical procedure of BPH treatment is the transurethral resection. However, BoNT may be offered as a treatment alternative in patients who are unfit for operation, whose general condition is impaired, have multiple comorbidities, or do not admit operation. BoNT-A toxin is efficacious by inhibiting autonomic efferent nerve effects on prostate growth and contractions (12, 18).

In a prospective, randomized, placebo-controlled, double-blind trial conducted by Maria et al. (43), which supports the therapeutic properties of BoNT-A in BPH, 200 IU BoNT-A was intraprostatically injected to 15 patients in 4 mL saline,. The procedure was performed using the transrectal ultrasound guideline perineally with 2 mL per prostate lobe. Patients were followed for 19.6±3.8 months, the authors reported prostate specific antigen (PSA) reduction in 51% of the patients and a 65% reduction in the American Urological Association Prostate Symptom Score in the BoNT-A group, while no significant change was observed in the saline group. In the study by Chuang et al. (44), the BoNT-A doses were adjusted to the measured prostate volume as 200 IU BoNT-A for those with prostate tissue above 30 mL, and 100 IU BoNT-A for those below 30 mL and injected by perineal transrectal ultrasound guidance. The International Prostate Symptom Scores (IPSS), Qmax values, and PVR values were compared with the preoperative values. There was a 30% improvement in lower urinary tract symptoms and quality of life scores in both groups. The improvement period started from the first week and maintained to the twelfth month. No local or systemic side effects were observed in any of the patient. Four of the 5 patients had urinary retention, and they voided spontaneously after 1 week.

Guercini et al. (45) administered 300 IU BoNT in patients with prostate volume >80 cc and Qmax <10 mL/s. After a 1-month follow-up, improvement rates were 38.7% in prostate volume, 45.8% in average IPSS, 38.4% in PSA levels, and 64.1% in PVR. In addition, patients' Qmax increased to 87.8%. Park et al. (46) reported symptomatic improvement in 39 of 52 patients injected with BoNT at different doses (100-300 IU) transperineally. A decrease of 30.3% in IPSS, 34.4% in quality of life index, and 13.3% in prostate volume and an increase of 15.5% in Qmax values were observed. Currently, BoNT-A is not routinely used in BPH therapy and has not been approved by the FDA. The EAU guidelines also state that BoNT injection should not be recommended in male patients lower urinary tract symptoms (level of evidence: 1a) (47). However, as shown in the studies conducted, developments are positively directed.

6- Chronic Pelvic Pain

Investigation of prostatitis began in 1998 by the National Institutes of Health (NIH) by classifying it into 4 groups: acute bacterial prostatitis, chronic bacterial prostatitis, CPP syndrome, and asymptomatic inflammatory prostatitis. Of these, type 3 chronic prostatitis is the most common cause (95%) of CPP syndrome (48). Due to the inadequacy of different treatment modalities, physicians treating this group of patients have started to seek different methods of treatment.

It was reported in 1998 for the first time by Maria et al. (49) that there was improvement in urinary symptoms after intraprostatic injections of BoNT in 4 patients with nonbacterial prostatitis. A 30 IU BoNT was injected to the proximal apex of these patients in a single transperineal dose. The uroflowmetric examinations showed significant improvement in 3 patients. None of these patients had symptoms for the following 12 months. In 2000, 11 patients with CPAS diagnosed by Zermann et al. (50) showed a significant decrease in pain after transurethral BoNT injection. The authors administered 200 IU BoNT-A injection transurethrally to the perisphincteric region. In 9 of the 11 patients, subjective pain reduction was observed, and the mean pain level (1: no pain, 10: unbearable pain) was reduced from 7.2 to 1.6 on the VAS. In urodynamic examinations performed before and after injections, a decrease in functional urethral length, urethral closure pressure, and PVR and an increase in mean and maximum flow rates were observed.

Although the number of patients is limited, it is promising that BoNT may be an effective treatment for CPP during preliminary studies. In these studies, injection localization, methods, and dosages vary widely. In large-scale randomized controlled trials, the introduction of standardized treatment methods is an important need in this regard.

CONCLUSION

Botulinum toxin is currently preferred as a minimally invasive treatment in the treatment of lower urinary tract pathologies. The FDA approval was received for OAB and NDO, and it is widely applied throughout the world. In these patients, a significant decrease in bladder phasic contractions and an increase in cystometric capacity were observed urodynamically; moreover, a significant decrease in the frequency of urgency, nocturia, and pollakuria were noted. In this regard, it is stated that the number of daily pad usage decreased or full dryness was provided

thus improving the quality of life. Patients administered with BoNT injections should be warned about urine retention and requirement of CIC. Patients should be informed that the effect of botulinum toxin injection is temporary, repeated injections may be necessary, and their efficacy may continue after repeated injections.

Current studies are suspicious about BoNT injection in BPH and do not clearly support it. BoNT injections are promising in CPP and IC/BPS due to limited evidence. Similarly, although the efficacy and reliability of BoNT in DSD has been shown in small studies, extensive, well-designed, randomized controlled trials are needed.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.B.; Design - Ö.B.; Supervision - İ.S.; Data Collection and/or Processing - R.O.; Analysis and/or Interpretation - Ö.B., İ.S.; Literature Search - R.R.D.; Writing Manuscript - Ö.B.; Critical Review - R.R.D.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Concept - Ö.B.; Design - Ö.B.; Supervision - İ.S.; Data Collection and/or Processing - R.O.; Analysis and/or Interpretation - Ö.B., İ.S.; Literature Search - R.R.D.; Writing Manuscript - Ö.B.; Critical Review - R.R.D.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Bayrak Ö, Seçkiner İ, Onur R, Dmochowski RR. Use of Botulinum Toxin in Urology: A Literature Review. Eur J Ther 2017; 23: 131–7.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.31

Original Investigation / Özgün Araştırma

Smoking status and effects of happiness on smoking in Turkish pregnant women

Türk gebe kadınların sigara kullanım durumu ve mutluluğun sigara kullanımına etkisi

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ABSTRACT

Objective: The aim of this research was to explore smoking during pregnancy, features of pregnant women who smoke, factors that affect smoking during pregnancy, and effects of anxiety and happiness on smoking during pregnancy.

Methods: This was a cross-sectional and analytical study. The study was conducted at 16 family health centers in Aydın, Turkey. In total, 187 pregnant women were selected through stratified random sampling. Data were collected using a questionnaire developed by researchers (D.S, H.A,) the Beck Anxiety Inventory, and Oxford Happiness Questionnaire. Data obtained were analyzed using descriptive statistics, Chi-square test, logistic regression analysis, Kolmogorov–Smirnov test, Mann–Whitney U test, and receiver operating characteristic analysis.

Results: The rate of smoking was 32.1% before pregnancy and 13.9% during pregnancy. Not having a civil marriage and moving to another place increased smoking. There was a statistically significant difference in the smoking status and the number of cigarettes smoked before and during pregnancy between the groups. Smoking of spouses and other people increased the number of smoking women. There was no statistically significant difference (U=-1.465, p=0.143) between anxiety scores and smoking during pregnancy; however, the difference between happiness scores and smoking during pregnancy was significant (U=-2.804, p=0.005).

Conclusion: Feeling happy, smoking spouses or other people around the women, and the number of cigarettes smoked before pregnancy were found to affect smoking during pregnancy.

Keywords: Smoking, pregnancy, happiness and anxiety

ÖZ

Amaç: Bu araştırmanın amacı gebelikte sigara içme durumu, sigara içen gebelerin özellikleri, gebelikte sigara içmeyi etkileyen faktörler, anksiyete ve mutluluk durumunun sigara içme üzerine etkilerini belirmektir.

Yöntemler: Bu araştırma analitik-kesitsel bir araştırmadır. Araştırma Aydın il merkezindeki 16 aile sağlığı merkezinde yürütülmüştür. Araştırma tabakalı rastgele örnekleme yöntemi ile seçilen 187 gebe ile gerçekleştirilmiştir. Veriler araştırmacının hazırladığı anket formu, Beck Anksiyete Ölçeği ve Oxford Mutluluk Ölçeği Kısa Formu ile toplanmıştır. Verilerin değerlendirilmesinde tanımlayıcı istatistikler, ki kare, lojistik regresyon analizi, Kolmogorov-Smirnov ve Mann-Whitney U testi analizi kullanılmıştır.

Bulgular: Kadınların sigara kullanma oranı gebelik öncesi %32,1 ve gebelikte %13,9 olarak bulunmuştur. Resmi nikâhlı olmaması, gebelerin taşınma durumu yaşaması sigara içmeyi artırmaktadır. Gebelik öncesi sigara kullanma ve içilen sigara sayısı ile gebelikte sigara kullanımı arasında yapılan istatistiksel analizde gruplar arası fark olduğu bulunmuştur. Eşinin ya da başka birinin gebe ile aynı ortamda sigara içmesi de gebenin sigara içmesini arttırdığı görülmüştür. Gebelerin anksiyete ölçek puanları ile gebelikte sigara kullanımı arasında yapılan istatistiksel analizde gruplar arası farkın olmadığı, fakat mutluluk ölçek puanları ile gebelikte sigara kullanımı arasında gruplar arası farkın anlamlı olduğu bulunmuştur

Sonuç: Mutlu olması, eşinin veya başka birinin gebenin yanında sigara içmesi, gebelik öncesi sigara içmesi, içilen sigara miktarının gebelikte sigara kullanmayı etkilediği belirlenmiştir.

Anahtar kelimeler: Sigara içme, gebelik, mutluluk, anksiyete

INTRODUCTION

There is an increase in the number of pregnant smokers because smoking is widespread in the society, 90% of smokers start smoking before the age of 20 years, and the number of female smokers has increased. Globally, although smoking in pregnancy has reduced in recent years, it has still shown to be common in recent research (9%-46%) (1). According to the Centers for Disease Control and Prevention (2015), approximately 10% of women are reported to smoke during the last 3 months of pregnancy (2). Of all women who smoked 3 months before pregnancy,

This study has been presented as a poster in the 15th National Nursing Congress, 10–12 September 2015, Erzurum, Turkey.
Bu çalışma poster bildiri olarak 15. Ulusal Hemşirelik Kongresi'nde sunulmuştur, 10–12 Eylül 2015, Erzurum, Türkiye.

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Received/Geliş Tarihi: 15.06.2017 • **Accepted/Kabul Tarihi:** 24.07.2017

55% quit during pregnancy. The rate of smoking in a pregnant population in France has been reported as 25.1% (3). In a field study from Germany [Schneider et al. (4)], the rate of smoking during pregnancy was found to be 13%. In a study in Lebanon, out of 102 smokers, only 21% stopped smoking, but 79% continued smoking in their pregnancy (5). The rate of smoking during pregnancy has been reported as 14.8% in a study conducted in Lithuania (6). According to Turkish Population and Health Study (TPHS; 2008), 11.4% of pregnant women smoke (7). A rise in the rate of smoking in a society increases smoking-related risks during pregnancy (8).

There is high risk of low birth weight, intrauterine growth retardation (IUGG), and sudden infant death syndrome due to smoking in pregnancy. In addition, the incidence of major birth defects increases. It has been reported that the incidence of cleft palate is higher among women smoking during the first trimester of their pregnancy. Smoking can also have effects on the respiratory system, such as deficiencies in the pulmonary functions, wheeze in the early infantile period, asthma, and lower respiratory tract infections. Effects of smoking on mental health and behavior include learning difficulties; hyperactivity; low intelligent quotient; mental retardation; behavioral, psychiatric, and cognitive side effects in childhood; attention deficit disorder; and low academic performance. Pregnant women can experience spontaneous abortion, placenta previa, abruptio placenta, early membrane rupture, placental hypertrophy, implantation dysfunction, hypertension, and preeclampsia (9, 10). Smoking in pregnancy is responsible for 5% of all newborn deaths, 10%-15% of preterm births, and 20%-30% of cases of low birth weight (11). In a study by Inoue et al. (12), a significant relation was found between the infant's height and weight and the mother's smoking status during pregnancy; however, the infant's height and weight was not significantly related to the father's smoking. They added that both the father's and the mother's smoking habit increased the risk of short stature.

Most people unable to overcome tobacco addiction note that they fail to quit smoking since they cannot manage stress. One-fourth of ex-smokers start to smoke again due to failure to manage stress (13). Pregnancy is considered a period during which many changes occur in the lives of pregnant women. Age at pregnancy, socio-economic status, low education levels, anxiety during pregnancy, and psycho-social stress play a role in increased smoking (14). In a study by Köse et al. (15), the most frequent reason to start smoking among women is stress (33.1%). One study revealed that depressed women were 4 times more likely to smoke during their pregnancy than were non-depressed women (16). As happiness scores during pregnancy increase, the rate of smoking decreases. Being happy during pregnancy has a positive effect on health behaviors (14).

Smoking during pregnancy is a health problem that prevents raising healthy generations due to its harmful effects on mothers and their babies. In fact, pregnancy is an opportunity for smoking women to give up this habit (17). Pregnancy itself has a supporting role in one's life and offering information about harmful effects of smoking can be an appropriate way of motivation (11). It has been reported that quitting smoking in pregnancy, regardless of trimesters, will improve pregnancy outcomes. Health professionals should revise their in-service training programs so that the rate of people ceasing to smoke can rise (17).

This study was performed to determine the rate of smoking in pregnancy, features of smoking pregnant women, effects of anxiety in pregnancy on smoking, effects of happiness in pregnancy on smoking, and factors affecting smoking during pregnancy.

METHODS

Design and Participants

This study has a cross-sectional analytical design and was conducted in 16 family health centers in Aydın, Turkey, between December 2, 2013, and April 11, 2014. The study population included pregnant women receiving care at family health centers in the city of Aydın during the study period. The study sample was created through stratified random sampling and included 187 volunteering pregnant women in their first, second, and third trimesters. Inclusion criteria were being literate, not diagnosed with any chronic diseases or psychiatric disorders, and aged 15-49 years.

Questionnaires and Interviews

Data were collected with a questionnaire developed by researchers (D.S, H.A), the Beck's Anxiety Inventory (BAI), and a short form of the Oxford Happiness Questionnaire (OHQ-SF). The questionnaire developed by the researcher composed of a total of 42 questions, of which 12 were open-ended and 30 were closed-ended questions. Of the 42 questions, 11 were about socio-demographic features, 16 were about social and psychological problems, 4 were about marriage, and 11 were about smoking status of the women and their spouses.

BAI is a self-rating scale developed by Beck et al. (18) to determine the frequency of anxiety experienced by individuals. The inventory is a 21-item, 4-point Likert scale, and each item is scored ranging from 0 to 3 (0: never, 1: mild, 2: moderate, and 3: severe). The lowest and the highest scores to be obtained are 0 and 63, respectively. High scores indicate severe anxiety. The validity and reliability for the Turkish population were tested by Ulusoy et al. (19). They found that the Cronbach's alpha internal consistency coefficient was 0.93 . In the present study, Cronbach's alpha was 0.83.

OHQ-SF was developed by Hills and Argyle (20) to evaluate happiness levels and is composed of 8 items. The validity and reliability for the Turkish population were tested by Doğan and Çötok (21). Internal consistency and test and re-test coefficients of the questionnaire were 0.74 and 0.85, respectively. A factor analysis of the questionnaire showed a one-factor structure. The original version of the questionnaire is a 6-point Likert scale (1: completely disagree, 6: completely agree). The Turkish version of the questionnaire is a 5-point Likert scale since more than 5 choices in Turkish causes difficulty in meaning and understandability, as the meanings of the choices can be very similar and can be difficult for respondents to discriminate between them. Items 1

and 7 were scored in the reverse order. The minimum and maximum scores to be obtained from the questionnaire are 5 and 35, respectively. Higher scores indicate higher levels of happiness. However, the questionnaire does not have a cut-off point. In addition, the Turkish version of the OHQ-SF is a self-report Likert scale composed of 7 items (1: completely disagree and 5: completely agree) (21). The Cronbach's alpha value of the OHQ-SF in this study was 0.64.

The pregnant women accepting to participate in the study were given the questionnaires and explained how to complete them. The women self-completed the questionnaires and requested the researcher to explain a question in case of lack of understanding. The participants completed all the data collection tools in 20-25 minutes.

Ethics

The ethical approval was obtained from the Public Health Directorate of Aydın Municipality and the Non-Interventional Clinical Research Ethical Committee of Adnan Menderes University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical Analysis

Obtained data were analyzed using Statistical Package for the Social Sciences Version 16.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics (numbers, percentages, and means), Chi-square test (Yates's correction for continuity and Fisher's and Monte Carlo Exact tests), and logistic regression analysis were used. Kolmogorov-Smirnov test was utilized to determine whether data were normally distributed. Since data about age were normally distributed, mean±standard deviation as descriptive statistics was used for the analysis, and since data about other variables were not normally distributed, median as descriptive statistics (25%-75%) was used for analysis. Mann-Whitney U test was used to compare groups when data were not normally distributed. Receiver operating curve (ROC) analysis was employed to determine the cut-off point of smoking-related continuous variables. The Cronbach's alpha values for BAI and OHQ-SF were determined using reliability analysis.

RESULTS

Out of all the smoking women, 42.3% were high school graduates, 73.1% were housewives, 61.5% had an income equal to their expenses, 96.2% had a health insurance, 88.5% were living with their spouses and children, and 80,8% lived in a city for most of their life. In addition, 11.5% women were living with their spouses' families. Table 1 shows the socio-demographic features of the women.

The most frequent stressor experienced by the women was financial problems (14.4%), followed by unemployment (8.6%), presence of a severe disease in a family member (5.9%), death of a family member (5.3%), moving to another place (5.3%), marital problems (2.1%), and changing job (0.5%). Most of the women

Table 1. Socio-demographic features of the women

Socio-demographic features of Nonsmokers	n (187) mean±SD	%
Age, years	27.8±5.1	
Duration of marriage years	6.0±4.76	
Marital status		
Civil marriage	176	94.1
Religious marriage	11	5.9
Education		
Primary school	53	28.3
Secondary school	43	23.0
High school	55	29.4
University or higher education levels	36	19.3
Occupation		
Housewife	150	80.2
Officer	9	4.8
Tradesman	4	2.1
Private sector	20	10.7
Having one's own business	3	1.6
Worker	1	0.6
Income		
Lower than expenses	47	25.1
Equal to expenses	127	67.9
Higher than expenses	13	7
Having an extended family		
Yes	35	18.7
No	152	81.3
Place of residence where women lived for most of their life		
Village	25	13.3
Small town	5	2.7
Town	22	11.8
City	135	72.2
Socio-demographic features of smokers	**n (26)**	**%**
Education		
Primary school	9	34.6
Secondary school	4	15.4
High school	11	42.3
University or higher education levels	2	7.7
Having a job providing income		
Yes	25	96.2
No	1	3.8
Income		
Less than expenses	9	34.6
Equal to expenses	16	61.5
Higher than expenses	1	3.8
Having a health insurance		
Yes	25	96.2
No	1	3.8
Family structure		
Nuclear family	23	88.5
Extended family	3	11.5
Place of residence where women lived for most of their life		
Village	1	3.8
Small town	1	3.8
Town	3	11.5
City	21	80.8

SD: standard deviation

Table 2. Stressors experienced by the women

Stressors experienced by the women	n	%
Financial problems		
Yes	27	14.4
No	160	85.6
Death of a family member		
Yes	10	5.3
No	177	94.7
Moving		
Yes	10	5.3
No	177	94.7
Changing job		
Yes	1	0.5
No	186	99.5
Marital problems		
Yes	4	2.1
No	183	97.9
Severe illness of a family member		
Yes	11	5.9
No	176	94.1
Unemployment		
Yes	16	8.6
No	171	91.4
Experiencing miscellaneous problems		
Yes	6	3.2
No	181	96.8
Satisfaction with marriage		
Yes	185	98.9
No	2	1.1
Experiencing a marital problem at the time of the study		
Yes	9	4.8
No	178	95.2
Presence of spouses' problems		
Yes	179	95.7
No	8	4.3

were satisfied with their marriage (98.9%) and did not have any marital problems recently (95.2%). Table 2 summarizes stressors experienced by the women.

In total, 66.8% of women received training to stop smoking during their antenatal screening; 54.8% of them were noted to receive the training mostly from midwives. Overall, 32.1% of the women smoked before pregnancy and 40% of the smokers smoked 6-10 cigarettes a day; 13.9% of the women smoked during their pregnancy and 57.7% of the smokers smoked 1-5 cigarettes a day. In addition, 57.7% of the smokers were very worried about harmful effects of smoking on their babies, while 7.7% of the smokers were not worried about it. The passive smokers' rate was 55.6%; 62% of the smokers smoked in the same environment as other smokers and at least 1-5 cigarettes a day. Also, 17.1% of the smokers smoked together with a person except their husbands; 80.8% of the women noted that they smoked because of habit (Table 3a).

In total, 84.6% of the women wanted to stop smoking and 50% of them wanted to do so to avoid its harm on their babies. The most frequent reason for stopping smoking was avoidance of harm on babies (77.8%), followed by nausea and vomiting, disturbing effects of its smell, disgust, pressure and support from others, and pressure and support from spouses. The women quitting smoking did not receive recommendations and support about the issue from nurses, midwives, or doctors (Table 3b).

The mean BAI score was 11.0 (min-max=5.0-17.25) in the smokers and 8.0 (min-max=4.0-13.0) in the nonsmokers without a significant difference (U=−1.465; p=0.143). The mean OHQ-SF score was 26.0 (min-max=23.75-29.0) in the smokers and 28.0 (min-max=26.0-31.0) in the nonsmokers with a significant difference (U=−2.804; p=0.005).

According to the ROC analysis, the cut-off point for the happiness score was 27 (area below the ROC curve: 0.671; p=0.005). The women were divided into 2 groups: those with a happiness score <27, i.e., the unhappy group, and those with a happiness score of >27, i.e., the happy group. The unhappy group smoked 2.938 times more than the happy group (p=0.012; odds ratio [OR]=2.938; 95% confidence interval [CI]=1.238-6.998).

There was no significant difference in the smoking status in terms of demographic features except for marital status. The women without a civil marriage smoked more than those with a civil marriage did, with a significant difference (χ^2=0.009; p=0.009). In fact, those without a civil marriage smoked 6.15 times more than those with a civil marriage did.

The rate of smoking was significantly higher among the women who moved to new homes during their pregnancy than those who did not (χ^2=0.035; p=0.035). Indeed, the women moving to a new place smoked 4.697 times more than those who did not (OR=4.697; 95% CI=1.228-17.967). Financial problems, unemployment, presence of a severe disease in a family member, death of a family member, and marital problems did not cause a significant difference in terms of smoking.

There was a significant difference in smoking during pregnancy between the women smoking in the antenatal period and those not smoking in the antenatal period (χ^2=60.352; p<0.0005). The higher the number of cigarettes the women smoked before pregnancy, the more likely they were to continue smoking during pregnancy. The higher the number of cigarettes was smoked in the antenatal period, the higher the number of cigarettes during pregnancy (χ^2=7.716; p=0.021).

The women whose spouses smoked in the same environment as them smoked significantly more than those whose spouses did not smoke in the same place (χ^2=21.426; p<0.0005), with a risk of smoking 9,324 times higher (OR=9.324; 95% CI=3.326-26.139). The women smoked significantly more when someone other than their spouses smoked in the same place as them (χ^2=0.021;

Table 3a. Smoking status of the women I

Information about the smoking status of the women	n	%
Did they receive education to stop smoking during antenatal visits?		
Yes	62	33.2
No	125	66.8
Who offered education to stop smoking?		
Midwives	34	54.8
Doctors	6	9.7
Midwives and doctors	22	35.5
Did they smoke before pregnancy?		
Yes	60	32.1
No	127	67.9
How many cigarettes a day did they smoke before pregnancy? (n=60)		
1-5	19	31.7
6-10	24	40.0
≥11	17	28.3
Did they smoke during their pregnancy?		
Yes	26	13.9
No	161	86.1
How many cigarettes did they smoke during their pregnancy? (n=26)		
1-5	15	57.7
6-10	9	34.6
≥11	2	7.7
How much worried were they due to smoking?		
Extremely	15	57.7
Quite	3	11.5
Slightly	6	23.1
Never	2	7.7
Do they know what passive smoking is?		
Yes	104	55.6
No	83	44.4
Do the spouses smoke in the same room as their wives?		
Yes	71	38.0
No	116	62.0
How many cigarettes do their spouses smoke in the same room as them? (n=71)		
1-5	30	42.2
6-10	17	24.0
≥11	24	33.8
Is there anyone smoking in the same room as the women except for their spouses?		
Yes	32	17.1
No	155	82.9
Why do the women smoke during their pregnancy?	**(n=26)**	**%**
Because their spouses smoke		
Yes	2	7.7
No	24	92.3
Because they have been smoking for years/it has been their habit		
Yes	21	80.8
No	5	19.2
Because they think it helps to solve their problems		
Yes	4	15.4
No	22	84.6

Table 3b. Smoking status of the women II

What do the women think about their smoking habit?	n	%
Does smoking harm them and their babies?		
Yes	0	0.0
No	26	100
Do they want to stop smoking?		
Yes	22	84.6
No	4	15.4
Why do they want to stop smoking?		
To protect their babies' health	13	50.0
To protect their health and their babies' health	9	34.6
To protect their own health	4	15.4
Why do they stop smoking during their pregnancy?	**(n=34)**	**%**
Nausea and vomiting		
Yes	14	41.2
No	20	58.8
The idea that smoking gives harm to their babies		
Yes	27	79.4
No	7	20.6
Bad smell of smoking		
Yes	8	23.5
No	26	76.5
Feeling disgusted		
Yes	5	14.7
No	29	85.3
Pressure and support from spouses		
Yes	1	2.9
No	33	97.1
Pressure and support from people around		
Yes	3	8.8
No	31	91.2
Recommendations and support from nurses		
Yes	0	0.0
No	34	100.0
Recommendations and support from doctors		
Yes	0	0.0
No	34	100.0

p=0.021). This situation caused an increase in the number of cigarettes smoked by 3.176 times (OR=3.176; 95% CI=1.265-7.976).

DISCUSSION

Only one stressor, moving homes, was found to increase smoking significantly. Financial problems, unemployment, presence of a severe disease in a family member, death of a family member, and marital problems did not cause a significant difference for smoking. Satisfaction with marriage, having problems related to marriage, and having a good relationship with spouses did not cause a difference for smoking. It can be suggested that moving home is a condition causing severe stress. However, in a study by Beijers et al. (22), no significant relation was found between the severity of stressful events and starting smoking.

It was noted that 13.9% of the women smoked during their pregnancy. Most of the women smoked 1-5 cigarettes a day during this period. The rate of smoking during pregnancy was reported to be 13% by Schneider et al. (4), 12%-25% by Lumley et al. (16), and 14.4% by Chomba et al. (23), which are consistent with the results of the present study. It was reported to be 25.1% by Gomez et al. (3), 42% by Jabbour et al. (5), and 48% by Vivilaki et al. (24), which are higher than that in the present study. In the study on smoking during pregnancy in the low- and middle-income countries by Caleyachetty et al. (25), the highest and the lowest rates of smoking were found in South Asia (5.1%) and Africa (2%), respectively . These rates are lower than the ones in Turkey and Europe.

The rate of smoking in pregnancy in Turkey was reported to be 11.6% by Doğu and Berkiten (14), 12.8% by Altıparmak et al. (26), and 14.8% by Karçaaltınçaba et al. (27), which are consistent with that found in the current study, and the rate was reported as 54.8% by Durualp et al. (8), which is higher than that in this study. According to TPHS, 15% of the pregnant women were smoking in 2003 and it decreased to 11.4% in 2008 (7). The fact that 1 in every 10 pregnant women smokes has been reported in the studies to be a serious problem.

Some studies have shown that the number of cigarettes smoked in pregnancy is 1-5 a day (14, 26). TPHS revealed that the mean number of cigarettes smoked daily in pregnancy was 10 in 2008 (7). Marakoğlu and Erdem (28) reported that 86.6% of the women were smoking continuously during their pregnancy, with 10 cigarettes daily. The aforementioned rates of smoking are higher than that found in the present study. The severity of preterm birth risk is proportional to the number of cigarettes smoked. The most severe effect appears in women smoking >10 cigarettes daily (29). As the number of cigarettes increases, harm inflicted on women and their babies also increases.

More than one-half of the women (57.7%) were worried due to their smoking in their pregnancy. Doğu and Berkiten (14) found that 52.8% of the women were very worried about their babies' health and that only 2% of the women were not worried about it. Even if it is a small percentage, the presence of women never anxious about their babies' health is actually disturbing.

Thirty-eight percent of the women's spouses were smoking in the same environment as them. The spouses (42.2%) were smoking at least 1-5 cigarettes a day. Also, 17.1% of the women were accompanied by someone other than their spouses. The rate of the women accompanied by their spouses while smoking was reported to be 53.6% by Doğu and Berkiten (14), 70.2% by Altıparmak et al. (26), and 55,4% by Durualp et al. (8). The foregoing reported rates are higher than that in the present study. The rate of the women accompanied by someone other than their spouses was reported to be 35.9% by Nakamura et al. (30), 31.9% by Altıparmak et al. (26), and 56.2% by Durualp et al. (8). Kadir et al. (31) investigated passive smoking in pregnant women in Latin America, Africa, and South Asia and found that smoking was most frequently allowed at home in Pakistan (91.6%). The reported rates of pregnant women accompanied by their spouses or others while smoking are higher than those found in the current study. These high rates suggest that people do not have sufficient information about effects of passive smoking on pregnant women and their babies.

While most of the pregnant women were planning to stop smoking, some proportion of the women did not have such a plan. One-half of the women planning to stop smoking in pregnancy noted that their primary aim was to protect their babies' health. Most of the pregnant women had already stopped smoking (77.8%) in case it harmed their babies, which is consistent with the results of the studies by Marakoğlu and Erdem (28), Doğu and Berkiten (14), and Durualp et al. (8). In a study by Vivilaki et al. (24), 83.3% of the women wanted to stop smoking during pregnancy, but 45.1% of them achieved their goal. Moreover, 55.8% of the women continuing to smoke during their pregnancy did so because they could not achieve it, and 9.3% of the women continuing to smoke did so because they did not consider it as an important health problem. The finding that the mothers quit smoking for protection of their babies' health is favorable, and indeed pregnancy can be considered an opportunity for smokers to give up their habit.

None of the women stopping smoking reported that they received recommendations or support about the issue from nurses. In a study by Marakoğlu and Sezer (9), 29% of the pregnant women were found to be given recommendations to stop smoking, and 18% were found to be provided guidance for the issue. In a study by Marakoğlu and Erdem (28), 6.8% and 4.5% of the pregnant women were recommended to stop smoking and offered support and guidance by physicians, respectively. In addition, 4.5% and 6.8% of the pregnant women were recommended to quit smoking and provided support and guidance by nurses, respectively. This evidence shows that a very low rate of smoking pregnant women could receive help from physicians and nurses about elimination of their habit. In the present study, the finding that none of the women could be offered help about cessation of smoking is striking. This suggests that health professionals are not very aware of effects of smoking during pregnancy.

The analysis of the relation between demographic features and smoking showed that a higher rate of the pregnant women without a civil marriage smoked. It may suggest that not having a civil marriage may cause worries. In addition, the analysis of the relation between stressors and smoking revealed a significant difference in the smoking status between the women moving to another place and those not moving, probably because moving home may cause severe stress in pregnant women.

Compared to the women whose spouses did not smoke in their presence, those whose spouses smoked in their presence smoked a significantly higher number of cigarettes. The women whose spouses smoked were 9 times more likely to have the risk of smoking in pregnancy. In a study by Marakoğlu and Erdem (28), 81.8% of the women whose spouses were smokers smoked during pregnancy. The women whose relatives and friends were also smokers smoked 3 times more frequently than other women. Marakoğlu and Sezer (9) found that 20% of the women

whose spouses were smokers and 10% of those whose spouses were nonsmokers smoked at some stages of pregnancy. It can be suggested that smoking spouses, relatives, and friends create a serious risk of smoking in pregnancy.

The mean scores of OHQ-SF were found to affect the smoking status in pregnancy; the women with low scores smoked 3 times more than those with high scores did. Doğu and Berkiten (14) noted in their study that as scores for happiness with marriage increased, the amount of smoking decreased. Doğu and Berkiten (14) found out that smoking was one of the mechanisms used by pregnant women to cope with stress. It is known that smoking is used as a mode to reduce unhappiness. It is clear that pregnant women need positive mechanisms to relieve stress.

Study Limitations

The limitation of this study is that data were collected with self-rated data collection tools: a questionnaire, BAI, and OHQ-SF. Therefore, the reliability of the findings is limited to the information provided by the participants.

CONCLUSION

Smoking is an unwanted behavior and pregnancy can be considered an opportunity to quit smoking. As it was clear in the present study, women are worried that smoking causes the most serious damage to their babies. Since this concern can force women to quit this habit, they should be provided support. This study also revealed that smoking spouses, relatives, and friends; prenatal smoking; and the extent of smoking before pregnancy had an effect on smoking during pregnancy. It is obvious that both pregnant women and their spouses and other people around them need education to stop smoking during pregnancy and that awareness of health professionals about the issue should also be raised. In addition, the present study showed that happy pregnant women smoked fewer cigarettes. Therefore, pregnant women could be encouraged to have activities that will keep them happy.

Ethics Committee Approval: Ethics committee approval was received for this study. Ethical approval was obtained from the Non-interventional Clinical Research Ethical Committee of Adnan Menderes University.

Informed Consent: Informed written consent was obtained from the patients participating in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - D.S., H.A..; Design - D.S., H.A..; Supervision - H.A.; Resource - xD.S., H.A..; Materials -D.S.; Data Collection and/or Processing - D.S.; Analysis and/or Interpretation - D.S., H.A..; Literature Search - D.S., H.A.; Writing -H.A.; Critical Reviews - H.A.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik kurul onayı Adnan Menderes Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Bu çalışmaya katılan hastalardan yazılı onam alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir -D.S., H.A.; Tasarım - D.S., H.A. .; Denetleme - H.A.; Kaynaklar - D.S., H.A.; Malzemeler - D.S.; Veri Toplanması ve/veya İşlemesi - D.S.; Analiz ve/veya Yorum - D.S., H.A.; Literatür Taraması - D.S., H.A.; Yazıyı Yazan - H.A.; Eleştirel İnceleme - H.A.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Sönmez D, Aksu H. Smoking status and effects of happiness on smoking in Turkish pregnant women. Eur J Ther 2017; 23: 138–45.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.49

Original Investigation / Özgün Araştırma

Comparing peer-led and adult-led education to promote a healthy diet among Turkish school children

Türk okul çocuklarında sağlıklı beslenmenin geliştirilmesi için yetişkinden ve akrandan eğitim yöntemlerinin karşılaştırılması

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ABSTRACT

Objective: The aim was to compare the effect of peer-led and adult-led educational models that deliver educational programs to promote healthy dietary habits among school children.

Methods: Pre-test and post-test design was used for group comparisons. The participants were 51 fourth-grade students. The data were collected with a socio-demographic questionnaire, the Children's Dietary Self-Efficacy Scale (CDSS), and the Diet Behavior Scale (DBS). Descriptive, chi-square test, paired sample t-test, Mann-Whitney U test, Wilcoxon test and a Multivariate Analysis of Variance (MANOVA) test were administered for data analysis.

Results: No statistically significant difference was found between the groups with regard to pre-test diet scores ($p>0.05$). After education, diet self-efficacy and diet behavior scores significantly improved in the adult-led group ($p<0.05$). No significant difference was observed between the groups with regard to post-test diet scores ($p>0.05$).

Conclusion: Use of an integrated educational approach that contains both adult-led and peer-led education can be more effective in the improvement of student's dietary scores.

Keywords: Adult-led education, diet behavior, diet education, peer-led education, school children

ÖZ

Amaç: Okul çocuklarında sağlıklı beslenme alışkanlığını geliştirmek için kullanılan akrandan ve yetişkinden eğitim modellerinin etkisini karşılaştırmaktır.

Yöntemler: Grup karşılaştırmaları için ön-test son-test araştırma tasarımı kullanılmıştır. 51 tane dördüncü sınıf öğrencisi çalışmaya katılmıştır. Veriler sosyo-demografik soru formu, Çocuk Beslenme Özyeterlik Ölçeği (ÇBÖÖ) ve Çocuk Beslenme Davranış Ölçeği (ÇBDÖ) ile toplanmıştır. Veri analizi, tanımlayıcı, ki-kare, iki eş arasındaki farkın önemlilik testi (t testi), Mann-Whitney u-test, Wilcoxon testi, çok yönlü varyans analizi (MANOVA) ile yapılmıştır.

Bulgular: Gruplar arasında ön-test beslenme sonuçları bakımdan istatistiksel olarak anlamlı bir fark bulunmamıştır ($p>0,05$). Eğitimden sonra, yetişkinden eğitim alan grubun beslenme öz-yeterlik ve beslenme davranış puanlarında artış olmuştur ($p<0,05$). Gruplar arasında son-test beslenme sonuçları bakımdan istatistiksel olarak anlamlı bir fark bulunmamıştır ($p>0,05$).

Sonuç: Çocukların beslenme sonuçlarını iyileştirmek için yetişkinden ve akrandan eğitim modellerini içeren entegre eğitim yaklaşımının kullanılmasının daha etkili olacağı düşünülmektedir.

Anahtar kelimeler: Yetişkinden eğitim, beslenme davranışı, beslenme eğitimi, akrandan eğitim, okul çocukları

INTRODUCTION

Childhood obesity has become a rapidly growing epidemic (1, 2). In several studies conducted in Turkey, the overweight rate among school-aged children ranges from 12% to 22.1% (3-6). Overweight children are at an increased risk of being overweight, developing diabetes, certain cancers, and cardiovascular diseases during adulthood (7). The Healthy Nutrition and Active Living Program launched by the Ministry of Health considers that school-aged children and young people are the most important target groups between 2013 and 2017, due to the increasing rates of obesity in Turkey in recent years. In this context, children's knowledge, attitudes, and behaviors toward nutrition are expected to be affected by training program that aim to promote healthy dietary habits in schoolchildren (8). Therefore, for the improvement of public health, it is essential that schoolchildren are taught healthy dietary habits that encourage them to consume less fat and salt, but more fruit and vegetables (9).

To prevent diseases, it is essential to focus on children. Lifelong health habits and beliefs develop early in life. Prevention efforts targeting children strengthen health protection and disease-preventive behaviors (1). Schools play a critical role in the development of children's lifelong health behaviors since they provide an environment where most children in a community

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Received/Geliş Tarihi: 04.07.2017 • **Accepted/Kabul Tarihi:** 04.08.2017

can be directly contacted, and where their effects on children's social, psychological, physical, and intellectual development last for many years (2).

Nurses play a key role in conducting healthy nutritional programs in schools (10). Nurses can prevent childhood obesity by training children on healthy food choices (how to reduce calories and fat, sugar, and salt consumption, and how to increase fruit and vegetable consumption) at home, in school, and at other places (11). In Turkey, about 6 million students attended elementary school in the 2012–2013 school year (12). A very large number of these students attend government schools, yet in many of these schools, there are no nurses. Despite the efforts to prevent obesity in Turkey, attempts to promote health education via students' healthy dietary habits are insufficient, due to the lack of nurses in schools. Therefore, effective approaches to ensure healthy dietary habits in schools should be put into action urgently.

Peer-led training is defined as the education of young people by young people. After being trained by adults, peers can share health-related knowledge with each other by using social factors (13). Peer-led training has been found to increase knowledge, attitudes, and beliefs, and to promote health behaviors more than adult-led training (13, 14). Peer-led training has been used in the school environment for the following purposes: prevention of obesity (15), prevention of substance abuse (16), prevention of smoking (17), nutrition promotion (14, 18), and prevention of injuries (19). In schools lacking nurses, promoting students' healthy dietary habits through peer-led training should be considered as a method that will contribute to the promotion of public health. The purpose of this study was to evaluate the effects of diet education programs on Turkish primary schoolchildren's diet self-efficacy and diet behaviors, and to compare the effects of peer-led and adult-led diet education programs in this context.

METHODS

Design and Sample

In this study, a pre-test and post-test design was used. The participants in the study were fourth-grade children from an urban primary school within a large city in western Turkey during the fall of the 2013–2014 school year. Children who were randomly assigned to the adult-led group received a healthy diet curriculum delivered by researchers. Children randomly assigned to the peer-led group received a healthy diet curriculum delivered by their peers who were trained by researchers.

This study was reviewed and approved by the Dokuz Eylül University Ethical Committee. The verbal consent of both children and teachers was received. The children were informed about the aim and method of the study, and they were guaranteed that their identities and answers would be kept confidential.

Using G Power 3 and based on a large effect size (0.4), a power of 0.80 and a significance level of 0.05, the sample size was calculated as 25 per group. However, all students in a class were included in the group since it was a class health education. In the primary school where the study was conducted, via a simple random method, 1 fourth grade was selected as the peer-led diet education group (29 students in the class) and 1 fourth grade was selected as the adult-led diet education group (29 students in the class). However, 3 students in the peer-led diet education group and 4 students in the adult-led diet education group did not participate due to illness. Twenty-six students participated in the peer-led education, and 25 students participated in the adult-led education. In the end, 51 students participated in the study.

Procedure

First, before education about diet was delivered to the adult-led group of students, a pre-test was administered. After the researchers provided the necessary information to the students about the study's aim and details, pre-test data were obtained from the socio-demographic questionnaire, and Children's Dietary Self-Efficacy Scale (CDSS) and the Diet Behavior Scale (DBS) were collected in the classroom; data collection took only 20 minutes. After the pre-test, the adult-led diet education was completed. The post-test was administered to the adult-led group 2 weeks after their initial instructions. After the adult-led group's post-test was completed, pre-test data from the peer-led group were obtained with the same instruments, and then peer-led diet education was completed. The post-test was administered to the peer-led group after 2 weeks of teaching. The students filled in the CDSS and DBS to take the post-test. The tests were performed under the supervision of the researchers, and students were encouraged to complete the questionnaire unaided and in private.

Description of Intervention

The education program for adult-led group consisted of three 1-hour diet lessons (with 1 lesson hour in a school day) that were delivered using traditional educational methods. Researchers who are specialists in the field of public health nursing gave information regarding a healthy diet. Within the context of this information, researchers taught students about a healthy diet, food groups, principles of a healthy diet, the properties of foods, and healthy food choices. A brochure summarizing the contents of the teaching was handed out to students.

The students in the adult-led group gave peer-led diet education for 3 class hours (with 1 lesson hour in a school day) to the students in the peer-led group. During this teaching time, each peer educator was paired with a student in the peer-led group and used flashcards prepared in advance by the researchers. The flashcards summarized the principles of a healthy diet and healthy food choices. The teaching methods included questions and answers, discussion and expression. Throughout the peer-led education, the researchers did not interfere in the teaching process.

Measurements

The study questionnaire consisted of a socio-demographic questionnaire, a CDSS, and a DBS. The socio-demographic questionnaire included four items questioning the children's age, gender, and their parents' educational status.

Table 1. Distribution of the students' socio-demographic characteristics in the groups

	Adult-led group (n=25)		Peer-led group (n=26)			
Socio-demographic characteristics	**n**	**%**	**n**	**%**	χ^2	**ρ**
Age						
9	4	16.0	6	23.1	0.406	0.816
10	20	80.0	19	73.1		
11	1	4.0	1	3.8		
Gender						
Female	13	52.0	11	42.3	0.481	0.340
Male	12	48.0	15	57.7		
Mother's education						
Primary school	13	52.0	12	46.2	2.507	0.775
High school and above	12	48.0	14	53.8		
Father's education						
Primary school	14	56.0	14	53.8	7.480	0.187
High school and above	11	44.0	12	46.2		

Chi-square test

The CDSS developed by Edmundson et al. (20) Parcel et al. (21) was used in this study to measure the self-efficacy of the children's diet. This encourages children to prefer less fatty and less salty foods to fattier and saltier food options; the scale was translated into Turkish by Haney and Erdogan (4). It consisted of a total of 15 questions using a 3-point scale. The scale items included various foods and food groups with fat and salt content. The possible score range was from −15 to +15, and a higher total score suggested higher self-efficacy. The reliability of this instrument was expressed by Cronbach's alpha (α=0.77).

The DBS developed by Edmundson et al. (20) Parcel et al. (21) was used in this study to measure the children's usual food consumption; the scale was translated into Turkish by Haney and Erdogan (4). It consists of 14 pictorial items using a forced-choice format where a higher fat or higher sodium food was always paired with a lower-fat or lower-sodium food. The students marked the food they ate most often. The possible score range was from −14 to +14, and higher scores indicated healthy dietary habits. The reliability of this instrument in the study was expressed by KR-20, and it was 0.72.

Statistical Analysis

Descriptive statistics were used for the analysis of the data, while a chi-square test was used to evaluate the homogeneity of the groups. To compare the pre-test and post-test scores of the all students, a paired sample t-test was performed. To compare the pre-test and post-test scores of the intervention and control groups, a Mann–Whitney U test was used. Pre- and post-training scores of both groups were compared with a Wilcoxon test. A Multivariate Analysis of Variance (MANOVA) was used on the pre-test/post-test scores relative to CDSS and DBS to assess differences among the groups. The study data were analyzed using Statistical Package for the Social Sciences Version 15 (SPSS Inc.; version 15.0, Chicago, IL, USA), and the statistical significance was defined as p<0.05.

Table 2. Dietary scores of students (n=51)

	Median	**Mean±SD**	**ρ**
CDSS			
Pre-test	6.00	5.84±5.36	0.166
Post-test	8.00	7.01±5.83	
DBS			
Pre-test	6.00	4.27±6.09	0.016*
Post-test	8.00	6.03±6.16	

*a paired sample t-test: p<0.05

CDSS: Dietary Self-Efficacy Scale; DBS: Diet Behavior Scale ; SD: standard deviation

RESULTS

Table 1 shows the socio-demographic characteristics of the students who participated in the study. The chi-square analysis conducted to ensure homogeneity between the groups revealed that the socio-demographic characteristics of the students in the peer-led and adult-led groups were similar.

The mean pre-test and post-test dietary self-efficacy scores and diet behavior scores of all students are shown in Table 2. No significant difference was found between the pre-test and post-test dietary self-efficacy scores of the students (p=0.166). It was determined that there was a statistically significant difference between the mean pre-test and post-test diet behavior scores (p=0.016).

A comparison of the dietary self-efficacy scores and diet behavior scores of the students according to their groups is presented in

Table 3. No significant difference was found between the groups according to the pre-test diet scores (p=0.117, p=0.465). After education, the mean post-test diet scores between the groups were not statistically significant either (p=0.473, p=0.909). This finding indicated no intergroup difference before and after education. According to the intragroup comparisons, there was a significant difference between pre-test and post-test diet scores of the adult-led group (p=0.044 and 0.014, respectively). No significant difference was found between the pre-test and post-test diet scores of the peer-led group (p=0.914, p=0.333, respectively).

Table 4 shows results of the MANOVA test used to determine if students' pre-test and post-test scores on dietary self-efficacy and dietary behavior were significantly different between the peer-led and adult-led groups. The results indicated no significant differences between the groups in dietary self-efficacy (Wilks' lambda λ=0.900; F=2.676; p>0.05) and dietary behavior (Wilks' lambda λ=0.943; F=1.438; p>0.05) at both pre-test and post-test.

DISCUSSION

The study's findings revealed there was no difference between the peer-led diet education group and the adult-led diet education group in terms of pre-education self-efficacy and behavior scores. For both groups, the students' diet self-efficacy scores ranged between −6 and +15 (the total possible score that could be obtained from the scale is between −15 and +15). This confirmed students should be encouraged so they could maintain healthy dietary habits. Similarly, the students' dietary behavior scores ranging between −10 and +14 (the total possible score that could be obtained from the scale is between −14 and +14) indicated the students were at a greater risk from unhealthy dietary habits and had a tendency to consume foods rich in fat and salt.

Table 3. Comparison of the mean dietary scores between groups, and within groups

	Adult-led group (n=25) Mean±SD	Peer-led group (n=26) Mean±SD	p
CDSS			
Pre-test	4.60±5.65	7.03±4.87	0.117
Post-test	7.64±5.76	6.42±5.94	0.473
p	0.044*	0.914	
DBS			
Pre-test	3.04±7.28	5.46±4.50	0.465
Post-test	5.84±6.90	6.23±5.49	0.909
p	0.014*	0.333	

* Wilcoxon test, p<0.05; Mann-Whitney U test
CDSS: Dietary Self-Efficacy Scale; DBS: Diet Behavior Scale; SD: standard deviation

After the education, there was a partial improvement in the adult-led group's scores, but the MANOVA test results evidenced this development as not expressive between the groups. This result showed adult-led diet education could increase the children's healthy diet self-efficacy and help them to develop favorable behavioral changes in a short time. As stated in previous studies, adult-led, school-based diet education had a positive impact on children's diet self-efficacy and behaviors (22, 23).

Planned and continuous health education, organized in accordance with the needs of society, plays an active role in people's health-related knowledge and behaviors. Elementary school age is an ideal time to provide planned and continuous health education. This is because at this age, children are eager to learn new things, their learning ability is great, and they believe what they learn at school is true (24). It is easier to train school-age children and encourage them to acquire healthy lifestyle habits, before they gain unhealthy habits. Planned and continuous health education programs, prepared in accordance with the age and needs of children, become etched in their memory. These programs also enable them to acquire positive lifelong habits. Children not only acquire these habits, but also transfer them to their families, peers, or other people around them (25).

The findings of this study revealed there were no improvements in diet self-efficacy and the behaviors of the peer-led diet education group. Peer-led education is an effective method in providing health education for children and encouraging them to change their health behaviors (26). This is because peers can share their health-related knowledge informally using social factors (13). Previous studies indicate peer leaders, students, and teachers consider peer-led interventions as feasible and highly acceptable, and they can be used to promote children's health-related knowledge, attitudes, and behaviors (15, 27). In addition, in their critical review study, Mellanby et al. (13) reported peer-led interventions were more effective than adult-led interventions, but they also added this was not thoroughly proven due to the analytical and methodological problems related to the studies. Another study supporting these results stated teachers provided more information than peer educators in school-based sex education program (28).

In our study, there were no significant improvements in the diet scores of the peer-led group, which is in line with the findings of another study conducted in Turkey (29). In that study, which investigated the effectiveness of peer-led nutritional education

Table 4. Multivariate tests-MANOVA pre-test/post-test scores for the CDSS and DBS

Group		Value	F	Hypothesis df	Error df	p	η^2
CDSS	Wilks' Lambda	0.900	2.676	2.000	48.000	0.079	0.100
DBS	Wilks' Lambda	0.943	1.438	2.000	48.000	0.247	0.57

MANOVA: Multivariate Analysis of Variance; CDSS: Dietary Self-Efficacy Scale; DBS: Diet Behavior Scale

among preschool children, the researcher stated dietary attitudes improved more in the adult-led education group than in the peer-led education group. This result was explained by the fact that the students were trained by the teacher, and strengthened the knowledge they acquired because they had the opportunity to practice that knowledge and transfer it to others. In our study, the adult-led group of students received more formal education from the researchers experienced in their fields. They transferred knowledge to their peers and thus had the opportunity to strengthen their knowledge. On the other hand, the education that the peer-led group students received from their peers was more informal, and they did not have any opportunity to transfer their knowledge to another group; that there was no improvement in their scores was related to this fact.

The findings of the present study indicated no difference between the peer-led and adult-led groups' dietary scores. This finding confirmed that although adult-led education seems more effective, the effects of adult-led and peer-led educational methods on the improvement of school-age children's diet self-efficacy and behaviors were not different. Thus, it was concluded that peer-led dietary education could be used as an alternative approach in future school-based health education interventions, even though it did not lead to any changes in the children's diet self-efficacy and behaviors in this study. This result supported the findings of other studies in which peer-led education was implemented to prevent school injuries and to improve students' oral health behaviors (19, 30).

Although the study enabled us to obtain some useful data, it had some limitations. First, due to the relatively small sample size of the study, the data cannot be generalized to other schoolchildren. Second, in order not to take too much time from the students' formal education, the duration of the diet education program was kept short; therefore, it did not give any clues to long-term, peer-led dietary programs. Third, the children may not have given truthful answers, but the desired answers; thus, their answers are susceptible to response bias.

CONCLUSION

This study indicated that differences between adult-led and peer-led dietary education programs were not significant. This result provided an important tip that the use of an integrated training approach containing both adult-led and peer-led education can be more effective. Nurses can promote health education in the community by establishing a peer education network in schools, particularly in countries such as Turkey, where the number of nurses in schools is limited and where the peer-led education method can be used as an alternative approach in preventing childhood obesity and encouraging children to acquire healthy dietary habits. Thus, this will allow nurses sufficient time to focus on other roles such as caregiving, researching, coordinating, performing early diagnoses and referrals, liaising, creating a healthy school environment and promoting health policy, in addition to their health educator role. We recommend nurses and other health professionals, working in the field of school health, investigate the effects of peer-led education interventions on children's dietary habits in future studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University.

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.Ö.H.; Design - M.Ö.H.; Supervision - M.Ö.H., A.Y.; Resource -M.Ö.H., A.Y.; Materials - M.Ö.H., A.Y.; Data Collection and/or Processing - M.Ö.H., A.Y.; Analysis and/or Interpretation - M.Ö.H.; Literature Search - M.Ö.H., A.Y.; Writing - M.Ö.H.; Critical Reviews - M.Ö.H.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Dokuz Eylül Üniversitesi Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Sözlü hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - M.Ö.H.; Tasarım - M.Ö.H.; Denetleme - M.Ö.H., A.Y.; Kaynaklar - M.Ö.H., A.Y.; Malzemeler - M.Ö.H., A.Y.; Veri Toplanması ve/veya İşlemesi - M.Ö.H., A.Y.; Analiz ve/veya Yorum - M.Ö.H.; Literatür Taraması - M.Ö.H., A.Y.; Yazıyı Yazan - M.Ö.H.; Eleştirel İnceleme - M.Ö.H.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Öztürk Haney M, Yeşiltepe A. Comparing peer–led and adult–led education to promote a healthy diet among Turk–ish schoolchildren. Eur J Ther 2017; 23: 146–51.

European Journal of Therapeutics

DOI: 10.5152/EurJTher.2017.139

Original Investigation / Özgün Araştırma

Effects of pulsed electromagnetic fields on lipid peroxidation and antioxidant levels in blood and liver of diabetic rats

Pulslu elektromanyetik alanın diyabetik ratlarda kan ve karaciğerde antioksidan düzeylerine ve lipid peroksidasyonuna etkileri

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ABSTRACT

Objective: The present study investigated the protective effects of a pulsed electromagnetic field (PEMF) in a rat model of diabetes by analyzing oxidative/nitrosative stress parameters.

Methods: Rats were randomly divided into four groups of eight each: a control group, a sham PEMF group, a diabetes group, and a diabetes+PEMF group. Diabetes was induced in the sham PEMF, diabetes, and diabetes+PEMF groups by treatment with 50 mg/kg streptozotocin (STZ). Rats in the sham PEMF group were treated identically, without running the instrument. Following the development of diabetes, rats in the diabetes+PEMF group were treated with PEMF for 60 min/day for 4 weeks.

Results: Levels of oxidants, such as malondialdehyde (MDA), nitric oxide (NO), and myeloperoxidase (MPO), and antioxidants, such as superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT), were measured in blood and liver tissue samples. MPO, MDA, and NO levels were significantly higher, and SOD levels significantly lower, in the sham PEMF and diabetes groups than in the control group ($p<0.05$ each), whereas the levels of all these four (i.e.: MPO, MDA, NO, and SOD) in the diabetes+PEMF group were close to those in the control group. GSH levels were significantly lower in the sham PEMF, diabetes, and diabetes+PEMF groups than in the control group ($p<0.05$ each), whereas CAT levels were similar in all the four groups.

Conclusion: Results indicate that PEMF affects MDA, NO, MPO, SOD, and GSH levels and regulates diabetes-associated damage by reducing oxidative stress and increasing the levels of antioxidants. PEMF may be a non-invasive treatment option for diabetes and associated complications.

Keywords: Antioxidants, diabetes, free radicals, oxidative stress, pulsed electromagnetic fields

ÖZ

Amaç: Deneysel diyabet modelinde pulslu elektromanyetik alanın (PEMA) koruyucu etkileri oksidatif/ nitrozatif stres parametreleriyle incelenmiştir.

Yöntemler: Deney protokolüne uygun olarak, sıçanlar rastgele kontrol (K; n=8), sham (SPEMA; n=8), diyabet (D; n=8), diyabet+-PEMA (D+PEMA; n=8) olmak üzere toplam 4 gruba bölünmüştür. SPEMA, D, ve D+PEMA gruplarında 50 mg/kg STZ uygulanarak diyabet oluşturulmuştur. PEMA'nın etkisini araştırmak amacıyla SPEMA grubuna aynı çevre koşulları altında cihaz çalıştırılmadan uygulama yapılmıştır. PEMA uygulaması diyabet tanısı konduktan sonra başlayıp günlük 60 dakika olmak üzere 4 hafta D+PEMA grubuna uygulanmıştır.

Bulgular: Elde edilen kandan ve karaciğer dokusundan antioksidan parametrelerden Glutatyon (GSH), Süperoksit Dismutaz (SOD), Katalaz (CAT) oksidan parametrelerden Nitrik Oksit (NO), Malondialdehid (MDA), Miyeloperoksizdaz (MPO) seviyeleri incelenmiştir. K grubuna göre SPEMA ve D gruplarında MPO, MDA ve NO seviyelerindeki artma ile SOD seviyelerindeki azalma istatistiksel olarak anlamlı bulunmuştur ($p<0,05$). D+PEMA grubunda MPO, MDA, SOD ve NO seviyelerinin K grubu seviyesine yaklaştığı saptandı. GSH seviyesinin kontrol grubuna göre SPEMA, D ve D+PEMA grubunda düştüğü görüldü ($p<0,05$).

Sonuç: Pulslu elektromanyetik alanın (PEMA) MDA, NO, MPO, SOD ve GSH parametrelerinde etkin olduğunu ve diyabete bağlı hasarda düzenleyici rolünü oksidatif stresi azaltıp antioksidanların artışını destekleyerek ortaya çıkardığını düşünmekteyiz. Çalışmamızın PEMA'nın, diyabet ve komplikasyonlarına yönelik non-invaziv bir tedavi seçeneği olarak daha kapsamlı araştırmalara katkıda bulunacağını umuyoruz.

Anahtar kelimeler: Antioksidanlar, diyabet, serbest radikaller, oksidatif stress, pulslu elektromanyetik alan

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Received/Geliş Tarihi: 08.09.2017 • **Accepted/Kabul Tarihi:** 11.09.2017

INTRODUCTION

Levels of antioxidants in individuals with diabetes increase initially as a response to increases in reactive oxygen species (ROS) and later decrease due to reactions between free radicals and antioxidants. As the disease progresses, antioxidant mechanisms can be damaged in parallel to tissue damage, reducing antioxidant levels. Generalization should be avoided, however, due to increases in vitamin E levels due to hyperlipidemia and increases in ferritin levels due to of inflammation (1).

The effects of antioxidants in organs are dependent on tissue physiology. Enzymatic antioxidants are more effective within cells, whereas non-enzymatic antioxidants have a greater effect in the extracellular environment. Vitamin E, β-carotene, and coenzyme-Q have effects on cell membranes (2).

Under normal conditions, the physiological levels and reactivity of free oxygen radicals are finely balanced by detoxification mechanisms, especially by antioxidant defense systems. Recent studies on oxidant–antioxidant equilibria have focused on the enzyme superoxide dismutase (SOD), which represents the first step in the reactions of catalase (CAT). Lipid peroxidation is measured most frequently using the malondialdehyde assays (MDA-TBARS) reaction and by measuring the levels of the oxidative stress marker nitric oxide (NO) and the inflammation marker myeloperoxidase (MPO) (3). CAT activity is high in the liver and kidneys but is much lower in connective tissues. CAT catalytically detoxifies H_2O_2 by converting it into water and molecular oxygen (4). Glutathione (GSH), a tripeptide consisting of glutamic acid, cysteine, and glycine, is a major intracellular antioxidant due to the thiol group on the cysteine residue. GSH directly interacts with superoxide, hydroxyl radicals, and hydrogen peroxide, keeping-SH groups in proteins in a reduced state (5). GSH constitutes the first defense system within the cell, as it leads to the dismutation of superoxide radicals. It also prevents lipid peroxidation and atherosclerosis development (6). MPO, an enzyme derived from neutrophils, plays a role in the pathogenesis of atherosclerosis by oxidizing apolipoproteins and making high-density lipoprotein (HDL) pathogenic (7). Lipid peroxidation primarily affects the cell membrane, as well as damaging other cellular components via the production of reactive aldehydes. The concentration of malondialdehyde (MDA), which is produced byperoxidation of polyunsaturated fatty acids, shows a good correlation with the degree of lipid peroxidation (8).

Diabetes is a condition that is both caused by and results in oxidative stress. The pathogenesis and clinical manifestations of diabetes are heterogeneous. This chronic condition is characterized by a lack of insulin secretion from pancreatic beta cells, resulting in hyperglycemia due to insulin resistance or dysregulated insulin secretion and affecting carbohydrate, lipid, and protein metabolism. Oxidative stress in diabetes starts with increased intracellular and extracellular glucose levels and increases with glucose auto-oxidation, protein glycosylation, and formation of glycosylation end-products, which in turn lead to complications (6).

The effects of static and pulsed electromagnetic fields (PEMF) in the treatment of chronic pain and other biological problems have not yet been determined precisely. Nevertheless, electromagnetic field therapy has been shown to be effective in the treatment of rheumatic diseases, delayed union fractures, and ischemic disorders of the lower extremities. Moreover, electromagnetic field therapy has shown promising effects in multiple sclerosis, peripheral facial paralysis, craniofacial pain, spasticity, and degenerative diseases of the retina (9), as well as having positive effects on blood glucose and calcium levels, the latter of which affects insulin secretion in diabetes (10). Low-frequency PEMF application had significant benefits in the treatment of resistant peripheral neuropathic pain, as well as reductions in subjective symptoms, and increases in nerve conduction functions and quality of life (11).

This study evaluated the antioxidant effects of PEMF in a rat model of streptozotocin (STZ) induced diabetes by analyzing the oxidants, NO and MPO, and the antioxidants, CAT, SOD, GSH, and thiol-SH, in blood and tissue samples.

METHODS

The study protocol was approved by the Experimental Animals Ethics Committee of the Gaziantep University School of Medicine (number 28.05.2012/18).

Animals

Thirty-two male Wistar rats, mean weight 200±50 g (range, 180-220 g), were maintained at 21°C±2°C, 55%-60% humidity, and 12: 12 dark: light cycles. The animals were fed standard rat chow, and any rat in poor health condition was excluded from the study.

Groups

Following an adaptation period, the rats were randomly divided into four groups of eight each: a control group, a sham PEMF group, a diabetes group, and a diabetes+PEMF group. Diabetes was induced by intraperitoneal injection of a single dose of 50 mg/kg STZ (2-deoxy-2-([(methylnitrosoamino)carbonyl]amino)-D-glucopyranose; Sigma 308-5003) dissolved in citrate buffer (pH 4.5). Animals in the control group were intraperitoneally injected with 0.09% NaCl solution. Seventy-two hours after STZ treatment, blood samples were collected from the tail of each rat, and blood glucose levels were measured. Concentrations over 300 mg/dl were considered diabetic.

Exposure System

PEMF application was performed at the Gaziantep University Medical Faculty Biophysics Laboratory. PEMF was obtained from a Helmholtz coil pair (İlfa; Adana, Turkey), fed with a power supply that could be programmed with an internal PIC-16F877A microprocessor. This power supply was developed for application of PEMF at various frequencies (0-100 Hz), amplitudes (0-10 mT), and durations (0-2500 μs). The PEMF instrument consisted of two parallel 60-cm Helmholtz bobbins placed 30 cm apart.

Helmholtz bobbins were placed in a 90´90´50 cm^3 Faraday cage to prevent any potential effects of EMF from the surrounding environment. A 30´30´25 cm^3 Plexiglas box was placed in the middle of the straight magnetic field, which was created be-

Figure 1. The average GSH levels in experimental and control groups (mean±SD)
GSH: glutathione; SD: standard deviation

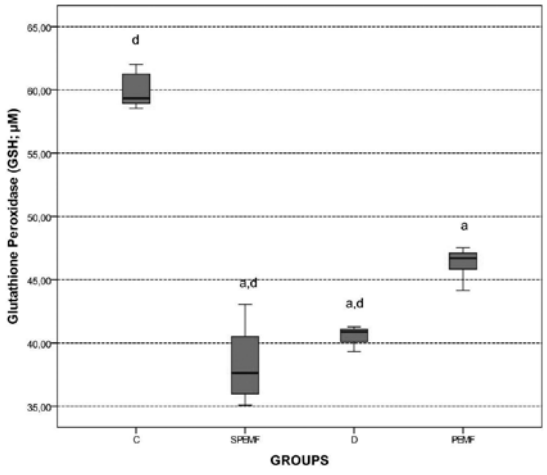
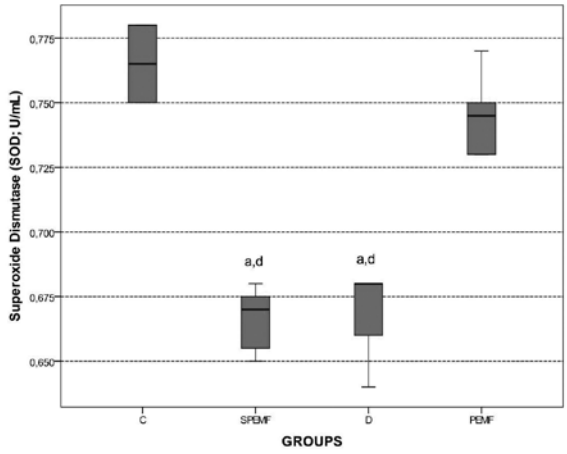


Figure 2. The average SOD levels in experimental and control groups (mean±SD)
SOD: superoxide dismutase; SD: standard deviation



tween the upright coils. During each application, a maximum of eight rats were placed in the PEMF system at the same time. To keep other animals from the magnetic field, a 3´2 m^2 grounded sheet of metal was used. The bobbins were connected to the programmed power supply, and magnetic field application was performed automatically. Prior to each application, a hall-effect probe-bound Teslameter (Sypris Model 6010; F.W. Bell, Orlando, FL, USA) was used to control the strength of the magnetic field between the coils (preferably 1.5 mT). Temperature was maintained at 21°±2°C with an air conditioner.

All treatments were performed during the same time period (9:00-11:00), and all animals were exposed to the same environmental conditions. Rats in the sham PEMF group were treated identically to those exposed to PEMF but without running the instrument.

The eight rats in the diabetes+PEMF group were placed in the PEMF system after confirmation of diabetes (glucose > 300 mg/dL). The rats were exposed to PEMF by applying a consecutive pulse train at four different frequencies (1, 10, 20, and 40 Hz) in three series. The transition period of each pulse train was four minutes, followed by one minute of rest. Each series was performed for 20 min, for a total of 60 min/day. Times were controlled using a digital timer. PEMF applications lasted for 4 weeks.

Biochemical Measurements

At the end of the experiment, the rats were anesthetized by the intraperitoneal injection of a mixture of 50 mg/kg ketamine-HCl (Ketalar) and 10 mg/kg xylazine-HCl (Rompun) and sacrificed by decapitation. All dissections were performed under sterile conditions. Half of each liver tissue sample was stored in 10% neutral-buffered formalin for pathological examination, and the rest at -85°C for biochemical assays.

Blood samples were transferred into anticoagulant-free tubes, incubated at room temperature for 30 min, and centrifuged at 1000 ´ g at 4°C for 10 min to obtain serum samples, which were stored at -85°C. Blood samples in heparin-containing tubes were also centrifuged at 1000´ g at 4°C for 10 min. Plasma samples were separated, and erythrocyte bags were prepared, aliquoted, and stored at –85°C until analysis.

Measurements of NO, MPO, MDA, GSH, CAT, and SOD

NO levels were measured using nitrate/nitrite colorimetric assay kits (Cayman, #780001), with results expressed as micromoles. MPO was measured by ELISA (Immunodiagnosis, #REF K 6631B), with results expressed as ng/mL. MDA (Cayman, #10009055), GSH (Cayman, #703002), and CAT (Cayman, #707002) levels were also measured colorimetrically, with results expressed as micromoles. SOD levels were also measured colorimetrically (Cayman #706002), with results expressed as U/mL.

Statistical Analysis

Statistical Package for the Social Sciences statistical software (SPSS version 17, 2009, SPSS Inc.; Chicago, IL, USA) was used for data analysis. One-way ANOVA test was used to determine the significance levels among the groups.

RESULTS

Glutathione levels were significantly lower in the sham PEMF, diabetes, and diabetes+PEMF groups than in the control group ($p<0.001$), but the decreases in the sham PEMF and diabetes groups were greater. There was no significant difference between these two groups (Figure 1). Mean SOD level was significantly and equally lower in the sham PEMF and diabetes groups than in the control group ($p<0.001$) but was as high in the diabetes+PEMF group as in the control group (Figure 2). CAT levels were similar in the four groups (Figure 3). Similar to SOD, NO levels were significantly and equally higher in the sham PEMF and diabetes groups than in the control group C ($p<0.01$) but were similar in the diabetes+PEMF and control groups (Figure 4). MDA levels were also significantly and equally higher in the sham PEMF and diabetes groups than in the control group C ($p<0.001$) but were similar in the diabetes+PEMF and control groups (Figure 5). Compared with the

Figure 3. The average CAT levels in experimental and control groups (mean±SD)
CAT: catalase; SD: standard deviation

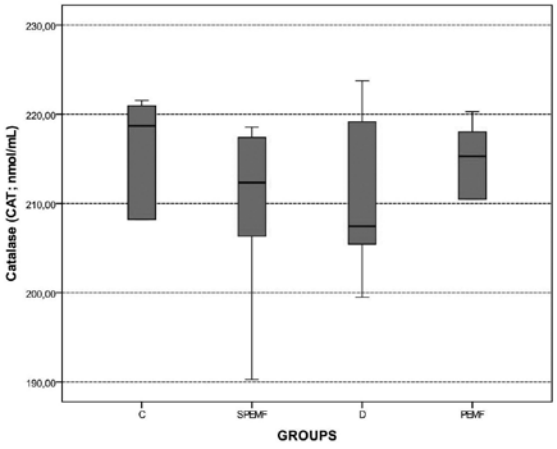


Figure 4. The average NO levels in experimental and control groups (mean±SD)
NO: nitric oxide; SD: standard deviation

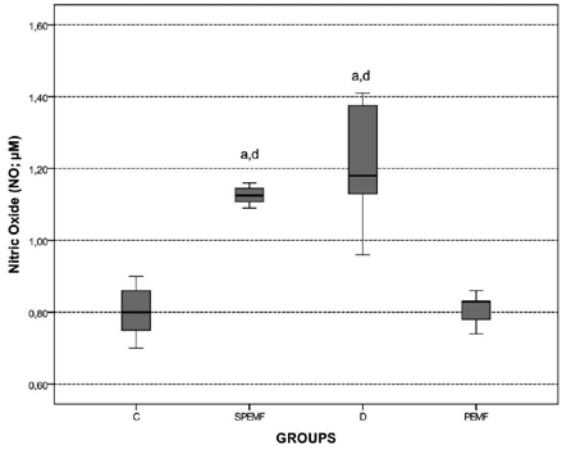


Figure 5. The average MDA levels in experimental and control groups (mean±SD)
MDA: malondialdehyde; SD: standard deviation

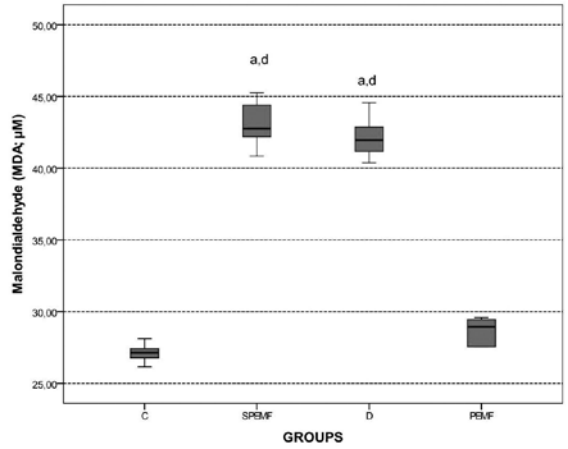
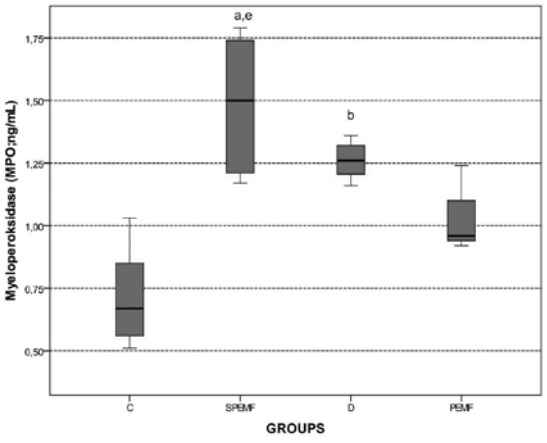


Figure 6. The average MPO levels in experimental and control groups (mean±SD)
MPO: myeloperoxidase; SD: standard deviation



control group, MPO levels were significantly higher in the sham PEMF ($p<0.001$) and diabetes ($p<0.01$) groups but were similar in the diabetes+PEMF and control groups. MPO levels did not differ significantly in the diabetes and diabetes+PEMF groups but differed significantly in the sham PEMF and diabetes+PEMF groups (Figure 6) (Table 1).

DISCUSSION

Magnetic field treatment has been shown to be successful in patients with non-union fractures, osteoporosis, tendinitis, chronic ulcers, and musculoskeletal disorders, due to its effects on mineralization, collagen formation, and endochrondral ossification, as well as its non-invasive nature and low cost. Moreover, it has been shown effective in stroke, insomnia, depression, bowel diseases, diabetes, and circulation disorders. Magnetic field treatment has shown positive effects in patients with diabetes, by affecting levels of blood glucose and calcium, the latter of which affects insulin secretion. In addition, magnetic field treatment can affect angiogenesis, neuronal protein synthesis, synaptic neurotransmitters, and axoplasmic transport, resulting in positive outcomes in patients with diabetic neuropathy (11, 12).

Culture of insulin-secreting beta cells in a 60 Hz–5 mT magnetic field resulted in increased cell numbers and insulin secretion, suggesting a possibility for transplantation of beta cells (13). PEMF involving a pulse train of 1, 10, 20, 40 Hz, and 1.5 mT in rats with STZ-induced diabetes had no effect on reduced body weight due to STZ but reduced blood glucose levels (14). Assessment of the effects of exposure of rats to 10-Hz square waves (1.8-3.8 mT) or 40 Hz sinusoidal (1.3-2.7 mT) magnetic fields on pancreatic structure and function showed that, after application for 14 days, glucose concentrations decreased in both groups, whereas insulin concentrations increased. However, long-term

Table 1. NO, MPO, CAT, GSH, SOD, and MDA levels in the four experimental groups of rats (mean±SD)

	Control group	Sham PEMF group	Diabetes group	Diabetes+ PEMF group
NO	0.8±0.081	1.13±0.027[a,d]	1.19±0.18[a,d]	0.81±0.05
MPO	0.72±0.22	1.47±0.28[a,e]	1.26±0.07[b]	1.03±0.14
CAT	217.62±5.54	207.55±11.94	210.65±10.38	215.87±3.67
GSH	60.02±1,53[d]	38.12±2.98[a,d]	40.53±0.82[a,d]	46.26±1.34[a]
SOD	0.76±0.013	0.67±0.01[a,d]	0.66±0.09[a,d]	0.75±0.015
MDA	27.1±0.73	42.8±1.72[a,d]	42.52±1.54[a,d]	28.9±0.81

All results reported as mean±SD.
PEMF: Pulsed Electromagnetic Field; NO: nitric oxide; MPO: myeloperoxidase; CAT: catalase; GSH: Glutathione; SOD: superoxide dismutase; MDA: Malondialdehyde
[a]p<0.001, [b]p<0.01, [c]p<0.05 compared with the control group.
[d]p< 0.001, [e]p<0.01, [f]p<0.05 compared with the diabetes+PEMF group

exposure can lead to adaptive changes in hormone levels. This mechanism may be responsible, at least in part, for the effect of magnetic fields on calcium ions in beta cells. Changes were greater, and reversibility lower, with square than with sinusoidal waves (15). A comparison of 10 Hz and 100 Hz PEMF soon after *diabetic* peripheral neuropathy treatment showed that the lower frequency was more effective (16). Low-frequency PEMF was effective in treating resistant peripheral neuropathic pain, as well as in reducing subjective symptoms, increasing nerve conduction, and enhancing quality of life (17).

Although studies have examined the effects of low-frequency PEMF on diabetes and its associated complications, as well as on other diseases, the present work investigated the effects of PEMF on oxidative stress and antioxidant mechanisms in diabetes. Similar to a study showing that PEMF using a pulse train (1,10, 20, 40 Hz, and1.5 mT) had no effect on reduced body weight due to STZ, but did reduce blood glucose levels (10), our study found that PEMF had no effect on decreased body weight due to STZ administration.

Certain diseases, such as diabetes, have been linked to increased NO production (18). In diabetes, glycosylated proteins donate electrons to oxygen in the presence of Cu and Fe, generating ROS, inactivating enzymes, and increasing the activation of transcription factor nuclear factor kappa B (NF-κB), thus enhancing NO levels. Increases in superoxide (O_2^-) radicals and NO lead to the formation of the more reactive peroxynitrite radical (6). We found that mean NO levels were significantly higher in sham PEMF and diabetic rats than in control rats C (p<0.01) but were significantly lower in diabetes+PEMF rats than in diabetic rats.

Superoxide dismutase activity in diabetes has been shown to decrease (19), remain unchanged (20), and even increase (21). Increased O_2 production leads to an initial increase in SOD activity, whereas glycosylation of the enzyme and/or hydrogen peroxide (H_2O_2) accumulation decreases SOD activity. SOD activity was found to be lower due to increased lipid peroxidation in types 1 and 2 diabetes than in controls (22). This study found that SOD activity was significantly lower in diabetic and sham PEMF-treated than in control rats (p<0.001).

Biochemical changes in patients with diabetes were assessed by comparing MDA, SOD, CAT, NO, and GSH levels. Compared with controls, SOD and CAT activities were reduced, MDA and NO levels were increased, and GSH levels significantly reduced in diabetic patients. Oxidative stress plays a major role in protein glycosylation in diabetes and in the formation of advanced glycosylation end-products (23). Hyperglycemia was shown to increase oxidative stress, with the inequilibrium between antioxidants and oxidants increasing lipid peroxidation, leading to diabetic complications (24). An assessment of 40 female and 40 male patients with diabetes showed that MDA levels were increased and GSH levels reduced. We found that MDA levels were significantly higher in sham PEMF-treated and diabetic rats than in control rats (p<0.001) but were similar in the sham PEMF and diabetic groups.

The liver and kidneys are exposed to various endogenous and exogenous oxidants, increasing oxidative stress. Administration of carbon tetrachloride (CCl4) to mice enhanced MDA and MPO levels in liver and kidney tissues while reducing GSH-Px and CAT activities (25). In contrast, vitamin C and/or N-acetylcysteine (NAC) reduced oxidative damage in the liver and kidneys, whereas melatonin and NAC treatment increased antioxidant enzyme levels. MPO is derived from neutrophils and plays a role in the pathogenesis of atherosclerosis. MPO exerts its effects by oxidizing apolipoproteins and has been shown to add nitrate to the main lipoprotein of HDL, Apo-A1, making HDL proatherogenic. MPO levels have been associated with the risk of coronary artery disease (CAD) (7). Generally, MPO levels are increased in patients with diabetes and its complications. We found that, compared with control rats, MPO activity was significantly higher in sham PEMF-treated (p<0.001) and diabetic (p<0.01) rats but was similar in control and diabetes+PEMF-treated rats. Moreover, MPO levels did not differ significantly in diabetic- and diabetes+PEMF-treated rats but did differ significantly in diabetes+PEMF and sham PEMF-treated animals (p<0.05).

Glutathione plays a role in antioxidant defense, decreasing in the presence of oxidants and delaying wound healing (26). Studies on patients with diabetes have shown a decrease in erythrocyte GSH levels and increased erythrocyte lipid peroxidation. Hepatic GSH levels were normal or mildly decreased, whereas GSH peroxidase activity was lower (27). Similarly, we found that GSH levels were lower in sham PEMF–treated and diabetic rats than in control rats (p<0.001).

Catalase activity is high in liver and kidneys but considerably lower in connective tissues. In addition, higher CAT activity has been reported in diabetic kidneys due to a protective mechanism (28). However, kidney CAT activity was found to be lower in an STZ-induced experimental diabetes model than in control an-

imals (29). We found that CAT activity in liver homogenates was somewhat lower in diabetic- and sham PEMF-treated rats than in control rats, but the differences were not statistically significant.

Superoxide dismutase, CAT, and GSH-Px levels have been found to be lower and MDA levels higher in inflamed than in non-inflamed tissues. However, PEMF treatment was found to enhance SOD, CAT, and GSH-Px activities and reduced MDA levels (30). Similarly, we found that MDA and SOD levels were higher in STZ-treated diabetic rats but were reduced in these rats by PEMF treatment ($p<0.001$). In contrast, GSH levels were significantly lower in diabetic-, sham PEMF-, and diabetes+PEMF-treated rats than in control rats ($p<0.001$), whereas CAT levels were similar in the four groups.

CONCLUSION

In conclusion, this study investigated the antioxidant effects of PEMF in a rat model of diabetes. PEMF altered the levels of MDA, NO, MPO, SOD, and GSH, suggesting that it regulates diabetes-associated damage. PEMF exerts these effects by reducing oxidative stress and increasing antioxidant levels. These findings suggest that PEMF may become a widespread non-invasive treatment option for diabetes and its complications.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University Animal Experiments Local Ethics Committee.
Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.G., C.D.; Design - H.G., C.D.; Supervision - Can Demirel; Resource - H.G., C.D.; Materials - H.G., C.D.; Data Collection and/or Processing - H.G., C.D., M.A., M.T.; Analysis and/or Interpretation - H.G., C.D., M.A., M.T.; Literature Search - H.G., C.D.; Writing - H.G., C.D.; Critical Reviews - C.D.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Gaziantep Üniversitesi Hayvan Deneyleri Yerel Etik Kurulu'ndan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - H.G., C.D.; Tasarım - H.G., C.D.; Denetleme - C.D.; Kaynaklar - H.G., C.D.; Malzemeler - H.G., C.D.; Veri Toplanması ve/veya İşlemesi - H.G., C.D., M.A., M.T.; Analiz ve/veya Yorum - H.G., C.D., M.A., M.T.; Literatür Taraması - H.G., C.D.; Yazıyı Yazan - H.G., C.D.; Eleştirel İnceleme - C.D.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Gözen H, Demirel C, Akan M, Tarakçıoğlu M. Effects of pulsed electromagnetic fields on lipid peroxidation and antioxidant levels in blood and liver of diabetic rats. Eur J Ther 2017; 23: 152–8.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.207

Original Investigation / Özgün Araştırma

Effect of intravenous nitrate treatment on serum BNP level and 30-day follow-up events in decompensated systolic heart failure

Dekompanze sistolik kalp yetmezlikli hastalarda intravenöz nitrat tedavisinin serum BNP seviyesi ve 30 günlük takip olayları üzerine etkisi

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ABSTRACT

Objective: The aim of this study was to evaluate the potential of intravenous (IV) nitroglycerine (NTG) administration to accelerate the reduction of B-type natriuretic peptide (BNP) levels in patients with decompensated systolic heart failure (HF) and to evaluate its impact on follow-up events.

Methods: A total of 165 patients with systolic HF who were hospitalized due to acute decompensation were enrolled into the current study. Study patients were divided into two groups. Patients who were receiving standard HF therapy (angiotensin-converting enzyme [ACE] or angiotensin receptor blocker [ARB], beta-blockers, loop diuretics, and anticoagulant or anti-aggregant agents for venous prophylaxis) were categorized as the standard HF therapy group (n=72), and patients receiving a standard dose of IV NTG in addition to standard HF therapy were categorized as the IV NTG group (n=93). BNP levels and blood gas analyses were measured at admission and after 48 h; all patients were followed up along the first month after discharge.

Results: Serum BNP levels decreased in all patients after 48 h. The decreasing of BNP level was higher and the improvement of blood gas analysis was better in the IV NTG group than in the standard therapy group (1347.1±314.3 vs. 280.0±196.2 pg/mL for the IV NTG group and 1178.3±305.5 vs. 495.4±229.9 pg/mL for the standard therapy group; p<0.001). In the multi-logistic regression analysis, serum sodium at admission, BNP level at 48 h, and use of IV NTG were found as predictors of 30-day follow-up events.

Conclusion: We have shown that IV NTG therapy in addition to standard HF therapy has a markedly better effect on lowering of plasma BNP levels, improves blood gas analyses, and may reduce follow-up events in patients with systolic HF.

Keywords: Intravenous nitrate, systolic heart failure, B-type natriuretic peptide

ÖZ

Amaç: Bu çalışmanın amacı intravenöz (IV) Nitrogliserin (NTG) tedavisinin akut dekompanze kalp yetmezlikli hastalarda B- tipi natriuretik peptid (BNP) seviyesinde azalma hızına ve takip olayları üzerine etkilerini incelemektir.

Yöntemler: Çalışmaya akut dekompanze kalp yetmezliği semptomları ile başvuran toplam 165 sistolik kalp yetmezlikli hasta alındı. Hastalar 2 gruba ayrıldı. Standart tedavi (ACE veya ARB, beta-bloker, loop diuretiği ve venöz profilaksi için antikoagülan veya anti-agregan ajan) alan grup (72 hasta) ve standard tedaviye ek olarak intravenöz Nitrogliserin alan hastalar (93 hasta) IV NTG grubu olarak ayrıldı. Tüm hastalardan başvuruda ve 48 saat sonra BNP ve arteryel kan gazı örnekleri alındı ve hastalar ilk 1 ay boyunca takip edildi.

Bulgular: Serum BNP seviyeleri tüm hastalarda 48 saat sonra azaldı. IV NTG grubunda serum BNP seviyelerinde azalma ve kan gazı değerlerinde iyileşme standard tedavi grubuna göre daha iyi bulundu (NTG grubu değişimi: 1347,1±314,3 vs 280,0±196,2 pg/mL Standart grup değişimi: 1178,3±305,5 vs: 495,4±229,9 pg/mL; p<0,001). Multi-lojistik analizde başvurudaki sodyum değeri, 48. saatteki serum BNP değeri ve IV NTG kullanımı 30 günlük olaylar için prediktif olarak bulundu.

Sonuç: Plazma BNP değerlerini belirgin olarak azaltan ve kan gazı değerlerinde düzelme sağlayan intravenöz nitrogliserin tedavisinin standart tedaviye eklenmesi sistolik kalp yetmezlikli hastalarda takip olaylarını azaltabilir.

Anahtar kelimeler: İntravenöz nitrat, sistolik kalp yetmezlik, B- tipi natriuretik peptid

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Received/Geliş Tarihi: 11.09.2017 • **Accepted/Kabul Tarihi:** 19.09.2017

INTRODUCTION

Systolic heart failure (HF) is one of the most common reasons for re-hospitalization and associated with substantially increased morbidity and mortality (1-3). In clinical practice, vasodilators and diuretics are the primarily used therapies for relieving symptoms in patients with systolic HF during decompensation (4). Although nitrates have been used for over a century for the treatment of angina pectoris as a coronary vasodilator agent, it has also been used to provide vasodilation in patients with systolic HF.

A number of studies have suggested that organic nitrates could result in clinical improvement, and there is a strong, rational, physiologic reason for their use in HF patients (5). Recently, Breidthardt investigated the safety and efficacy of sublingual and transdermal nitrates in patients with acute HF and found that patients treated with noninvasive nitrates in addition to standard HF therapy had better outcomes. The authors concluded that the beneficial effect of nitrate on patients' outcome was primarily due to the reduced effect of nitrates on B-type natriuretic peptide (BNP) levels. In fact, as a strongly independent predictor of mortality in both acute and chronic systolic HF, BNP has been evaluated in several HF studies, and its level was shown to diminish with nitrate therapy due to a fall in afterload and preload (6-8). BNP can also predict clinical outcomes in patients with systolic HF as well as at admission and discharge periods (9).

In contrast, recent research suggest that nitrates are used sporadically in clinical practice and appear to be less standardized in decompensated HF due to the lack of high-quality evidence that supports the use of these agents, especially the intravenous (IV) forms (10-13). Hitherto, no data are available on the effect of the IV form of nitroglycerine (NTG) on HF with reduced ejection fraction (HFREF) outcomes, such as death and re-hospitalization during acute decompensation and after discharge. In this study, we aimed to investigate the effect of IV NTG on serum BNP levels and evaluate its effect on follow-up events in patients with acute decompensated systolic HF to demonstrate a clinical benefit of IV NTG in terms of mortality and major morbidity.

METHODS

A total of 165 consecutive patients with systolic HF who were hospitalized because of acute decompensation were prospectively enrolled into the current study. HF was defined as current symptoms of disease, or a history of symptoms controlled by ongoing therapy, in the presence of reduced left ventricular (LV) systolic function (≤45%) on transthoracic echocardiography, and in the absence of any other cause for symptoms (14, 15). Patients were divided into two groups. The IV NTG group included 93 patients receiving standard IV NTG (a standard nitrate infusion of between 0.3 and 0.5 μg/kg/min) in addition to the standard HF therapy (angiotensin-converting enzyme [ACE] or angiotensin receptor blocker [ARB], beta-blockers, mineralocorticoid receptor antagonists, loop diuretics, and anticoagulant agents for deep venous prophylaxis); the standard therapy (ST) group included 72 patients treated with only the standard HF therapy.

Patients with hypotension (systolic blood pressure <100 mmHg) or in cardiogenic shock with acute coronary syndrome, severe aortic stenosis, presence of any acute or chronic inflammatory disease, any known malignancy, acute, or chronic hepatic failure, chronic kidney disease that required hemodialysis, and previous adverse reactions to nitrate therapy were excluded from the study. All participants' age, sex, and duration of HF were recorded. Informed consent was obtained from all study patients, and the study protocol was approved by the local ethics committee.

Laboratory Tests

Serum samples for hematologic and biochemical parameters, including BNP, were collected from a peripheral vein in the intensive care unit (ICU) and measured using an automated chemistry analyzer with commercial kits (Beckmann Assay 360, Bera, California, USA). The BNP levels were assessed using immunoturbidimetry at admission, after 48 h, and at a 1-month follow-up examination. Hematologic parameters were measured from tripotassium ethylenediaminetetraacetic acid-based anti-coagulated blood samples and assessed using a Sysmex K-1000 auto-analyzer within 30 min of sampling. Samples for blood gas analyses were collected via radial artery puncture at admission and at 48 h.

The study patients were followed up throughout the first month. Follow-up events were defined as death and/or re-hospitalization for cardiac dyspnea or rapid congestion as a sign of decompensation. In addition, patients were questioned if they had been re-hospitalized at any other clinic during the follow-up period.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) software (SPSS version 16.0, Chicago, IL, USA) was used for the statistical analysis. Descriptive statistical methods, such as mean, standard deviation, interquartile range, frequency distributions, and independent t-test for comparison of groups of binary variables with normal distribution were used. The Mann-Whitney U test was used for the comparison of two groups with abnormal distribution of variables, and the Chi-square test was used for comparison of qualitative data. Logistic regression analysis was used to identify factors that may predict 30-day follow-up events. A p value <0.05 was accepted to be statistically significant.

RESULTS

The baseline characteristics of the study patients are summarized in Table 1. Baseline demographic, laboratory, and echocardiographic parameters of the groups were similar. The outpatient medication and medications given in the ICU setting including the amount of diuretics were also similar in both groups. In laboratory analyses, blood gas analysis parameters and mean BNP level were similar between the two groups (p=0.41 for BNP, p=0.38 for SpO_2, p=0.21 for $SpCO_2$, p=0.73 for HCO_3, and p=0.33 for O_2 saturation.); none of the study patients had metabolic or respiratory acidosis at admission (Table 1).

Table 2 displays the characteristics of groups after 48 h of treatment. Although BNP levels were decreased in both groups, the amount of decrease in BNP level was higher in the NTG group than that in the ST group (80% of initial level in IV NTG group and 50% of initial level in the ST group, p<0.001). The follow-up pO_2

Table 1. Baseline characteristics of the study groups

	IV NTG group (n=93)	ST group (n=72)	p
Age, years, mean±SD	67.3±8.5	66.4±8.4	0.76
Sex, n (%), female	35	65	0.40
Medical history, (%)			
Hypertension	49	51	0.28
Diabetes mellitus	60	40	0.13
Chronic kidney disease	48	52	0.26
Outpatient medication use, (%)			
Beta-blockers	48	47	0.36
ACE Inhibitors/AT-Antagonists	50	52	0.29
MRA	53	55	0.36
Nitrates	47	49	0.36
Loop diuretics	74	69	0.22
Given HF therapies in the ICU			
Beta-blocker, number of treated patients (%)	46	51	0.64
ACE inhibitors, number of treated patients, (%)	61	77	0.44
MRA, number of treated patients, (%)	47	57	0.52
Loop diuretics, number of treated patients, (%)	78	81	0.62
Anticoagulants, number of treated patients, (%)	88	94	0.38
Vital signs, mean±SD			
Systolic blood pressure, mmHg	138.5±22.3	130.4±15.9	0.13
Diastolic blood pressure, mmHg	81.4±10.8	80.0±10.2	0.63
Heart rate, bpm	99.1±24.1	87.0±20.3	0.06
Laboratory parameters, mean±SD			
Hemoglobin, g/dL	11.2±1.7	11.8±2.8	0.25
Serum creatinine, mg/dL	1.7±0.9	1.6±0.8	0.42
Serum urea, mg/dL	33.2±7.5	31.8±8.4	0.62
Serum sodium, mg/dL	134.2±9.4	136.2±9.7	0.48
BNP, pg/mL	1347.1±314.3	1178.3±305.5	0.41
Hs-CRP, mg/L	1.6±1.4	2.0±2.1	0.33
Blood gas analyses			
SpO_2, mmHg	63.1±14.7	67.9±26.1	0.38
$SpCO_2$, mmHg	43.0±14.7	38.3±14.1	0.21
HCO_3, mmol/L	21.8±4.6	21.4±4.7	0.73
pO_2 saturation, %	89.0±3.4	90.0±4.1	0.33
Echocardiographic findings, mean±SD			
LVEF, %	33.6±11.1	33.2±9.9	0.88
LVsD, cm	4.5±0.8	4.6±0.9	0.96
LVdD, cm	5.8±0.8	5.7±1.0	0.39
IVsD, cm	1.24±0.2	1.21±0.2	0.71
PwD, cm	1.18±0.2	1.19±0.2	0.95

MRA: Mineralocorticoid receptor antagonist; BNP: B-type natriuretic peptide; Hs-CRP: High sensitive C-reactive protein; ST: Standard therapy; SpO_2: Peripheral oxygen saturation; $SpCO_2$: Peripheral carbon dioxide saturation; HCO_3: Bicarbonate; LVEF: Left ventricular Ejection fraction; LVsD: Left ventricular systolic diameter; LVdD: Left ventricular diastolic diameter; IVsD: Interventricular septum diameter; Pwd: Posterior wall diameter; SD; standard deviation; IV: intravenous; ACE: Angiotensin-converting enzyme; ICU: Intensive care unit; NTG: Nitroglycerine; $p<0.05$ was accepted as significant

Table 2. Comparison of the clinical characteristics of patients per groups after 48 h

	NTG group (n=93)	ST group (n=72)	p
Diuretic, total dose, mg	42.5±7.5	44.5±8.5	0.56
Vital signs, mean±SD			
Systolic blood pressure, mmHg	121.5±21.9	129.5±32.1	0.23
Diastolic blood pressure, mmHg	80.5±12.0	82.1±8.3	0.51
Laboratory parameters			
Serum creatinine, mg/dL	1.8±0.97	1.61±0.84	0.53
Serum urea, mg/dL	37.2±8.4	34.3±8.1	0.37
BNP, pg/mL	280.0±196.2	495.4±229.9	<0.001
Blood gas analyses			
SpO_2, mmHg	83.3±9.5	74.5±8.4	<0.001
$SpCO_2$, mmHg	34.4±6.4	40.5±13.3	0.028
HCO_3, mmol/L	25.1±4.6	24.3±4.5	0.72
O_2 saturation, %	92.9±2.8	93.4±3.3	0.43
Diuretic, total dose, mg	42.5±7.5	44.5±8.5	0.38

BNP: Brain natriuretic peptide; HCO3: Bicarbonate; SpO_2: Peripheral oxygen saturation; $SpCO_2$: Peripheral carbon dioxide saturation; ST: Standard therapy; NTG: Nitroglycerine; SD: Standard deviation; p<0.05 was accepted as significant

Table 3. Comparison of the two groups at the end of the follow-up period

	NTG group (n=93)	ST group (n=72)	p
Number of events, n	16	27	0.003
Death, n	5	9	0.1
Re-hospitalization, n	11	18	0.027
BNP value, pg/mL	332±228	654±226	<0.001

BNP: Brain natriuretic peptide; ST: Standard therapy; NTG: Nitroglycerine; p<0.05 was accepted as significant

and pCO_2 saturations were improved after 48 h in both groups; the follow-up pO_2 saturation was higher and follow-up pCO_2 saturation was lower than the initial levels in both groups. However, the follow-up pO_2 and pCO_2 saturations were more improved compared with baseline in the IV NTG group than those in the ST group (Table 2).

Follow-up events were defined as death and/or re-hospitalization. In the 30-day follow-period, the total number of events seen among patients in IV NTG group was 16 (5 deaths and 11 re-hospitalizations) and 27 patients (9 deaths and 18 re-hospitalizations) in the ST group (p=0.027 for re-hospitalization, p=0.1 for death, and p=0.003 for total events). The BNP values were also higher in the ST group than those in the IV NTG group at the end of follow-up (654±226 vs. 332±228 pg/mL, p<0.001; Table 3).

Table 4. Multi-logistic regression analysis results for predicting follow-up month events

	Odds ratio (95% CI)	p
Age,	1.0 (0.96-1.50)	0.82
Sex, female	1.6 (0.48-5.7)	0.43
Serum creatinine	1.1 (0.67-1.75)	0.72
Hemoglobin	1.12 (0.56-1.65)	0.61
Hs-CRP	1.13 (0.86-1.47)	0.36
Serum sodium	0.92 (0.88-0.96)	0.001
Using IV NTG	7.7 (2.26-26.6)	0.001
BNP levels on admission	1.01 (0.85-1.2)	0.34
BNP levels at 48 h	0.99 (0.98-1.0)	<0.001
Heart rate	0.95 (0.88-1.01)	0.20
Systolic blood pressure	1.02 (0.98-1.04)	0.21

BNP: Brain natriuretic peptide; Hs-CRP: High sensitive C-reactive protein; CI: Confidence interval; IV NTG: Intravenous nitroglycerine; p<0.05 was accepted as significant

In the multi-logistic regression analyses, sodium level at admission, BNP at 48 h, and use of IV NTG were found as predictors of 30-day follow-up events (Table 4).

DISCUSSION

The main finding of this study was that IV NTG, which has favorable effects on cardiovascular hemodynamics, may also have an effect on the outcomes of patients with systolic HF. This is the first study to report that IV NTG may improve HF patients' outcomes during hospitalization and reduce firstmonth adverse events following discharge.

All available forms of organic nitrates have been widely used in cardiovascular medicine. In clinical practice, IV nitrate infusion has been used to reduce pulmonary capillary wedge pressure and systemic vascular resistance in patients with HF who have pulmonary congestion/edema with systolic blood pressure >110 mmHg. Organic nitrates mainly produce dilatation in veins, arteries, and arterioles. All the forms (oral, IV, or transdermal) have an effect that substantially reduces right and LV filling pressure, systemic vascular resistance, and systemic blood pressure due to the decreased LV filling pressure and improves forward cardiac output and stroke volume (16). All these hemodynamic effects of organic nitrates can provide symptomatic relief in systolic HF during acute decompensation.

The current data about nitrate use in decompensated HF patients are based on a review that included a few low-quality studies, and studies regarding its effect on mortality are limited (5). Moreover, the beneficial effect of IV form of NTG on the outcomes of HF patients has not been previously studied. In the current study, we showed an early benefit of IV nitrate in terms of re-hospitalization and death throughout the first month following discharge. In this regard, the current study results are important. In

the V-HeFT trial, the combination of hydralazine and isosorbid dinitrate (ISDN) decreased the 2-year mortality of patients with HF compared with placebo (17). After the encouraging results of the V-HeFT study on mortality, organic nitrates have been extensively studied regarding the outcomes in patients with HF in clinical practice. In one such study by Cotter et al. (18), 110 patients with HF were randomized to receive a high-dose nitrate in addition to a low-dose diuretic and a high-dose diuretic with a low-dose ISDN infusion. The authors found a significant reduction in the need for ventilation and incidence of myocardial infarction (MI), as well as a trend toward less mortality in the high-dose nitrate/low-dose diuretic group. In another nitrate trial, 40 patients were randomized to receive 4 mg ISDN every 4 min or bi-level positive airway pressure (BiPAP) plus a standard-dose ISDN infusion starting at 10 µmol/min and increased every 5-10 min, which is considered a conventional treatment. The researchers found a lower mortality rate (0% compared with 40%) in the 4 mg ISDN group, less need for mechanical ventilation (20% compared with 80%), and a lower incidence of MI (10% compared with 55%) (19). Recently, Breidthardt showed that sublingual and transdermal nitrates had an improving effect on the mortality in patients with acute HF. Breidthardt showed that high-dose sublingual or transdermal nitrate on top of standard HF therapy was safe and accelerated cardiac recovery (20). In another study, it was found that IV nitrate improved cardiac function in patients with acute HF due to severe aortic stenosis (21), in which vasodilators are generally thought to be contraindicated.

In our study, there was no hospital mortality among the study patients. Furthermore, IV NTG on top of ST was well tolerated and laboratory parameters of patients were not affected by nitrate therapy in the IV NTG group. We followed up all patients through the first month after discharge. The therapies throughout follow-up were similar between the groups. Although BNP levels were elevated in both groups at the end of first month, patients who were treated with IV nitrate therapy during hospitalization had lower BNP levels. Also, the rate of re-hospitalization was lower in the IV NTG group than that in the ST group during the follow-up period. The use of IV NTG was found a predictor of the following adverse events according to our logistic regression analyses results. The beneficial effect of IV NTG on first month events may be explained by two possible mechanisms. First, patients in the IV NTG group had lower level of BNP during discharge and at the end of follow-up period. We evaluated cardiac recovery through measurements of BNP levels. We found that if the IV NTG therapy was initiated early after patient admission, it could accelerate cardiac recovery, as assessed by serum BNP, which was found lower in the IV nitrate group compared with the ST alone within the first 48 h of treatment. As a natriuretic peptide, BNP is released from cardiomyocytes in response to pressure or volume-overloaded states, and its plasma levels are an independent predictor of outcomes in HF and elevated levels are associated with poor prognosis (22). We adjusted all factors that might contribute toward the decrease of BNP levels. Due to the effect on serum BNP level, we attempted to homogenize the groups in terms of given medication, such as diuretics, ACE inhibitors, and beta blocking agent. Also, the groups were similar in terms of previous medications, initial BNP levels, and echocardiographic and hemodynamic findings. After adjusting all these factors, we found that the decrease in BNP was higher in the IV NTG group than that in the ST group at the end of 48 h. The BNP values reduced more and faster in the IV NTG group, probably due to the reduction in ventricular filling pressures and the increase in cardiac output due to the NTG therapy. The dilatation in veins leads to a reduction of venous return to the right ventricle. Thus, the LV preload is decreased. This is potentially beneficial in systolic HF. We thought that the lower re-hospitalization rate in the IV nitrate group may also be explained by the effect of IV NTG on blood gas analysis results as well as its lowering effect of serum BNP level. Thus, the beneficial effects of IV nitrates on blood gas analysis were previously described in two randomized trials. It was shown that nitrates can decrease the need for mechanical ventilation as well as lower the incidence of MI in patients with pulmonary edema (18). Moreover, high-dose IV nitrates improved outcomes in patients with pulmonary edema compared with standard doses of nitrates (19). In this regard, our findings about blood gas analysis were in line with previous studies. Finally, the lower discharge BNP level may explain why the patients treated with IV NTG had lower re-hospitalization rate throughout first month. It was previously shown that BNP levels >400 pg/mL at 30 days after discharge or with an increase of >4% at follow-up could predict repeated re-hospitalization and death (23).

Limitations

Although the sample size is similar to previous larger studies, the most important limitation of our study is the short follow-up period. Also, the evaluation of renal function and respiratory parameters over a longer observational period should be performed. In contrast, the randomization was well matched based on the patients' baseline characteristics, disease severity, and treatments. All of these randomizations were similar to those observed in large registry studies.

CONCLUSION

This is the first study to evaluate the clinical benefit of IV NTG in acute decompensated phase of systolic HF. The IV NTG therapy in addition to standard HF therapy can accelerate cardiac recovery as quantified by BNP level, improve blood gas analyses within the first 48 h of treatment in the ICU, and may reduce adverse events during the first month following discharge.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Çukurova University.

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

Peer-review: Externally peer-reviewed.

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

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

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Çukurova Üniversitesi'nden alınmıştır.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan ve hastanın ailesinden alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - M.T.; Tasarım - M.T.; Denetleme - M.T.; Malzemeler - M.T., M.K.; Veri Toplanması ve/veya İşlemesi - M.K.; Analiz ve/veya Yorum - M.T.; Literatür Taraması - M.T.; Yazıyı Yazan - M.T.; Eleştirel İnceleme - M.K., M.T.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Topuz M, Kaplan M. Effect of intravenous nitrate treatment on serum BNP level and 30–day follow–up events in decompensated systolic heart failure. Eur J Ther 2017; 23: 159–64.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.67

Özgün Araştırma / Original Investigation

Diyabetli hastaların hastalıkları hakkındaki bilgi düzeyleri ve tutumları

Knowledge levels and attitudes of diabetic patients about their disease

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ÖZ

Amaç: Diyabet, dünya çapında büyüyen ciddi bir sağlık sorunu olup önemli ölçüde morbidite ve mortaliteye yol açmaktadır. Bu araştırma, diyabetli hastaların hastalıkları hakkındaki bilgi düzeyleri ve tutumlarının belirlenmesi amacıyla yapılmıştır.

Yöntemler: Kesitsel olarak yapılan bu araştırmanın evrenini, Mayıs-Kasım 2012 tarihleri arasında bir ilin devlet hastanesinin Dahiliye Polikliniklerine ayaktan başvuran tip 1 ve tip 2 diyabetli hastalar oluşturmuştur. Araştırmada örneklem seçimine gidilmemiş olup araştırmaya katılmaya gönüllü olan, iletişime açık 335 diyabet hastası alınmıştır. Veriler, araştırmacılar tarafından oluşturulan hastaların tanıtıcı özellikleri ve hastalığa ait bilgileri içeren kişisel bilgi formu ve Diyabet Tutum Ölçeği kullanılarak yüz yüze görüşme yöntemi ile toplanmıştır. Verilerin analizinde yüzdelik, ortalama hesapları, Mann Whitney U ve Kruskall Wallis testleri kullanılmıştır.

Bulgular: Hastaların hastalık hakkındaki bilgi düzeylerine bakıldığında; %70,4'ünün hastalığın kaynaklandığı organı, %43,3'ünün kan şekerinin düşme belirtilerini, %52,8'inin diyabetin zarar verdiği organları ve %37'sinin ayak yıkama sıklığı ve kontrolünü bilmediği saptanmıştır. Hastaların Diyabet Tutum Ölçeği toplam puan ortalamasının 3,58±0,30 olduğu ve diyabete ilişkin olumlu tutum geliştirdikleri belirlenmiştir. Ayrıca hastaların ilaçlarını düzenli kullanma durumu ile özel eğitim gereksinimi, kan glikoz kontrolü ve komplikasyonlar, hasta otonomisine karşı tutum, ekip bakımına karşı tutum alt boyutları ve diyabet tutum ölçeği toplam ortalama puanı arasında önemli düzeyde fark olduğu tespit edilmiştir.

Sonuç: Sonuç olarak diyabetli hastaların hastalıklarına yönelik bilgi durumlarının yetersiz olduğu ancak diyabete yönelik olumlu tutum geliştirdikleri belirlenmiştir.

Anahtar kelimeler: Diyabet, bilgi düzeyi, tutum

ABSTRACT

Objective: Diabetes is a serious health problem worldwide that leads to high morbidity and mortality rates. The current study was conducted to determine the knowledge levels and attitudes of diabetic patients about their disease.

Methods: The population of this cross-sectional study comprised type 1 and type 2 diabetic patients who presented to the outpatient internal disease polyclinic of a public hospital. No sampling was done, and 335 diabetic patients who volunteered to participate and were able to communicate were included. Data were gathered using a personal information form that contained questions on the descriptive characteristics of the patients and disease features, using the Diabetes Attitude Scale (DAS), and using the face-to-face interview technique. To analyze data, percentages and arithmetic means were calculated and Mann–Whitney U and Kruskal–Wallis tests were performed.

Results: When the knowledge levels of the patients about the disease were investigated, 70.4% of the patients did not know the organ that caused the disease and 37% did not know how often they should wash and control their foot. The mean DAS score of the patients was 3.58±0.30, and the patients developed a positive attitude about their disease. Further, there were significant differences between regular medicine use and the need for special training to provide diabetes care, blood glucose control and complications, patient autonomy, team care, and the DAS total score.

Conclusion: The knowledge levels of the patients about the disease were not satisfactory, but the patients developed a positive attitude about the disease.

Keywords: Diabetes mellitus, knowledge levels, attitude

Bu çalışma 2. Ulusal Kültürlerarası Hemşirelik Kongresi'nde sunulmuştur, 3-5 Haziran 2013, Antalya, Türkiye.
This study was presented as 2nd National Intercultural Nursing Congress, 3-5 June 2013, Antalya, Turkey.

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Geliş Tarihi/Received: 23.06.2017 • **Kabul Tarihi/Accepted:** 28.09.2017

GİRİŞ

Diyabet, dünya çapında büyüyen ciddi bir sağlık sorunu olup önemli ölçüde morbidite ve mortaliteye yol açmaktadır (1). Dünya Sağlık Örgütü'ne göre (2012) dünya çapında 346 milyondan fazla insanın diyabetli olduğu tahmin edilmektedir. Bu sayının herhangi bir müdahale yapılmazsa 2030 yılında iki katından daha fazla olacağı belirtilmektedir (2, 3). Ayrıca tip 1 ve tip 2 diyabet, dünyada bulaşıcı olmayan hastalıklar arasında en yaygını olarak yer almaktadır (4). Ülkemizde diyabet sıklığına bakıldığında Türkiye Diyabet Epidemiyoloji Çalışması (TURDEPII) verilerine göre Türk erişkin toplumunda diyabet sıklığının 20 yaş ve üzeri grupta %13,7 olduğu belirlenmiştir (5, 6). Türkiye'de 10 milyon civarında diyabetli olduğu tahmin edilmektedir (4).

Tutum, bireyin yaşantı yoluyla öğrendiği, devamlılık gerektiren, birey ve obje arasında düzenliliği gerektiren olumlu/olumsuz davranışları sergileyen bir kavramdır (7). Bireylerin hastalıklarını algılaması, hastalığa yönelik tutumları, onların hastalıkla baş etmeleri üzerinde önemli bir etkiye sahiptir. Diyabete yönelik tutum ve algılar ne kadar doğru ve gerçekçi olursa, diyabetle hem bireysel hem de toplumsal baş etme çabaları o denli başarılı olacaktır. Diyabete yönelik yanlış algı ve tutumların değiştirilmesi, önleme ve müdahale çalışmalarının mutlaka bir parçası olmalıdır (4). Bu durumda hastaların hastalıklarına yönelik olumlu tutum geliştirmelerine yardımcı olacaktır. Diyabetli hastalar, bilgileri ve olaya katılımlarının yetersizliği nedeniyle sorunlarının çözümsüz olduğunu sanmakta, bunun açmazlarını ve mutsuzluğunu yaşamaktadırlar. Uzun süren hastalıklarda uzun dönemdeki tedavi uyumunu değerlendiren çalışmaların çoğunda, 6 aydan sonra tedaviye uyum başarısının %50'yi geçmediği görülmüştür. Günümüzde; kronik hastalıkların tedavisinde başarılı olabilmenin yolunun hasta ve yakınlarının eğitimi ile yakından ilgili olduğu anlaşılmıştır (8). Diyabetli hastalarla yapılan eğitimsel çalışmalarda da eğitim sonrası hastaların bilgi ve tutumlarının daha iyi olduğu belirlenmiştir (9-13). Eğitimlerin verilebilmesi için de hastaların öncelikle hastalıkları hakkındaki bilgi seviyelerinin belirlenmesi gerekmektedir. Hastayla en çok iletişim ve etkileşim içinde olan hemşireye bu konuda önemli rol ve sorumluluklar düşmektedir.

Diyabetli hastaların bilgi ve tutumlarıyla ilgili yapılan bir çalışmada hastaların diyabet bilgi düzeylerinin çok kötü olduğu buna bağlı olarak toplumun da diyabete karşı tutumlarının ve uygulamalarının aynı şekilde çok kötü olduğu belirlenmiştir (14). Diyabetli hastalarla yapılan başka bir çalışmada da, hastaların çoğunluğunun diyabete neden olan durumları, komplikasyonları, önlenmesi ve yönetimi gibi diyabetin çeşitli yönleriyle ilgili bilgilerinin zayıf olduğu belirlenmiştir (15). Ayrıca diyabetli hastalarla yapılan tutum çalışmalarında hastanın yaşamı üzerine diyabetin etkisi konusunda negatif tutum sergileyen bireylerde diyabet bakımında daha fazla engelle karşılaştıkları belirlenmiştir (16, 17). Bilgi ve tutumla ilgili yapılan çalışmalarda da hastaların yarısının diyabet konusunda bilgilerinin olduğu buna rağmen olumlu tutum sergiledikleri belirtilmiştir (18-20). Hastaların diyabeti yönetebilmeleri ve yaşamlarını daha kaliteli sürdürebilmeleri için olumlu tutum içinde olmaları gerekir. Bu olumlu tutumun toplum içinde gelişebilmesi için hemşirelere önemli rol ve sorumluluklar düşmektedir.

Diyabet toplumda sık rastlanan bir hastalık olması nedeni ile hemşirelerinde toplumdaki riskli ve hasta bireylerle (poliklinik, hastane, aile sağlığı merkezi gibi) her alanda karşılaşabileceklerinden hemşire diyabetin primer, sekonder ve tersiyer korunmasında aktif rol almaktadır (21). Hastanın izlenmesinde hekim, diyabet eğitim hemşiresi, diyetisyen gibi diyabet konusunda uzman sağlık ekibi hasta ve hastaya bakım veren kişi arasında sıkı iletişim olmalıdır (22). Diyabetli bireylerin hastalıkları hakkında bilgilendirilmelerinde ve olumlu tutum geliştirmelerinde hemşirelere önemli sorumluluklar düşmektedir. Hastalar da, yaşam tarzlarına dikkat ederek ve hastalıklarıyla ilgili bilgi sahibi olarak yaşamlarında olumlu tutum geliştirebilirler. Bu bilgiler ışığında bu araştırma diyabetli hastaların hastalıkları hakkındaki bilgi düzeyleri ve tutumlarının belirlenmesi amacıyla yapılmıştır.

YÖNTEMLER

Kesitsel özellikte olan bu araştırmanın evrenini, Mayıs-Kasım 2012 tarihleri arasında Erzincan Devlet Hastanesinin dahiliye polikliniklerine ayaktan başvuran tip 1 ve tip 2 diyabetli hastalar oluşturmuştur. Araştırmada örneklem seçimine gidilmemiş olup araştırma kapsamına iletişime açık, duyma sorunu olmayan, en az 6 ay ve üzeri diyabet tanısı alan, tanı konulmuş herhangi bir psikiyatrik sorunu olmayan, araştırmaya katılmaya gönüllü olan 335 diyabet hastası alınmıştır. Hastaların tanıtıcı ve hastalıklarına ilişkin özellikleri bağımsız değişkenleri, diyabete yönelik tutumları ve bilgi düzeyleri ise bağımlı değişkeni oluşturmaktadır. Veriler, araştırmacılar tarafından oluşturulan hastaların tanıtıcı özellikleri ve hastalığa ait bilgileri içeren kişisel bilgi formu ve Diyabet Tutum Ölçeği (DTÖ) kullanılarak yüz yüze görüşme yöntemi ile toplanmıştır.

Veri Toplama Araçları

Tanıtıcı Özellikler Formu: Form, hastaların tanıtıcı özellikleri ile hastalıklarına ilişkin (yaş, cinsiyet, eğitim durumu, mesleği, hastalıkla ilgili eğitim alma, başka hastalığının olma durumu, hastalık süresi, kan şekerini kontrol ettirme durumu, ailede diyabet hastalığı varlığı, düzenli ilaç kullanma durumu ve hastalığa ilişkin11 soru içeren bilgi durumu) toplam 21 sorudan oluşmuştur.

Diyabet Tutum Ölçeği (DTÖ): Amerika'da Ulusal Diyabet Komisyonu tarafından geliştirilmiş olan Diyabet Tutum Ölçeği'nin (DTÖ) ülkemizdeki geçerlilik ve güvenilirlik çalışması Özcan (17) tarafından 1999 yılında yapılmıştır. Diyabet Tutum Ölçeği, 7 alt gruptan oluşmaktadır. Bunlar; özel eğitim gereksinimi, hasta uyumuna karşı tutum, insüline bağımlı olmayan diyabetin ciddiyeti, kan glikoz kontrolü ve komplikasyonlar, hastanın yaşamına diyabetin etkisi, hasta otonominse karşı tutum ve ekip bakımına karşı tutumdan oluşmaktadır. Ölçeğin alt gruplarında bulunan madde sayısı üç ile yedi arasında değişmektedir. Ölçek maddeleri 1'den 5'e kadar değişen, likert tipi puanlama ile puanlanmıştır. Ölçekteki olumlu maddeler için 5,4,3,2,1, şeklinde puanlama olumsuz maddeler için de 1,2,3,4,5 şeklinde puanlama yapılmıştır. Maddeleri değerlendirirken 5,6,12,18,23,24, numaralı maddeleri olumsuz diğer maddeleri ise olumlu değerlendirmek gerekir. Puan >3 ise pozitif tutumu, puan ≤3 ise negatif tutumu ifade etmekte ve puanın artışı veya düşüşü o yöndeki tutumu güçlendirmektedir. Ölçek puanının 5'e doğru artışı veya düşüşü o yöndeki tutumu güçlendirmektedir. Hem diyabetli bireyler hem de diyabet bakım

ekibine uygulanabilen ölçek, bu iki grubun tutumlarının değerlendirilmesini sağlamaktadır. Ölçeğin alfa iç tutarlılık katsayısı 0,61-0,93 olarak belirlenmiştir. Bu araştırmada da DTÖ'nin cronbach alfa iç tutarlılık katsayısı 0,73 olarak bulunmuştur.

Uygulama
Araştırmanın verileri, tanıtıcı özellikler formu ve DTÖ kullanılarak yüz yüze görüşme yöntemi ile toplanmıştır. Formların doldurulması ortalama 25-30 dakika sürmüştür.

İstatistiksel Analiz
Araştırma sonucu elde edilen verilerin değerlendirilmesi bilgisayar ortamında, SPSS (Statistical Package for Social Sciences) 15.0 paket programında (SPSS Inc.; Chicago, IL, ABD) uygun istatistiksel analizler kullanılarak yapılmıştır. Tanımlayıcı istatistikler sayı, yüzde ve ortalama olarak verilmiştir. Verilerin normal dağılıma uyup uymadığını anlamak amacıyla Shapiro – Wilk analizi yapılmış ve verilerin normal dağılıma uymadığı görüldüğünden nonparametrik analizlerin uygulanmasına karar verilmiştir. Bu analizler; Mann Whitney U ve Kruskal Wallis testi olarak belirlenmiştir. Anlamlılık seviyesi p<0,05 olarak kabul edilmiştir.

Etik İlkeler
Bu araştırma Türkiye Cumhuriyeti Cumhurbaşkanlığı himayesinde başlatılan "Diyabeti Durduralım Projesi" kapsamında Erzincan Devlet Hastanesiyle işbirliği ile gerçekleştirilmiştir. Araştırmaya başlamadan önce başhekimlikten dahiliye polikliniklerine araştırmanın yapılabilmesi için yazı yazılmış olup polikliniklere yakın bir yerde stand kurularak hastalar bu standa yönlendirilmiştir. Hastalara da araştırmanın amacı ve yöntemi anlatılarak sözel onamları alınmış ve gizlilik ilkesine saygı gösterilmiştir. Araştırma Helsinki Deklarasyonuna uygun olarak yapılmıştır. Araştırmanın yürütülmesinde Aydınlatılmış Onam İlkesi'ne bağlı kalınmıştır. Araştırmaya katılacak bireylerin sözel onamları alınarak gönüllü olanlar çalışmaya alınmıştır.

BULGULAR
Hastaların %29,9'unun 50-59 yaş aralığında, %66'sının kadın, %32,2'sinin 1-5 yıl arası diyabet hastası olduğu, %66'sının kan şekerini düzenli kontrol ettirdiği, %68,1'inin diyabet dışında başka bir hastalığı olduğu, %86'sının düzenli ilaç kullandığı, %74,3'ünün hastalığı hakkında eğitim aldığı belirlenmiştir.

Hastaların DTÖ'nin hasta yaşamına diyabetin etkisi alt boyutu puanı ile cinsiyetleri arasında istatistiksel olarak anlamlı bir fark bulunurken (p<0,05), yaş, eğitim durumu ve mesleğinin puan ortalamaları arasındaki farkın anlamsız olduğu belirlenmiştir (p>0,05) (Tablo 1).

Tablo 2'ye bakıldığında; hastalıklarıyla ilgili daha önce eğitim alma durumu ile özel eğitim gereksinimi, insüline bağımlı olmayan diyabetin ciddiyeti ve hasta yaşamına diyabetin etkisi alt boyutlarının puan ortalamaları arasında istatistiksel olarak anlamlı bir fark olduğu belirlenmiştir (p<0,05, p<0,001). Hastaların kan şekerini düzenli kontrol ettirme durumu ile ölçeğin alt boyutları olan özel eğitim gereksinimi (p<0,05), insüline bağımlı olmayan diyabetin ciddiyeti (p<0,01), DTÖ toplam puanı arasında (p<0,05) istatistiksel olarak anlamlı fark olduğu belirlenmiştir. Diyabetli hastaların ilaçlarını düzenli kullanma durumu ile özel eğitim gereksinimi (p<0,001), kan glikoz kontrolü ve komplikasyonlar (p<0,001), hasta otonomisine karşı tutum (p<0,05), ekip bakımına karşı tutum (p<0,01) alt boyutları ve DTÖ toplam puanı arasında (p<0,001), ailede diyabet hastalığı varlığı ile insüline bağımlı olmayan diyabetin ciddiyeti (p<0,001) alt boyutu puan ortalamaları arasında önemli düzeyde fark olduğu tespit edilmiştir.

Hastaların DTÖ toplam puan ortalamasının 3,58±0,30 olduğu ve diyabete ilişkin olumlu tutum geliştirdikleri belirlenmiştir. Ölçeğin alt boyutlarından alınan puan ortalamalarına bakıldığında, en düşük 2,77±0,93 ile en yüksek 3,90±0,53 arasında değiştiği görülmektedir. Özellikle en güçlü pozitif tutumun "özel eğitim gereksinimi" alt boyutunda (3,90±0,53) en zayıf pozitif tutumun ise "İnsüline bağımlı olmayan diyabetin ciddiyeti" alt boyutunda (2,77±0,93) olduğu belirlenmiştir (Tablo 3).

Hastaların hastalık hakkındaki bilgi düzeylerine bakıldığında; %70,4'ünün hastalığın kaynaklandığı organı, %43,3'ünün kan şekerinin düşme belirtilerini, %52,8'inin diyabetin zarar verdiği organları, %45,1'inin tırnak kesme şeklini, %44,8'inin ayakkabı giyerken dikkat edilmesi gerekenleri, %37'sinin ayak yıkama sıklığı ve kontrolünü bilmediği saptanmıştır (Tablo 4).

TARTIŞMA
Diyabet her yaşta görülebilen kronik bir hastalıktır. Dünyadaki diyabet hastalarının 113 milyonu 40-59 yaş grubunda yer almakta ve bunların %70'i endüstrileşmekte olan ülkelerde bulunmaktadır (4). Ayrıca yaşlanmaya bağlı olarak diyabet prevalansının arttığı görülmektedir (6). Yaşlanan dünya nüfusuna bağlı olarak bu rakamın 2025 yılında 166 milyon olması beklenmektedir. Ayrıca 60-79 yaş arası diyabetli hasta sayısının 165 milyonu bulacağı hesaplanmaktadır (4). Bu araştırmada da hastaların %49,6'sının 40-59 yaş grubunda yer aldığı belirlenmiştir. Hastalardan 60-69 yaş grubunda olanların toplam DTÖ puan ortalaması diğer yaş gruplarından yüksek bulunurken alt boyutlardaki puan ortalamaları değişkenlik göstermektedir. Ayrıca yaşın hastaların diyabete yönelik tutumlarını etkilemediği belirlenmiştir (p>0,05). Kartal ve ark. (19) diyabetli hastalarla yaptığı çalışmada da yaşın bakım ve tedaviye yönelik tutumu etkilemediği saptanmıştır. Diyabetli hastalarla yapılan bir çalışmada 35 yaşın altında olanların 65 yaş ve üzerinde olan hastalardan daha olumlu tutum sergiledikleri belirlenmiştir (23).

Araştırma kapsamına alınan hastaların cinsiyetinin hasta yaşamına diyabetin etkisi alt boyutunu olumlu yönde etkilediği (p<0,05) toplam DTÖ ve diğer alt boyutların puan ortalamasını etkilemediği belirlenmiştir (p>0,05). Kadın hastaların DTÖ alt boyutlarından; özel eğitim gereksinimi, hasta uyumuna karşı tutum, hasta yaşamına diyabetin etkisi, hasta otonomisine karşı tutum, ekip bakımına karşı tutum ve toplam DTÖ puan ortalamalarının erkek hastalardan daha yüksek olduğu belirlenmiştir. Diyabetli hastalarla yapılan çalışmalarda da cinsiyet ile diyabet tedavilerine yönelik tutumla herhangi bir anlamlı ilişki bulunmadığı belirlenmiştir (23, 24).

Hastaların eğitim durumu ile diyabete yönelik tutum puan ortalamaları arasında anlamlı bir fark saptanmamıştır (p>0,05). Okur-yazar, ilkokul mezunu olan hastaların, özel eğitim gereksinimi, hasta

Tablo 1. Hastaların tanıtıcı özelliklerine göre Diyabet Tutum Ölçeği puanlarının dağılımı (n=335)

		Diyabet Tutum Ölçeği							
Tanıtıcı Özellikler	Sayı (%)	Özel eğitim gereksinimi	Hasta uyumuna karşı tutum	İnsüline bağımlı olmayan diyabetin ciddiyeti	Kan glikoz kontrolü ve komplikasyonları	Hasta yaşamına diyabetin etkisi	Hasta otonomisine karşı tutum	Ekip bakımına karşı tutum	Toplam ölçek
Yaş									
39 yaş ve altı	27 (8,1)	4,23±0,64	3,73±0,61	2,78±0,95	3,85±0,69	3,82±0,48	3,89±0,54	3,76±0,73	3,80±0,37
40–49	66 (19,7)	4,26±0,55	3,81±0,56	2,84±0,90	3,79±0,63	3,97±0,53	4,08±0,48	3,76±0,70	3,87±0,37
50 –59	100 (29,9)	4,27±0,42	3,82±0,47	2,84±0,96	3,90±0,47	3,85±0,50	4,02±0,50	3,86±0,66	3,87±0,28
60–69	71 (21,2)	4,30±0,44	3,91±0,44	3,11±1,01	4,01±0,48	3,81±0,52	4,05±0,45	4,00±0,62	3,95±0,29
70 yaş ve üzeri	71 (21,2)	4,31±0,50	3,93±0,48	2,69±0,95	3,94±0,45	3,79±0,57	4,15±0,49	3,92±0,60	3,91±0,30
KW, p		1,154 .886	4,537 .338	7,189 .126	4,035 .401	4,558 .336	7,951 .093	5,496 .240	4,169 .384
Cinsiyet									
Kadın	221 (66,0)	4,29±0,50	3,87±0,46	2,81±0,98	3,89±0,54	3,90±0,51	4,06±0,47	3,90±0,66	3,90±0,30
Erkek	114 (34,0)	4,26±0,47	3,81±0,56	2,96±0,92	3,95±0,49	3,76±0,55	4,05±0,52	3,82±0,65	3,87±0,34
M–WU, p		12104,000 .555	11782,000 .329	11335,000 .131	11941,500 .430	10953,000 .049	12552,500 .957	11856,500 .374	11784,000 .333
Eğitim Durumu									
Okur–yazar değil	111 (33,1)	4,25±0,51	3,85±0,48	2,72±0,91	3,91±0,49	3,80±0,50	4,10±0,49	3,91±0,64	3,88±0,30
Okur–yazar İlkokul	150 (44,8)	4,31±0,46	3,91±0,43	2,90±1,01	3,89±0,54	3,91±0,57	4,05±0,46	3,89±0,65	3,92±0,29
Ortaokul mezunu	27 (8,1)	4,24±0,47	3,89±0,50	2,89±0,50	3,98±0,43	3,90±0,40	4,10±0,46	3,76±0,64	3,90±0,31
Lise mezunu	47(14,0)	4,25±0,54	3,65±0,66	3,65±0,66	3,93±0,62	3,75±0,48	3,94±0,59	3,78±0,75	3,83±0,41
KW, p		,568 .904	6,754 .080	4,502 .212	1,172 .760	4,490 .213	2,700 .440	2,285 .515	2,851 .415
Meslek									
Çalışıyor	93 (27,8)	4,27±0,49	3,82±0,56	2,94±0,92	3,88±0,55	3,84±0,53	4,06±0,49	3,80±0,66	3,88±0,36
Çalışmıyor	242 (72,2)	4,28±0,49	3,86±0,47	2,83±0,98	3,92±0,51	3,86±0,52	4,05±0,49	3,90±0,65	3,90±0,30
M–WU, p		11177,000 .923	10877,000 .634	10344,500 .250	10808,500 .571	11093,500 .840	11186,500 .932	10346,500 .250	10915,500 .671

KW: Kruskal Wallis; M–WU: Mann–Whitney U

uyumuna karşı tutum, insüline bağımlı olmayan diyabetin ciddiyeti, hasta yaşamına diyabetin etkisi alt boyutlarının ve toplam DTÖ puan ortalamalarının diğer eğitim gruplarına sahip olan bireylerden daha yüksek olduğu belirlenmiştir. Diyabetli hastalarla yapılan çalışmalarda da eğitim durumu ile diyabete yönelik tutum arasında anlamlı bir fark bulunmadığı belirlenmiştir (19, 23, 24).

Diyabetli hastaların mesleği ile diyabete yönelik tutum puan ortalamaları arasında anlamlı bir fark belirlenmemiştir (p>0,05). Diyabet tedavisinin planlanmasında, hastanın sosyoekonomik durumu, yaşam şekli ve bakım desteğinin bulunup bulunmaması da önemlidir (22). Çalışan diyabetli hastaların hem sosyal güvencelerinin olması hem de sosyoekonomik durumları göz önüne alındığında olumlu tutum sergilemeleri muhtemel bir durum olabilir. Çalışmayan hastaların ise hastalıklarının yönetimi için daha çok zamanlarının olması, yaşam şekli ve bakım desteğinin bulunması olumlu tutum göstermelerini sağlamış olabilir.

Tablo 2. Hastaların hastalık özelliklerine göre Diyabet Tutum Ölçeği puanlarının dağılımı (n=335)

		Diyabet Tutum Ölçeği							
Hastalık Özellikler	Sayı (%)	Özel eğitim gereksinimi	Hasta uyumuna karşı tutum	İnsüline bağımlı olmayan diyabetin ciddiyeti	Kan glikoz kontrolü ve komplikasyonları	Hasta yaşamına diyabetin etkisi	Hasta otonomisine karşı tutum	Ekip bakımına karşı tutum	Toplam ölçek
Hastalık Süresi 1<									
1-5yıl	54 (16,1)	4,33±0,49	3,89±0,51	2,67±0,91	3,97±0,50	3,90±0,50	4,08±0,53	3,86±0,66	3,91±0,31
6-10 yıl	108 (32,2)	4,25±0,47	3,75±0,48	2,99±0,95	3,85±0,55	3,85±0,51	4,03±0,51	3,81±0,65	3,86±0,32
11 yıl ve üzeri	89 (26,6)	4,30±0,47	3,95±0,51	2,79±0,92	3,88±0,48	3,90±0,47	4,06±0,50	3,90±0,63	3,92±0,30
KW,p	84 (25,1)	4,26±0,52 2,079 .556	3,86±0,48 10,121 .054	2,89±1,04 5,252 .154	3,97±0,56 3,308 .347	3,76±0,60 3,609 .307	4,05±0,43 ,686 .876	3,93±0,69 1,660 .646	3,89±0,33 1,315 .726
Hastalıkla ilgili eğitim alma durumu									
Evet	249 (74,3)	4,24±0,51	3,83±0,51	2,98±0,95	3,91±0,55	3,78±0,53	4,05±0,49	3,86±0,67	3,88±0,34
Hayır	86 (25,7)	4,40±0,40	3,93±0,44	2,51±0,93	3,90±0,46	4,05±0,47	4,07±0,49	3,92±0,62	3,93±0,24
M-WU, p		8924,500 .021	9652,500 .170	7675,000 p<0.001	10166,500 .480	7466,500 p< 0.001	10622,500 .912	10290,000 .587	10332,000 .628
Başka hastalık varlığı									
Evet	228 (68,1)	4,27±0,48	3,83±0,50	2,83±0,95	3,91±0,52	3,85±0,54	4,03±0,48	3,82±0,66	3,87±0,31
Hayır	107 (31,9)	4,29±0,51	3,90±0,50	2,93±0,99	3,89±0,55	3,86±0,49	4,11±0,51	3,99±0,64	3,93±0,32
M-WU, p		11718,000 .559	10899,500 .114	11493,000 .391	11872,000 .690	11882,500 .700	10578,500 .051	10322,500 .022	10753,500 .080
Düzenli ilaç kullanma durumu									
Evet	288 (86,0)	4,32±0,45	3,83±0,50	2,83±0,95	3,91±0,52	3,85±0,54	4,03±0,48	3,82±0,66	3,87±0,31
Hayır	47 (14,0)	4,02±0,62	3,90±0,50	2,93±0,99	3,89±0,55	3,86±0,49	4,11±0,51	3,99±0,64	3,93±0,32
M-WU,p		4818,500 p<0.001	5932,000 .172	6646,000 .842	4636,500 p<0.001	6731,500 .952	5714,500 .049	4652,500 .001	5000,500 p<0.001
Ailede Diyabet Öyküsü									
Var	170 (50,7)	4,30±0,48	3,84±0,44	2,68±0,84	3,86±0,54	3,90±0,54	4,02±0,52	3,83±0,71	3,87±0,32
Yok	165 (49,3)	4,26±0,49	3,86±0,55	3,04±1,04	3,95±0,50	3,80±0,51	4,09±0,45	3,92±0,60	3,91±0,31
M-WU, p		12435,500 .494	12152,000 .306	9781,500 .001	11565,000 .082	11433,000 .059	12212,500 .339	12311,500 .404	11336,500 .052
Kan şekerini düzenli kontrol ettirme durumu									
Evet	221 (66,0)	4,32±0,45	3,86±0,49	2,97±1,02	3,93±0,54	3,85±0,54	4,07±0,47	3,92±0,65	3,92±0,30
Hayır	114 (34,0)	4,20±0,55	3,83±0,51	2,65±0,81	3,87±0,50	3,85±0,50	4,03±0,54	3,78±0,66	3,83±0,34
M-WU, p		11199,500 .046	12353,500 .770	10132,000 .003	11720,000 .291	12332,500 .751	12559,500 .964	11228,000 .101	10923,500 .046

KW: Kruskal Wallis; M-WU: Mann-Whitney U

Hastalık süresi 6-10 yıl arasında olan hastaların diyabete yönelik tutum puan ortalamalarının diğer gruplara göre daha yüksek olduğu, ancak hastalık süresi ile diyabet tutum ölçeği ve alt boyutları arasında anlamlı bir fark olmadığı belirlenmiştir (p>0,05). Diyabetli hastalarla yapılan çalışmalarda da diyabet hastalığının süresi ile diyabet tutum ölçeği puanı arasında anlamlı fark bulunmamıştır (17, 19, 24). Hastalık süresi 1 yıldan daha az olan hastaların özel eğitim gereksinimi, hasta yaşamına diyabetin etkisi, hasta otonomisine karşı tutum alt boyutlarının puan ortalamalarının diğer gruplara göre daha yüksek olduğu saptanmıştır. Bu durum, hastaların tanı sürelerinin daha yeni olması, hastalıklarına daha özen göstermeleri ve hastalıklarına yönelik kronik komplikasyonların gelişmemesi ile açıklanabilir.

Diyabet yaşam boyu süren bir hastalıktır, bu nedenle eğitim hastalığın önlenmesi, tedavisi, bakımın sağlanması ve izleminin ayrılmaz bir parçası olarak düşünülmelidir. Başka hiçbir hastalıkta bireyin eğitimi diyabetteki kadar önemli ve etkili değildir. Diyabet bakımının %90'ından fazlası diyabetlinin kendisi tarafından yapılmaktadır. Bu bakımdan hastanın bilinçlenerek ve beceri kazanarak kendi kendine bakım, izlem ve değerlendirme yapması, yani hastalığının yönetimini üstlenmesi gerekmektedir. Hastalık yönetimini öğrenmiş bireylerin hem sağlık sonuçları olumlu etkilenmekte hem de hastalıklarının maliyeti düşmektedir (4). Hastalıklarıyla ilgili daha önce eğitim alma durumu ile özel eğitim gereksinimi, insüline bağımlı olmayan diyabetin ciddiyeti ve hasta yaşamına diyabetin etkisi alt boyutlarının puan ortalamaları arasında istatistiksel olarak anlamlı bir fark olduğu belirlenmiştir (p<0,05, p<0,001). Diyabetli hastalarla yapılan çalışmalarda da hastalıklarıyla ilgili eğitim alan hastaların tutumlarının olumlu yönde değiştiği, bilgi ve uygulamalarında artış olduğu belirlenmiştir (9, 11, 13, 25).

Diyabet dışında başka hastalığın bulunması durumu ile ekip bakımına karşı tutum alt boyutu arasında önemli düzeyde fark olduğu tespit edilmiştir (p<0,05). Hastaların %68,1'inin diyabet dışında başka bir kronik hastalığı olduğu belirlenmiştir. Mollaoğlu ve ark. (11) çalışmasında da hastaların %81,7'sinde diyabet dışında başka bir hastalıkları olduğu belirlenmiştir. Yaşlanan dünya nüfusu ile birlikte ileriye dönük yapılan diyabet prevalansı ile ilgili tahminlerde, diyabetle birlikte görülen hastalıkların prevalansında da artış olacağı öngörülmektedir (4). Araştırma bulgusu literatür bilgilerine benzerlik göstermektedir.

Tablo 3. Hastaların diyabet tutum ölçeği (DTÖ) alt puan ve toplam puan ortalamalarının dağılımı (n=335)

Diyabet tutum ölçeği alt boyutları	Ortalama±SS
Özel eğitim gereksinimi	3,90±0,53
Hasta uyumuna karşı tutum	3,54±0,52
İnsüline bağımlı olmayan diyabetin ciddiyeti	2,77±0,93
Kan glikoz kontrolü ve komplikasyonlar	3,58±0,62
Hastanın yaşamına diyabetin etkisi	3,61±0,54
Hasta otonomisine karşı tutum	3,69±0,56
Ekip bakımına karşı tutum	3,55±0,69
Toplam ölçek	3,58±0,30

SS: standart sapma

Diyabetli hastaların düzenli ilaç kullanma durumları ile özel eğitim gereksinimi, kan glikoz kontrolü ve komplikasyonları, hasta otonomisine karşı tutum, ekip bakımına karşı tutum ve toplam diyabet tutum ölçeği puan ortalamaları arasında istatistiksel olarak anlamlı fark olduğu belirlenmiştir (p<0,001, p<0,001, p<0,05, p<0,01, p<0,001). Kartal ve ark. (19) diyabetli hastalarla yaptığı çalışmada da hastaların tedaviye uyumu ile diyabet tutum ölçeği puan ortalaması arasında anlamlı fark olduğu saptanmıştır.

Ailede diyabet öyküsü varlığı ile sadece insüline bağımlı olmayan diyabetin ciddiyeti alt boyutu arasında önemli düzeyde fark olduğu tespit edilmiştir (p<0,001). Hastaların %50,7'sinin ailede diyabet öyküsünün olduğu belirlenmiştir. Araştırma bulgusu Kartal ve ark. (19) ve İnkaya ve Karadağ (24) çalışma bulgularına benzerlik göstermektedir.

Hastaların kan şekerini düzenli kontrol ettirme durumları ile özel eğitim gereksinimi, insüline bağımlı olmayan diyabetin ciddiyeti ve toplam diyabet tutum ölçeği puan ortalamaları arasında önemli bir fark olduğu saptanmıştır (p<0,05). Kan şekerini düzenli kontrol ettiren hastaların toplam tutum puan ortalamalarının olumlu yönde pozitif tutum gösterdiği belirlenmiştir. Kara ve Çınar'ın (26) çalışmasında da hastanın diyabete karşı pozitif tutumu arttıkça açlık kan şekerinin azaldığı saptanmıştır. Kan şekerini düzenli kontrol ettiren hastaların %66 olduğu bulunmuştur. Kartal ve ark. (19) yaptığı çalışmada da hastaların %95,5'inin kan şekeri ölçümü yaptığı, ölçüm yapan hastaların %52,7'sinin ölçümü düzensiz yaptığı belirlenmiştir. Diyabet bakım ve tedavisinin

Tablo 4. Hastaların hastalık ile ilgili bilgi düzeylerinin dağılımı (n=335)

	Doğru biliyor		Yanlış biliyor		Bilmiyor	
Hastalık özellikleri	**Sayı**	**%**	**Sayı**	**%**	**Sayı**	**%**
Diyabet hastalığının kaynaklandığı organ	69	20,6	30	9,0	236	70,4
Kan şekeri düşme belirtileri	156	46,6	34	10,1	145	43,3
Diyabet hastalığının zarar verdiği organlar	125	37,3	33	9,9	177	52,8
Diyabet hastasının tırnak kesme şekli	112	33,4	72	21,5	151	45,1
Ayakkabı giyerken dikkat edilmesi gerekenler	123	36,7	62	18,5	150	44,8
Ayak yıkama sıklığı ve kontrolü	154	46,0	57	17,0	124	37,0
İnsülin kalemini saklama şekli	69	20,6	48	14,3	218	65,1
Diyabet hastasının tercih etmesi gereken besin grubu	233	69,6	48	14,3	54	16,1
Diyabet hastasının yemesi gereken öğün sayısı	214	63,9	61	18,2	60	17,9
Egzersizin yararları	237	70,7	28	8,4	70	20,9
Sigara içmemesi gerektiği	276	82,4	14	4,2	45	13,4

temel amacı glisemik kontrolü sağlamaktır (27). Bu araştırmada da hastaların yarıdan fazlasının düzenli olarak kan şekeri kontrolü yaptığı belirlenmiştir.

Hastaların DTÖ toplam puan ortalamasının 3,58±0,30 olduğu ve diyabete ilişkin olumlu tutum geliştirdikleri belirlenmiştir. En yüksek olumlu tutumun özel eğitim gereksinimi (3,90±0,53) alt boyutunda olduğu görülmektedir. Tutumla ilgili yapılan çalışmalarda da hastaların genellikle olumlu tutum sergiledikleri belirlenmiştir (9, 18-20, 24).

Hastaların diyabetin yönetimine yönelik bilgi düzeylerine bakıldığında; %70,4'ünün diyabetin kaynaklandığı organı, %65,1'inin insülin kalemini saklama şeklini, %52,8'inin diyabetin zarar verdiği organları ve %20,9'unun egzersizin yararlarını bilmediği saptanmıştır. Maina et al. (14) yaptığı çalışmada da diyabetli hastaların bilgi düzeyinin çok kötü olduğu belirtilmiştir. Foma et al. (15) yaptığı çalışmada diyabetli hastaların çoğunluğunun diyabete neden olan durumları, komplikasyonları, önlenmesi ve yönetimi gibi diyabetin çeşitli yönleriyle ilgili bilgilerinin zayıf olduğunu saptamışlardır. Danquah et al. (28) yaptıkları çalışmada hastaların karbonhidrat, sodyum ve yağdan zengin bir diyetle beslendiklerini, fiziksel aktivitelerinin ise genelde düşük olduğu, başka bir çalışmada ise tip 2 diyabetli hastaların ağız sağlığı konusunda bilgilerinin yetersiz olduğu belirlenmiştir (29). Dündar ve ark. (20) yaptıkları çalışmada diyabetli hastaların yarısının diyabet konusunda yeterli bilgiye sahip olduklarını belirtmişlerdir. Başka bir çalışmada ise hastaların %33'ünün diyabete yönelik genel bilgilerinin, diyabetin belirtileri ve komplikasyonlarına yönelik bilgilerinin iyi olduğu belirlenmiştir (30). Batkın ve Çetinkaya'nın (31) yaptığı çalışmada diyabetli bireylerin diyabetik ayak ve ayak bakımı ile ilgili bilgilerinin yetersiz, davranış puanlarının düşük olduğu bulunmuştur. Bu araştırma bulgusu da yapılan araştırma sonuçlarına benzerlik göstermektedir.

SONUÇ

Diyabetli hastalarla yapılan bu araştırmada hastaların yaşının, eğitim durumunun, mesleğinin diyabete yönelik tutumlarını etkilemediği cinsiyetin ise sadece diyabet tutum ölçeğinin alt boyutu olan hasta yaşamına diyabetin etkisi alt boyutunu olumlu yönde etkilediği belirlenmiştir. Hastalık süresinin diyabete yönelik tutumu etkilemediği, bunun yanı sıra düzenli ilaç kullanma ve kan şekerini düzenli kontrol ettirme durumlarının diyabete yönelik tutumu pozitif yönde olumlu etkilediği saptanmıştır. Hastaların diyabete yönelik pozitif yönde olumlu tutum sergiledikleri ancak diyabete yönelik bilgi düzeylerinin yetersiz olduğu belirlenmiştir. Bu sonuçlar doğrultusunda; hastaların bireysel özelliklerinin göz önünde bulundurularak, diyabete yönelik yetersiz bilgi ve negatif tutumlarının belirlenmesi, bilgi ve tutumlarını geliştirmeye yönelik eğitim programlarının düzenlenmesi, hastaların tutuma yönelik farkındalıklarının arttırılmasına yönelik çalışmalar yapılması önerilebilir.

Etik Komite Onayı: Yazarlar çalışmanın World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013) prensiplerine uygun olarak yapıldığını beyan etmişlerdir.

Hasta Onamı: Sözlü hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir – P.K., R.H.A., A.Y.; Tasarım – P.K., R.H.A., A.Y.; Denetleme – P.K., R.H.A., A.Y., H.S.; Kaynaklar - P.K., R.H.A., A.Y., H.S.; Malzemeler - P.K., R.H.A., A.Y.; Veri Toplanması ve/veya İşlemesi - P.K., R.H.A., A.Y., H.S.; Analiz ve/veya Yorum - P.K., R.H.A., A.Y.; Literatür Taraması - P.K., R.H.A., A.Y.; Yazıyı Yazan - P.K., R.H.A., A.Y.; Eleştirel İnceleme – P.K., R.H.A., A.Y.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.K., R.H.A., A.Y.; Design – P.K., R.H.A., A.Y.; Supervision – P.K., R.H.A., A.Y., H.S.; Resources - P.K., R.H.A., A.Y., H.S.; Materials - P.K., R.H.A., A.Y.; Data Collection and/or Processing - P.K., R.H.A., A.Y., H.S.; Analysis and/or Interpretation - P.K., R.H.A., A.Y.; Literature Search - P.K., R.H.A., A.Y.; Writing Manuscript - P.K., R.H.A., A.Y.; Critical Review – P.K., R.H.A., A.Y.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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How to cite:

Karakurt P, Hacıhasanoğlu Aşılar R, Yıldırım A, Sevinç H. Knowledge levels and attitudes of diabetic patients about their disease. Eur J Ther 2017; 23: 165–72.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.155

Özgün Araştırma / Original Investigation

Kronik hepatit C tedavisinde pegile-interferon ve ribavirin içeren rejimlerin etkinliği: Geriye doğru bir bakış

Efficacy of regimens containing pegylated interferon and ribavirin in the treatment of chronic hepatitis C: A retrospective overview

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ÖZ

Amaç: Kronik hepatit C (KHC) hastalarında, interferonlu tedavilere cevabı, kalıcı viral yanıtı etkileyen faktörleri ve nüksü değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya retrospektif olarak KHC'li 305 hasta alındı. Hastalara 48 hafta pegile interferon alfa-2A (PEG-IFN α-2A) + ribavirin (RİB) veya pegile interferon alfa-2B (PEG-IFN α-2B) + RİB tedavisi verildi.

Bulgular: Tedavinin 48. haftasında, tedavi sonu virolojik yanıt (TSVY) 305 hastanın 151'inde (%49,5) saptandı. PEG-IFN α-2A + RİB kullanan hastaların 70'inde (%50,7), PEG-IFN α-2B + RİB kullanan hastaların 81'inde (%48,5) TSVY saptandı (p>0,05). Tedavi bitiminden 6 ay sonra, kalıcı virolojik yanıt (KVY) ise tüm hastaların 138'inde (%45,2) saptandı. PEG-IFN α-2A + RİB kullanan hastaların 63'inde (%45,7), PEG-IFN α-2B + RİB kullanan hastaların 75'inde (%45,9) KVY saptandı (p>0,05). Tedavi sonrası 35 (%11,6) hastada nüks görüldü.

Sonuç: KHC enfeksiyonunda verilen tedavi ile hastaların uzun dönem prognozları olumlu yönde etkilenmektedir. PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisi ile hepatit C virüs ribo nükleik asit (HCV RNA) klirensinde henüz istenen düzeye ulaşılamamıştır. Bu nedenle yeni tedavi rejimlerine ihtiyaç duyulmaktadır.

Anahtar kelimeler: Pegile interferon alfa-2A + ribavirin, pegile interferon alfa-2B + ribavirin, hepatit C virüs ribo nükleik asit

ABSTRACT

Objective: We aimed to evaluate the response to interferon treatment, factors affecting permanent response, and recurrence in patients with chronic hepatitis C (CHC).

Methods: This retrospective study included 305 patients with CHC. They received either pegylated interferon alfa-2A (PEG IFNα-2A) + ribavirin (RIB) treatment or pegylated interferon alfa-2B (PEG IFNα-2B) + RIB treatment for 48 weeks.

Results: At the 48th week of treatment, hepatitis C virus ribonucleic acid (HCV RNA) clearance was seen in 151 (49.5%) of the 305 patients as end-of-treatment response (ETR). ETR was observed in 70 (50.7%) patients treated with PEG IFNα-2A + RIB and in 81 (48.5%) patients treated with PEG IFNα-2B + RIB (p>0.05). After 6 months of treatment, sustained virological response (SVR) was observed in 138 (45.2%) patients. SVR was observed in 63 (45.7%) patients treated with PEG IFNα-2A+RIB and in 75 (45.9%) patients treated with PEG IFNα-2B+RIB (p>0.05). After treatment, recurrence occurred in 35 (11.6%) patients.

Conclusion: The long-term prognosis of CHC infection is positively affected by the treatment regimen. PEG IFNα-2A + RIB and PEG IFNα-2B + RIB treatment regimens have not yet increased HCV RNA clearance to the desired level. Thus, new treatment regimens are required.

Keywords: Pegylated interferon alfa-2A + ribavirin, pegylated interferon alfa-2B + ribavirin, hepatitis C virus ribonucleic acid

GİRİŞ

Dünyada 200 milyondan fazla kişinin hepatit C virüsü (HCV) ile enfekte olduğu düşünülmektedir. Her yıl 250000 insan HCV'nin yol açtığı siroz veya hepatosellüler karsinom nedeniyle ölmektedir (1). HCV enfeksiyonu, karaciğerde kronik hepatit, fibrozis, siroz ve hepatosellüler karsinoma (HSK) gibi komplikasyonlara yol açar. HCV'ye bağlı karaciğer hastalığının tedavisinde, son 20 yılda önemli gelişmeler kaydedilmiştir. Tedavi kesildikten sonra 24 haftada saptanamaz hepatit C virüs ribo nükleik asit (HCV RNA) seviyeleri olarak tanımlanan kalıcı virolojik yanıt (KVY), sirozu olmayan hastalarda hastalığın iyileşmesiyle ilişkilidir (2).

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Geliş Tarihi/Received: 23.06.2017 • **Kabul Tarihi/Accepted:** 03.10.2017

Genel olarak KVY, 48 hafta sadece pegile-interferon (PEG-IFN) kullanan hastalarda %29 iken, PEG-IFN ve ribavirin (RİB) kombinasyon tedavisi alan hastalarda %44-56'ya çıkmıştır (3). Çeşitli çalışmalarda PEG-IFN α-2A ve PEG-IFN α-2B başarı oranı birbirine benzer bulunmuştur. Naiv hastalarda KVY oranı %54-56'dır ve bu oran büyük oranda HCV genotipine bağlıdır. Genotip 1 hastalarda %42-46, genotip 2- 3 hastalarda %76- 82 oranında KVY elde edilmiştir (4).

Düşük HCV RNA düzeyi, genotip 1 dışındaki HCV tipleri, sirozun yokluğu, 40 yaşından genç olma, kadın cinsiyet, karaciğerde yağlanma olmaması, obezite yokluğu ve beyaz ırktan olma KVY oranlarını artırmaktadır (5). Bilinen en kuvvetli prediktif faktör, virusun genotipi olup en iyi tedavi şeklinin seçimi için tedavi öncesi genotipin belirlenmesi önemli bir basamak olacaktır. Bunun dışında özellikle vücut kitle indeksinin 30'un üzerinde olması, insülin direnci, kromozom 19'da lokalize olan IL28B genetik polimorfizmi, ilerlemiş karaciğer fibrozisi diğer negatif prediktif faktörler olarak tanımlanmıştır (6).

KVY elde edilen hastalarda fibroziste ilerleme görülmez ve hatta mevcut fibroziste gerileme görülebilir. Karaciğer yetmezliği ve HSK ile ilişkili sağkalım yüzdeleri, KVY elde edilen sirotik hastalarda, tedaviye yanıtsız hastalara göre daha yüksek bulunmuştur. Bu yüzden, HCV tedavisinde nihai hedef virüsün eradikasyonu olmalıdır (7).

Önceki Sağlık Uygulama Tebliği (SUT)›ne göre, kronik hepatit C (KHC) hastalarında, PEG-IFN ve RİB tedavisi verilmekteydi. Bu çalışmada kliniğimizde takip ve tedavisi yapılan KHC hastalarında, interferon'lu tedavilere cevabı, kalıcı viral yanıtı etkileyen faktörleri ve nüksü değerlendirmeyi amaçladık.

YÖNTEMLER

Hasta Grubu

Çalışmaya retrospektif olarak Nisan 2008 - Şubat 2012 tarihleri arasında polikliniklerimize başvuran KHC'li 305 hasta alındı. KHC tanısı serolojik ve moleküler incelemeler ile kondu. Hastalara 48 hafta pegile interferon alfa-2A (PEG-IFN α-2A) + ribavirin (RİB) veya pegile interferon alfa-2B (PEG-IFN α-2B) + RİB tedavisi verildi. Hastaların tedaviye başlangıç alanin aminotransferaz (ALT), aspartat aminotransferaz (AST), alkalen fosfataz (ALP), gama glutamil transferaz (GGT), albumin, hemogram ve Child-pugh skorları değerlendirildi. PEG-IFN α-2A /2B + RİB tedavisinin sonuçları araştırıldı. Anti-HCV, serolojik olarak enzyme-linked immunosorbent assay (ELISA) yöntemi ile çalışıldı. Moleküler laboratuvarında, hastaların serumlarında HCV RNA düzeyleri, "real time polimeraz zincir reaksiyonu (PCR)" yöntemiyle (COBAS Taqman HCV, Roche Diagnostic Systems, Inc., Branchburg, NJ, ABD) tespit edildi. HCV RNA kantitatif olarak 15 IU/mL ve üzeri sonuçlar pozitif olarak kabul edildi. HCV RNA pozitif saptanan hastalarda, HCV genotiplendirmesi, real time PCR yöntemiyle Abbott m2000r (Abbott Molecular Diagnostic, ABD) sisteminde çalışıldı.

Çalışmaya dahil edilme kriterleri: I) 18 yaşından büyük olmak, II) Enzyme-linked immunosorbent assay (ELISA) ile Anti-HCV pozitif bulunmuş olmak, III) Serum HCV RNA kantitatif olarak ölçülmüş ve pozitif saptanmış olmak, IV) 48 haftalık PEG-IFN α-2A / 2B + RİB tedavisi almış olmak. Çalışmadan dışlanma kriterleri: İ) HCV RNA negatif olmak, İİ) Siroz, HCC ve otoimmun karaciğer hastalığı tanısı olmak.

Çalışma, 2008 yılında revize edilen 1975 Helsinki Bildirgesi ilkelerine ve Klinik Araştırmalar Etik Kurulu Komisyonunun 16.05.2016/149 numaralı onayına istinaden yürütüldü. Yazılı hasta onamı, çalışmaya dahil olan tüm hastalardan alındı.

İstatistiksel Analiz

Sürekli değişkenlerin normal dağılıma uygunluk kontrolünde, Kolmogorov Smirnov testi kullanıldı. Normal dağılıma sahip değişkenlerin iki bağımsız grup karşılaştırılmasında Student t testi, normal dağılıma sahip olmayan değişkenlerin iki bağım-

Tablo 1. Genotip alt türlerinin hasta grubundaki genel dağılımı

Değişken	Sayı (n)	Genotip 1b %	Genotip 1 %	Genotip 1a %	Genotip 1 ve 1b %	Genotip 3A %	Genotip 4A %	Genotip 5 %
Toplam	305	284 (93,1)	13 (4,3)	4 (1,3)	1 (0,3)	1 (0,3)	1 (0,3)	1 (0,3)
Kadın	133 (43,6)	121 (42,6)	8 (61,5)	2 (50)	0	1 (100)	0	1 (100)
Erkek	172 (56,4)	163 (57,4)	5 (38,5)	2 (50)	1 (100)	0	1 (100)	0
Yaş	55,8±12,8	55,8±12,9	54,7±13,3	62±4,5	62	46	32	66
Başlangıç ALT düzeyi(U/L)	43,3±33,6	42,71±33,76	49±24	84±49,74	30	24	30	26
Başlangıç HCV RNA Düzeyi (IU/mL)	4207225,8± 3687669,52	4238402,6± 3729767,86	3130977,6± 2761167,17	6675000± 3004857,17	226000	1900000	7900000	2100000
KC Bx yapılan	56	51	5	0	0	0	0	0
İleri fibrozis saptanan (ISHAK skoru 3-6)	37 (%66)	33 (%64,7)	4 (%80)	0	0	0	0	0

ALT: alanin aminotransferaz; HCV RNA: hepatit C virüs ribo nükleik asit; KC Bx: karaciğer biyopsisi

Tablo 2. Kalıcı virolojik yanıta etki eden faktörler

Değişken		Sayı (n)	KVY, n (%)	p
Cinsiyet	Kadın	133	78 (45,3)	0,967
	Erkek	172	60 (45,1)	
Yaş grubu	40 yaş altı	38	19 (50)	0,167
	40-49 yaş arası	36	21 (58,3)	
	50 yaş ve üzeri	231	98 (42,4)	
HCV genotipi	1b	284	129 (45,4)	0,255
	1	13	7 (53,8)	
	1a	4	0	
	1 ve 1b	1	1 (100)	
	3a	1	1 (100)	
	4a	1	0	
	5	1	0	
Diyabet,	Evet	31	11 (35,5)	0,249
Prediyabet	Hayır	274	127 (46,4)	
Başlangıç	<500000	37	17 (45,9)	0,586
HCV RNA	≥500000 <3000000	74	37 (50)	
(IU/mL)	≥3000000	193	83 (43)	
Fibrozis Varlığı	Var	37	15 (40,5)	0,713
	Yok	17	6 (35,3)	
Başlangıç	<40	185	109 (58,9)	0,000
ALT düzeyi	40- <80	88	24 (27,3)	
(U/L)	80- <120	20	3 (15)	
	120+	12	2 (16,7)	
Başlangıç	<14	247	108 (43,7)	0,271
Hb Düzeyi	≥14	58	30 (51,7)	
(g/dL)				
Başlangıç	<4000	21	6 (28,6)	0,112
WBC Düzeyi	≥4000	284	132 (46,5)	
(/µL)				
Başlangıç	<200	100	38 (38)	0,206
PLT Düzeyi	200- <300	141	69 (48,9)	
(10^3/µL)	≥300	64	31 (48,4)	

KVY: kalıcı virolojik yanıt; HCV: hepatit C virüsü; HCV RNA: hepatit C virüs ribo nükleik asit; ALT: alanin aminotransferaz; Hb: hemoglobin; WBC: beyaz küre; PLT: trombosit

sız grup karşılaştırılmasında ise Mann Whitney U Testi kullanıldı. Betimleyici istatistiklerle beraber ki-kare testi kullanıldı. İstatistiksel analizler için SPSS for Windows version 22.0 paket programı (Statistical Package for the Social Sciences IBM Corp-2011-IBM Corp.; Armonk, NY, ABD) kullanıldı ve $p < 0.05$ istatistiksel olarak anlamlı kabul edildi.

Tablo 3. Tedavi rejimine ve genotipe göre kalıcı virolojik yanıt düzeyleri

Tedavi rejimi	PEG-IFN α-2A + RİB, n (%)	PEG-IFN α-2B + RİB, n (%)	p
Hasta sayısı	138	167	-
Kalıcı virolojik yanıt	63 (%45,7)	75 (%45,9)	0,897
Genotip 1b, KVY	58/124 (%46,8)	71/160 (%44,4)	0,126
Genotip 1, KVY	3/7 (%42,9)	4/6 (%66,7)	
Genotip 1a, KVY	0/4 (%0)	0	
Genotip 1 ve 1b, KVY	1/1 (%100)	0	
Genotip 3a, KVY	1/1 (%100)	0	
Genotip 4a, KVY	0	1/1 (%100)	
Genotip 5, KVY	0/1 (%0)	0	

PEG-IFN α-2A + RİB: pegile-interferon α-2A + ribavirin; PEG-IFN α-2B + RİB: pegile-interferon α-2B + ribavirin; KVY: kalıcı virolojik yanıt

BULGULAR

Kliniğimizde KHC enfeksiyonu tanısı ile tedavi almış olan toplam 305 hastanın 18. ay sonunda tedavi yanıtı değerlendirildi. Tablo 1 de genotip alt gruplarının yaş, cinsiyet, başlangıç ALT düzeyleri, başlangıç HCV RNA düzeyleri, biyopsi yapılan ve ileri fibrozis saptanan (İSHAK 3-6) hastaların dağılımı gösterildi. Toplam 56 hastadan 37 (%66)'sinde ileri fibrozis saptanırken 51 genotip 1b hastasının 33 (%64,7)'ünde ileri fibrozis saptandı (Tablo 1).

Çalışmamıza 305 hasta katılmış olup 133'ü kadın (%43,6), 172'si erkek (%56,4) idi (p=0,967). KVY'i etkileyen faktörler araştırıldı. Yaş grupları 40 yaş altı, 40-49 yaş arası ve 50 yaş üzeri anlamlı bir fark saptanmadı (p=0,167). HCV genotip alt gruplarından genotip 1b hasta sayısı 284 (%93,1) idi. Diğer genotip alt gruplar arasında anlamlı bir fark saptanmadı (p=0,255). Başlangıç HCV RNA düzeylerinin KVY üzerinde anlamlı bir etkisi görülmedi. (p=0,586). Hastada ileri fibrozisin varlığı veya yokluğu KVY açısından anlamlı risk faktörü olarak saptanmadı (p=0,713). Başlangıç beyaz küre, hemoglobin ve platelet düzeyleri yine KVY açısından risk faktörü olarak değerlendirilmedi. Başlangıç ALT düzeylerinin < 40 IU / mL olması, KVY üzerinde olumlu faktör olarak saptandı ve bu sonuç anlamlı idi (p=0,000) (Tablo 2).

Tedavi rejiminin (PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB) genotip alt türlerine göre KVY oranları araştırıldı. KVY açısından her iki tedavi rejimleri arasında anlamlı bir fark saptanmadı (p>0,05). Buna göre PEG-IFN α-2A + RİB alan 138 hastanın 63'ünde (%45,7) KVY saptandı. PEG-IFN α-2B + RİB alan 167 hastanın 75'inde (%45,9) KVY saptandı. Genotip 1b grubunda PEG-IFN α-2A + RİB tedavisi alan 124 hastanın 58'inde (%46,8) KVY saptandı. PEG-IFN α-2B + RİB tedavisi alan 160 hastanın 71'inde (%44,4) KVY saptandı. Diğer grupların ayrı ayrı KVY'leri değer-

Tablo 4. Pegile İnterferon alfa-2A / 2B + ribavirin tedavisinin genotip alt türlerinde yanıt durumu

Genotip	Sayı (n)	Kalıcı virolojik yanıt (%)	Tedaviye yanıtsızlık (%)	Nüks vakalar (%)
Genotip 1b	284	129 (45,4)	86 (30,3)	35 (12,3)
Genotip 1	13	7 (53,8)	3 (23,1)	0
Genotip 1a	4	0	3 (75)	0
Genotip 1 ve 1b	1	1 (100)	0	0
Genotip 3a	1	1 (100)	0	0
Genotip 4a	1	0	1 (100)	0
Genotip 5	1	0	1 (100)	0

Tablo 5. Hastaların tedaviye yanıt dağılımları

Yanıt durumu	Sayı	Yüzde (%)
Primer yanıtsızlık	118	38,7
Kısmi virolojik yanıt	36	11,8
Tedavi sonu virolojik yanıt	151	49,5
Kalıcı virolojik yanıt	138	45,2
Nüks	35	11,6

lendirildi. Tüm genotipler açısından ise her iki tedavi kolunda anlamlı bir fark saptanmadı (p<0,05) (Tablo 3).

PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisinin genotip alt türlerinde yanıt durumuna bakıldığında genotip 1b olan 284 hastanın; KVY'si 129 (%45,4) hasta, tedaviye yanıtsızlık 86 (%30,3) hasta, nüks 35 (%12,3) hasta olarak saptandı. Diğer genotip alt gruplarının tedaviye yanıtı Tablo 4'te gösterildi.

Hastaların tedaviye yanıt durumları değerlendirildi. 118 hastada (%38,7) primer yanıtsızlık saptandı. 36 hastada (%11,8) kısmi virolojik yanıt saptandı. TSVY 151 hastada (%49,5) saptandı. KVY ise hastaların 138'inde (%45,2) saptandı. Hastaların 35'inde (%11,6) ise nüks saptandı (Tablo 5).

PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisinin 3. ayda laboratuvar yan etkilerine bakıldığında tüm hastaların 133'ünde (%43,6) anemi, 116'sında (%38) ALT yüksekliği, 16'sında (%5,2) lökopeni, 50'sinde (%16,4) trombositopeni saptandı. Her iki tedavi kolunda da tüm yan etkiler açısından anlamlı bir fark saptanmadı (p>0,05). PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisinin 12. ayda laboratuvar yan etkilerine bakıldığında tüm hastaların 110'unda (%36,1) anemi, 128'inde (%42,8) ALT yüksekliği, 18'inde (%6) lökopeni, 66'sında (%22,1) trombositopeni saptandı. Her iki tedavi kolunda da tüm yan etkiler açısından anlamlı bir fark saptanmadı (p>0,05).

PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisine göre klinik yan etkilere bakıldığında ön planda halsizlik ve ateş saptandı. Tüm klinik yan etkilere bakıldığında ise istatiksel olarak anlamlı bir fark saptanmadı (p>0,05).

TARTIŞMA

Son 10 yıl içerisinde, PEG-IFN'ların ortaya çıkmasıyla HCV enfeksiyonlarının tedavisinde önemli ilerlemeler sağlanmıştır (8). Tedavinin amacı, viral replikasyonun baskılanması, siroz ve HSK gibi geç komplikasyonların önlenmesidir. KHC tedavisinde antiviral tedavi ile hedeflenen başarı kriterleri biyokimyasal yanıt olarak ALT ve AST'nin normale dönmesi, virolojik yanıt olarak ise HCV RNA'nın negatifleşmesi ve histolojik yanıt olarak da karaciğerde nekroinflamasyonun azalmasıdır (3).

Tedavi sonu viral yanıtın değerlendirildiği çalışmalara baktığımızda; Manns ve ark. (4) yapmış oldukları çalışmada; TSVY, yüksek doz PEG-IFN α-2B + RİB kombinasyon tedavisi alan grupta %65, düşük doz PEG-IFN α-2B ile RİB kombinasyon tedavisi alan grupta %56, INF α-2B + RİB kombinasyon tedavisi alan grupta %54 olarak bulunmuştur. PEG-IFN α-2A 'nın etkinlik ve güvenilirliğini araştırdıkları çok merkezli ve 531 hastayı kapsayan bir çalışmada; PEG-IFN α-2A 48 hafta boyunca 180µg/kg haftada bir cilt altı uygulanmış, TSVY %69 saptanmıştır. Bu oran IFN α-2A tedavisiyle elde edilen %28 oranından belirgin yüksektir (9). Fried ve ark. (3) kronik HCV hastaları üzerinde yapmış oldukları çalışmada; PEG-IFN α-2A ile RİB kombinasyonu alan hastalarda TSVY oranı %69, INF α-2B + RİB kombinasyonu alan hastalarda TSVY oranı %52, PEG-IFN α-2A ile plasebo alan hastalarda TSVY oranı %59 olarak bulunmuştur.

Bizim çalışmamızda vermiş olduğumuz tedavi rejiminin (PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB) 12. Ayında TSVY, tüm hastaların 151'inde (%49,5) saptandı. PEG-IFN α-2A kullanan hastaların 70'inde (%50,7), PEG-IFN α-2B + RİB kullanan hastaların 81'inde (%48,5) HCV RNA klirensi saptandı. Her iki kolda da anlamlı bir fark saptanmadı (p>0,05). Elde etmiş oldugumuz TSVY oranları kimi yayınlardan düşük tespit edilmiş olup literatürdeki bazı çalışmalar ile de benzerlik göstermektedir. Bazı yayınlara göre daha düşük TVSY tespit edilmiş olması ise hastaların çoğunluğunun genotip 1 ve genotip 1b olmasından kaynaklanmış olabilir.

Yaptığımız çalışmamızda tedavi rejiminin (PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB) genotip alt türlerine göre KVY düzeylerine de bakılmış olup, PEG-IFN α-2A + RİB alan 138 hastanın 63'ünde (%45,7) KVY saptandı. PEG-IFN α-2B + RİB alan 167 hastanın 75'inde (%45,9) KVY saptandı. Genotip 1b grubunda PEG-IFN α-2A + RİB tevdisi alan 124 hastanın 58'inde (%46,8) KVY saptandı. PEG-IFN α-2B + RİB tedavisi alan 160 hastanın 71'inde (%44,4) KVY saptandı. KVY'nin değerlendirildiği diger çalışmalara baktığımızda; Reddy ve ark. (10) PEG-IFN α-2A 'nın dozunu belirlemek icin, daha önce INF tedavisi almamış KHC'li hastalar üzerinde yapmış oldukları çalışmada; 45 µg haftada bir doz uygulamada KVY %10 bulunmuş ve IFN α-2A haftada 3 doz tedavisine gore KVY acısından anlamlı fark olmadığı belirtilmiştir. 180 µg haftada bir doz PEG-IFN α-2A uygulamasında bu oran %36 bulunmuş ve PEG-IFN α-2A 'nın en uygun

dozunun haftada bir kez 180 µg olduğu belirtilmiştir. Zeuzem ve ark. (9) yapmış olduğu çalışmada; PEG-IFN α-2A 180µg haftada bir uygulama sonucu KVY %39 saptanmıştır. Bu oran INF α-2A tedavisiyle elde edilen %19 oranından belirgin yüksektir. Olut ve ark. (11) yaptığı çalışmada genotip 1 ile infekte 50 naiv KHC hastasına PEG-IFN α-2B 1,5 µg/kg/hafta ve vücut ağırlığına göre RİB 1000-1200 mg/gün tedavisi uygulanmıştır. Tedavi sonucunda nihai hedef, tedavi bitiminden 24 hafta sonra serumda HCV RNA saptanmaması olarak belirlenmiştir. Toplam 50 hastanın 30'unda (%60) KVY elde edilmiştir. Gonçalves ve ark. (12) yaptığı 141 hastayı içeren calışmada TSVY 77 (%54,6) hastada, KVY 56 (%39,7) olarak bulunmuştur. Bizim çalışmamızda da KVY literatüre benzer oranlarda saptanmıştır. Literatürdeki bazı çalışmalarda daha yüksek KVY elde edilmesi çalışmaya dahil edilen hasta popülasyonun farklılığı ve genişliği olabilir.

Literatürde, PEG-IFN α-2A ve PEG-IFN α-2B preparatlarının hangisinin KVY üzerine daha etkili olduğunu gösteren çok az çalışma vardır. İtalya'da yapılan bir çalışmada, PEG-IFN α-2A ve RİB kombinasyonu ile elde edilen KVY oranlarının, hem genotip 1-4 hem de genotip 2-3 hastalarda, PEG-IFN α-2B ve RİB kombinasyonu ile elde edilen KVY oranlarından anlamlı derecede yüksek olduğu, buna karşın her iki tedavi kolunda hastalarda tespit edilen yan etkilerin benzer olduğu bildirilmiştir (13).

Çalışmamızda PEG-IFN α-2A / 2B + RİB tedavisinin genotip alt türlerinde yanıt durumuna bakıldığında genotip 1b olan 284 hastanın; KVY 129 (%45,4) hasta, tedaviye yanıtsızlık 86 (%30,3) hasta, nüks 35 (%12,3) hasta olarak saptandı.

Hepatit C virüs ribo nükleik asit düzeyi < 400.000 IU/mL hastalarda, daha yüksek viral yükü olan hastalara göre daha yüksek bir kalıcı viral yanıt oranı elde edildiği gösterilmiştir. Klinik bir çalışmada > 600.000 IU/mL HCV RNA düzeyi ile düşük kalıcı viral yanıt oranı elde edildiği ve yüksek viral yükün kalıcı viral cevap oranını azalttığı belirtilmiştir (14, 15). İnterferon içeren rejimlerle, düşük serum viral yükü (< 800.000 IU/mL) olan hastalarda anlamlı derecede daha fazla kalıcı viral cevap sağlandığı görülmüştür (16, 17). Bazı çalışmalarda ise (> 850.000 IU/mL) yüksek viral yükü olan hastalarda, düşük viral yüklü hastalara göre daha fazla kalıcı viral cevap sağlandığı görülmüştür (9, 18-21). Fried ve ark. (3) yaptığı çalışmada PEG-IFN α-2A alan hastalar ile PEG-IFN α-2B alan hastalar karşılaştırıldığında, HCV RNA düzeyi > 800.000 IU/mL olan ve PEG-IFN α-2A ile tedavi alan hastalarda daha yüksek KVY sağlandığı tespit edilmiştir. Berg ve ark. (22) 260 hasta üzerinde yaptıkları çalışmada < 130.000 IU/mL HCV-RNA düzeyinin, tedaviye daha iyi yanıt verdiği belirtilmiştir. Ancak yine de tedaviye cevapı önceden predikte edecek net bir HCV-RNA düzeyi yoktur. PEG-IFN α-2A ile yapılan son çalışmalar göstermiştir ki viral yükten bağımsız olarak KVY oranları, HCV genotipine göre değişmektedir (23). Ancak bizim çalışmamızda başlangıç HCV RNA degerleri ile KVY arasında anlamlı bir fark saptanmadı ve KVY'yi etkilemedigi tespit edildi. Çalışmamızda tedavi rejiminin (PEG-IFN α-2A ve PEG-IFN α-2B) 12. ayında tüm hastaların 151'inde (%49,5) HCV RNA klirensi saptandı. PEG-IFN α-2A + RİB kullanan hastaların 70'inde (%50,7), PEG-IFN α-2B + RİB kullanan hastaların 81'inde (%48,5) HCV RNA klirensi saptandı. 18. ayda KVY ise tüm hastaların 138'inde (%45,2) saptandı. PEG-IFN α-2A + RİB kullanan hastaların 63'inde (%45,7), PEG-IFN α-2B + RİB kullanan hastaların 75'inde (%45,9) KVY saptandı. Her iki kolda da anlamlı bir fark saptanmadı (p>0,05).

Tedavi sonrası nüks ile ilgili yapılan bir çalışmada, 400 hastanın 7 (%2) sinde takiplerde HCV RNA tespit edilmiş ve 5 tanesi takip edilmiş ve 2 (%0,5) sinde 12 aylık tedavi sonrasında HCV RNA tekrar tespit edilmiştir (24). Öte yandan, geç nüks oranları yüksek izlenen çalışmalar da vardır: Lee ve ark. (25) %7,4, Reichard ve ark. (26) %8, Khokhar (27) ise %8,8 olarak bildirmişlerdir. Bu uyumsuzluklar değişken duyarlılıkta ve hasta populasyonlarında kullanılan PCR yöntemlerinden kaynaklanmaktadır. Sonuç olarak kalıcı viral yanıtın sürdürülebilirğinin ve optimal takip süresi bilinmemektedir (28). Bizim çalışmamızda ise PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisi alan hastaların, genotip alt türlerine göre yanıt durumuna bakıldığında, genotip 1b olan 284 hastada; kalıcı virolojik yanıt 129 (%45,4), tedaviye yanıtsızlık 86 (%30,3) ve nüks 35 (%12,3) olarak saptandı. Diger genotip alt gruplarında ise herhangi bir nüks saptanmadı. Literatüre göre daha az nüks izlenmiş olmasının, takibin uzun süreli olmamasından ve hasta sayısının yetersizliğinden kaynaklanmış olabileceği düşünüldü.

İnterferon alfa tedavisi verilen hastalarda istenmeyen yan etkiler sık gözlenmektedir. IFN ve RİB tedavisi alan hastalarda, hastaların en az %75'inde bir yan etki görülmektedir. Grip benzeri şikayetler ve depresyon bulguları PEG-IFN tedavisinde, klasik interferonlara göre daha az görülmektedir (29). Çalışmamızda PEG-IFN α-2A / 2B + RİB tedavisine göre klinik yan etkilere bakıldığında ön planda halsizlik ve ateş saptandı. Bunun dışında grip benzeri tablo, kas ağrısı, iştahsızlık, bulantı, baş ağrısı, döküntü, depresyon gibi yan etkiler açısından bakıldığında ise, her iki tedavi grubunda da hastalarda tespit edilen yan etkilerin birbirine benzer olduğu ve anlamlı bir farkın saptanmadığı gözlemlendi.

SONUÇ

Kronik hepatit C enfeksiyonunda verilen tedaviler ile hastaların uzun dönem prognozları olumlu yönde etkilenmektedir. PEG-IFN α-2A + RİB ve PEG-IFN α-2B + RİB tedavisi ile HCV RNA klirensinde, istenen düzeye ulaşılamamıştır.

Etik Komite Onayı: Bu çalışma için etik komite onayı, Gaziantep Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu Komisyonu'ndan alınmıştır (16.05.2016/149).

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - A.B.; Tasarım - A.B.; Denetleme - A.B., M.T.G.; Malzemeler - O.B.; Veri Toplanması ve/veya İşlemesi - O.B., T.M.; Analiz ve/veya Yorum - A.B., O.B.; Literatür Taraması - T.M.; Yazıyı Yazan - A.B.; Eleştirel İnceleme - A.B., M.T.G.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Ethics Committee Approval: Ethics committee approval was received for this study from Gaziantep University School of Medicine Clinical Research Ethics Committee (16.05.2016/149).

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

Peer-review: Externally peer-reviewed.

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

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

Financial Disclosure: The authors declared that this study has received no financial support.

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How to cite:

Balkan A, Batı O, Metin T, Gülşen MT. Efficacy of regimens containing pegylated interferon and ribavirin in the treatment of chronic hepatitis C: A retrospective overview. Eur J Ther 2017; 23: 173–9.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.134

Case Report / Olgu Sunumu

A rare manifestation of Crohn's disease in an adolescent: Optic neuritis

Adolesan Crohn hastasının nadir bir bulgusu: Optik nörit

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ABSTRACT

Crohn's disease (CD) affects the small and large intestines with focal transmural granulomatous inflammation. Some patients with inflammatory bowel diseases (IBD) also show ocular involvement. Optic nerve involvement in patients with IBD may present as neuroretinitis, papillitis, optic neuritis (demyelinating), or ischemic optic neuropathy. There is limited information on ocular involvement in adolescent and pediatric patients. We present a case of a 17-year-old male who applied to the gastroenterology department with abdominal pain, diarrhea, and sudden vision loss in the right eye and was eventually diagnosed with CD, optic neuropathy, and neuroretinitis. To best of our knowledge, this is the second report regarding optic nerve involvement in CD in the pediatric and adolescent population in literature.

Keywords: Adolescent, Crohn's disease, extraintestinal manifestations, optic neuritis, vision loss

ÖZ

Crohn hastalığı (CD) ince ve kalın barsaklarda fokal transmural granülomatöz inflamasyon yapan bir hastalıktır. İnflamatuvar barsak hastalığı (IBD) olan bazı hastalarda göz tutulumu olabilmektedir. Optik sinir tutulumu olan IBD hastalarında, neuroretinit, papillit, optic (demyelinizan) neurit veya iskemik optik nöropati saptanabilir. Bununla birlikte adolesan ve pediatrik hastalarda oküler tutulum ile ilgili çok az bilgi mevcuttur. Biz Gastroenteroloji bölümüne karın ağrısı, ishal, sağ gözde ani görme kaybı şikayeti ile başvuran ve yapılan incelemelerde Crohn hastalığı, optik nörit ve nöroretinit teşhisi konulan 17 yaşında erkek hastayı vaka sunumu olarak rapor ettik. Bildiğimiz kadarıyla, pediatrik ve adolesan dönemde, Crohn hastalığında optik sinir tutulumu hakkında şu anki literatürde ikinci vakayı rapor ettik.

Anahtar kelimeler: Adolesan, Crohn hastalığı, extraintestinal bulgular, optik nörit, görme kaybı

INTRODUCTION

Crohn's disease (CD) affects the small and large intestines with focal transmural granulomatous inflammation (1). Inflammatory bowel diseases (IBD) mostly present with gastrointestinal symptoms; however, 20%-40% of patients also have extraintestinal findings (2). Previous studies have shown that 1%-2% of the patients with IBD also have ocular involvement (3). The extent of bowel involvement does not correlate with ocular complications, and ocular involvement generally occurs in the early years of the disease. Ocular findings may precede IBD diagnosis in some patients (4).

Optic nerve involvement in patients with IBD may present as neuroretinitis, papillitis, optic neuritis (ON, demyelinating), or ischemic optic neuropathy (5). ON can be present in up to 4% of adult IBD patients (6, 7). Symptoms include blurry or decreased vision for few hours to several days and retrobulbar pain (5).

We report a case of a 17-year-old male who applied to the gastroenterology department with abdominal pain, diarrhea, and sudden vision loss and was eventually diagnosed with CD, ON, and neuroretinitis.

CASE PRESENTATION

A 17-year-old male Syrian refugee applied to another hospital with diarrhea, abdominal pain, hyperemia in his left eye, and was hospitalized. On the third day of hospitalization (DoH), patient described floaters in both eyes and blurry vision in the right eye but he was not referred to an ophthalmologist. On the sixth day, he was referred to another hospital due to unknown reasons. On the eight day, the patient had a temporary vision loss in his right eye, which lasted for 1 hour, and his ophthalmologic examination was evaluated as normal. On the tenth DoH, the patient had fever and permanent vision loss in his right eye. The two hospitals could not diagnose the condition and hence the patient did not receive any specific treatment. He was referred to our hospital on the twelfth DoH. Patient had yellow-colored watery diarrhea 10–15 times a day without blood, abdominal pain, high fever and vision loss in his right eye at his admission to gastroenterology department of our hospital. He was dehydrated and had lost 8 kg weight by this time. He had tenderness in the epigastric region and lower quadrant of the abdomen without defense or rebound. Laboratory tests revealed white blood cell (WBC), 11.000/μL; erythrocyte sedimentation rate (ESR), 40 mm/h; C-reactive protein (CRP), 130 mg/dL; and albumin, 2.7 g/

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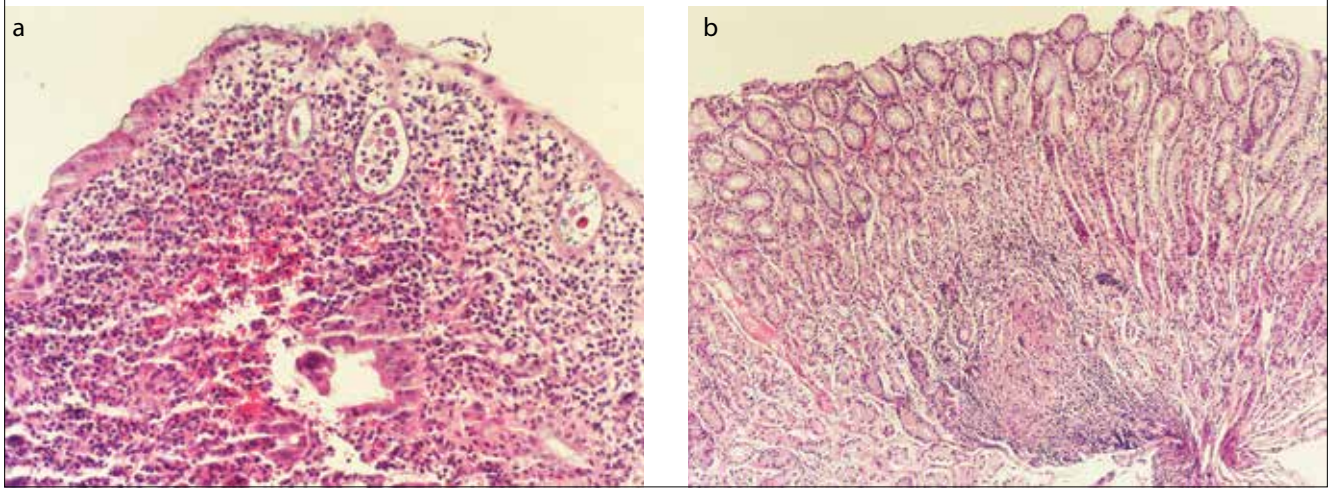
Received/Geliş Tarihi: 12.06.2017 • **Accepted/Kabul Tarihi:** 02.08.2017

Figure 1. a-c. (a) Macular OCT image at presentation shows submacular fluid in the right eye. (b) Anterior segment image of the right eye shows iris pigments on the lens. (c) Anterior segment image of the left eye shows iris pigments on the lens

Figure 2. a, b. Gastric and colonic involvement of CD. (a) Mixed inflammatory cell reaction attacking surface epithelium and crypts in colon mucosa (H and E ×200). (b) Granuloma at lamina propria of gastric mucosa (H and E ×100)



dL. We excluded infection and infestation but detected hemoglobin in the fecal matter. Posteroanterior chest X-ray, thorax and upper and lower abdominal computed tomographies (CTs) (Somatom Sensation 16, Siemens, Germany), and whole body CT angiography tests showed normal findings. Cytomegalovirus, parvovirus, Epstein-barr virus, and Venereal Disease Research Laboratory tests were negative. The patient was consulted to the ophthalmology department. His best-corrected visual acuities (BCVAs) were "light perception" and 20/20 in the right and left eyes, respectively. There were iris pigments on the lens of both eyes; fundus examination revealed papilledema and macular star and edema in the right eye (Figure 1).

Patient was diagnosed with ON and neuroretinitis in the right eye, and 1 g intravenous (IV) steroid treatment was started. Cerebral and orbital magnetic resonance imaging (MRI; Siemens Medical Solutions, Erlangen, Germany) tests were normal.

Colonoscopy showed focal aphthous ulcers in the rectum and skip areas of deep ulcerations with a cobblestone pattern in the transverse and descending colon. Biopsy revealed chronic active colitis with mixed inflammatory cell reaction. Esophagogastroduodenoscopy showed wide ulcerations at the great curvature of the stomach. Biopsy revealed granulomatous gastritis (Figure 2).

The pili structure of the jejunum and ileum was normal in MRI enterography. Endoscopy findings and pathologic investigations were compatible with CD. We started azathiopurine (Excella GmbH, Germany) 2 mg/kg/day and lansoprazole (Sanovel, İstanbul, Turkey) 15 mg/day. Methylprednisolone (Mustafa Nevzat, İstanbul, Turkey) was continued as 48 mg/day orally after 3 days. On the seventeenth DoH, laboratory tests were within normal limits. Patient's abdominal pain and diarrhea were improved but vision loss in the right eye unchanged. The patient was discharged and called for ophthalmologic follow-up after 1 month and gastroenterologic follow-up after 3 months.

At the first month follow-up, BCVA was "no light perception" and 20/20 in the right and left eyes, respectively. Fundus examination revealed optic and macular atrophy (Figure 3).

At the third month follow-up, laboratory tests were within normal limits. The methylprednisolone dosage was decreased to 32 mg/day and tapered 16 mg per week. Azathiopurine 2 mg/kg/day and lansoprazole 15 mg/day were continued. In the ophthalmologic examination, BCVA was no light perception and 20/20 in the right and left eyes, respectively. Fundus examination revealed optic and macular atrophy, which were also confirmed by optical coherence tomography (OCT; Figure 4). Fundus of the left eye was normal.

Figure 3. a-c. (a) Macular OCT of the right eye at the first month follow-up shows foveal atrophy. (b) Fundus photography of the right eye at the first month follow-up shows optic atrophy and maculopathy. (c) Fundus photography of the left eye at the first month follow-up is normal

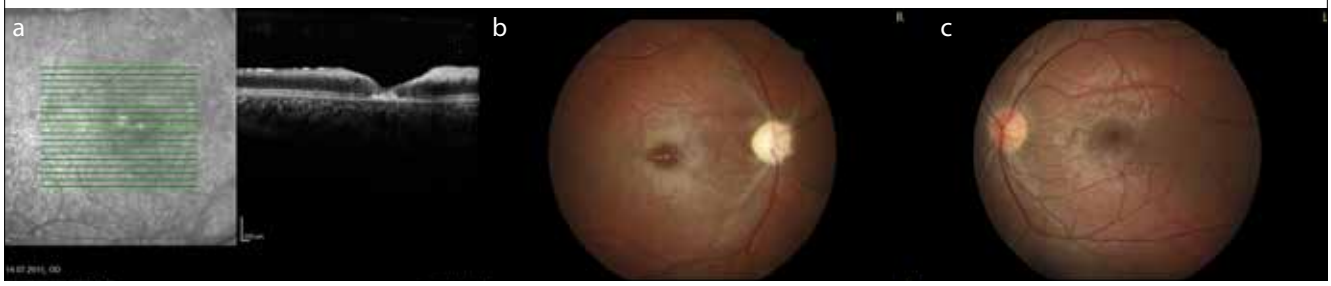
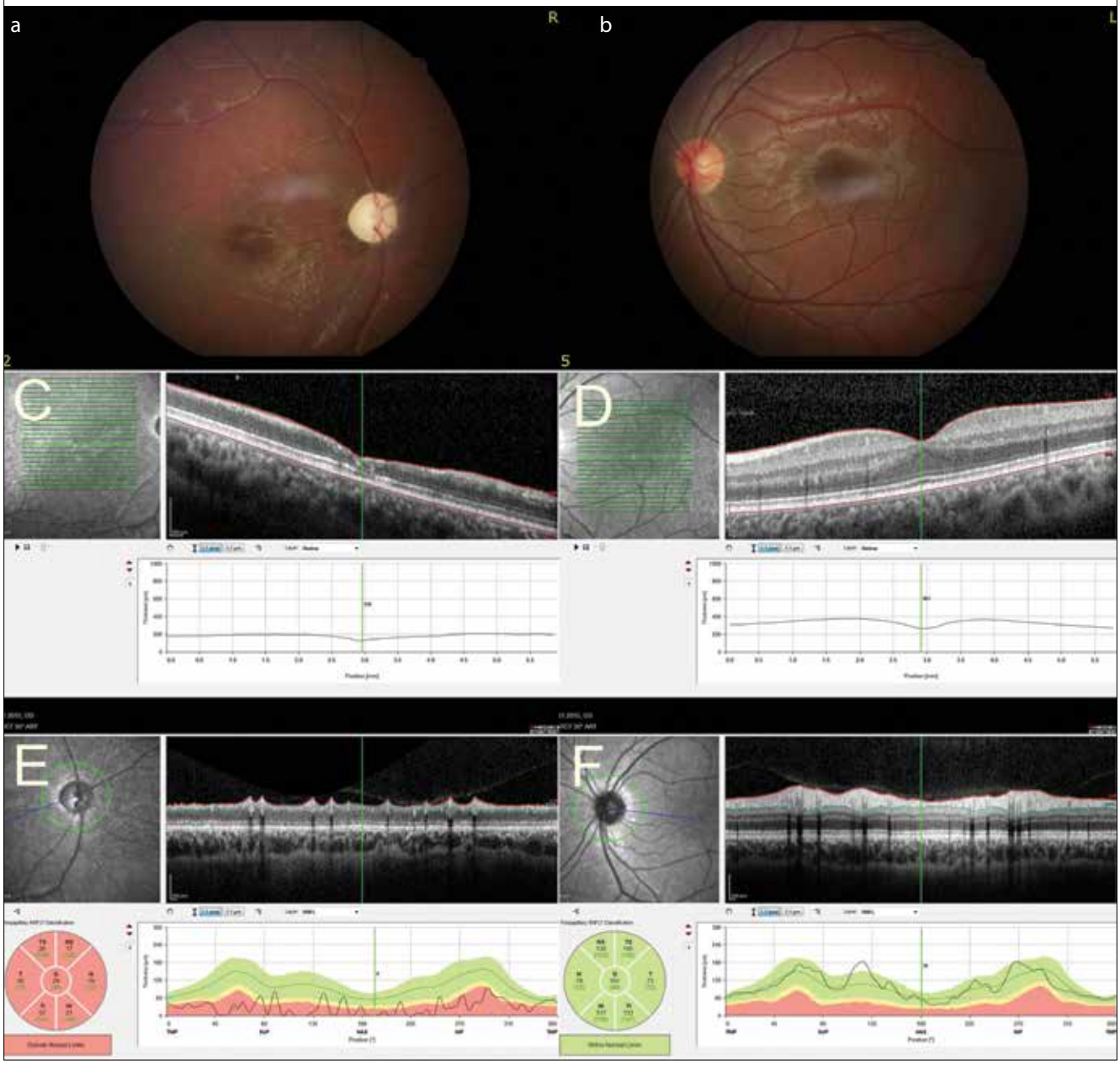


Figure 4. a-f. Ocular findings at the third month follow-up. (a) Fundus photography of the right eye shows optic atrophy and maculopathy. (b) Fundus photography of the left eye is normal. (c) Macular OCT of the right eye shows macular atrophy. (d) Macular OCT of the left eye is normal. (e) Retinal nerve fiber layer (RNFL) analysis of the right eye shows optic atrophy. (f) RNFL analysis of the left eye is normal



DISCUSSION

Ocular manifestation in IBD were reported in 3.5%-43% cases; interestingly, they are more common in colonic or gastric CD cases similar to our case (8). There is limited information on the ocular involvement in adolescent and pediatric patients (9). ON caused by IBDs can be treated with high-dose IV methylprednisolone (10).

We reported an adolescent patient with colonic and gastric CD who presented with severe abdominal pain and diarrhea and developed sudden vision loss in the right eye. The vision loss did not improve despite a 3-day high-dose IV methylprednisolone treatment. In our patient, the most important problem was delayed diagnosis and treatment. Fortunately, all gastrointestinal symptoms were completely resolved with methylprednisolone, azathiopurine, and lansoprazole treatment for CD.

It is unclear if the anti-inflammatory treatment given for IBDs prevents optic nerve inflammation or not; however, a treatment that resolves the gastrointestinal disease may also improve extraintestinal involvement. In our patient regular treatment and follow-up for CD might not be able to improve the vision of the right eye but at least it may be protective for the left eye. Additional studies are needed to clarify the protective effect of anti-inflammatory treatment.

CONCLUSION

Patients presenting with different systemic findings who also have ocular hyperemia, blurry vision, temporary vision loss, retrobulbar pain, or ocular motility disorders require extra attention, and the ophthalmological examination must be performed carefully to ensure that the diagnosis and treatment is not delayed. To best of our knowledge, this is the second report about optic nerve involvement in CD in the pediatric and adolescent population in literature (11).

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

Peer-review: Externally peer-reviewed.

Author contributions: Concept - A.B.; Design - A.B.; Supervision - M.T.G.; Resource - ; Materials - A.B.; Data Collection and/or Processing - A.B.; Analysis and/or Interpretation - A.B., A.M. Literature Search - A.B., S.K.; Writing - A.B.; Critical Reviews - A.M.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastadan alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir - A.B.; Tasarım - A.B.; Denetleme - M.T.G.; Kaynaklar - Malzemeler - A.B.; Veri Toplanması ve/veya İşlemesi - A.B.; Analiz ve/veya Yorum - A.B., A.M.; Literatür Taraması - A.B., S.K.; Yazıyı Yazan - A.B.; Eleştirel İnceleme - A.M.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Balkan A, Kimyon S, Mete A, Gülşen MT. A rare manifestation of Crohn's disease in an adolescent: Optic neuritis. Eur J Ther 2017; 23: 180–3.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.50

Case Report / Olgu Sunumu

Anterior sacral meningocele mimicking an adnexal mass in an infertile woman: a report of an extremely unusual case

İnfertil bir kadında adneksiyal kitleyi taklit eden anterior sakral meningosel: çok nadir görülen bir olgu sunumu

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ABSTRACT

The differential diagnosis of cystic adnexal masses, some placed retroperitoneally, includes various pathologies. Preoperative diagnosis is important to prevent major neurological deficits during surgery. Herein, we present a case of anterior sacral meningocele diagnosed in an infertile woman using magnetic resonance imaging (MRI) and eliminated with surgery. An MRI performed to determine the origin of retroperitoneal fixated masses helps direct the patient to the right consultant department and may avoid an inappropriate surgical approach, which may lead to a failure. A retroperitoneal mass, such as anterior sacral meningocele, may contribute to the pathogenesis of infertility by distorting the utero-tuboovarian anatomy.

Keywords: Adnexal cyst, anterior sacral meningocele, retroperitoneal mass

ÖZ

Kistik adneksiyal kitlelerin ayırıcı tanısında bazıları retroperitoneal olan çeşitli patolojiler düşünülmelidir. Preoperatif tanı operasyon sırasında gelişebilecek nörolojik sorunları önlemek için önemlidir. Makalemizde, infertil bir kadında manyetik rezonans görüntüleme (MRI) yöntemiyle teşhis edilen ve opere edilen anterior sakral meningosel vakasını sunduk. Retroperitoneal bölgeye fikse olmuş kitlelerinin kökenini bulmak için yapılan MRI hastaya daha sonra büyük sorunlara neden olabilecek yetersiz bir cerrahi işlem uygulamayı önlemenin yanında, hastanın uygun bir bölüme yönlendirilmesine yardımcı olur. Anterior sakral meningosel gibi retroperitoneal bölgeye yerleşmiş bir kitle utero-tuboovarian anatomiyi bozarak infertilite gelişmesine yol açabilir.

Anahtar kelimeler: Adneksiyel kist, anterior sakral meningosel, retroperitoneal kitle

INTRODUCTION

An adnexal mass with a completely cystic appearance is a frequently encountered clinical entity and most often arises from the ovaries. The differential diagnosis includes various pathologies, some of which are very rare and are placed retroperitoneally. The differential diagnosis of retroperitoneal cystic masses includes arachnoid cyst, anterior sacral meningomyelocele (ASM), schwannoma, teratoma, hamartoma, neuroenteric cyst, adrenal cyst, or primary mucinous cystic tumor of the retroperitoneum (1). Retroperitoneal masses should be considered particularly when dealing with uncertain or unusual pelvic symptoms and physical findings (2). In this report, we present a very rare case of ASM mimicking a cystic adnexal mass in a primary infertile woman.

CASE PRESENTATION

A 26-year-old null gravid woman, who was married for 6 years, had been admitted to a state hospital complaining about infertility. She also had complaints of dyspareunia, lower back pain with numbness, and pain in both legs over a period of 20 years. Her pain was increased when she bent over or walked a short distance. The pain was relieved after resting. She previously had undergone an elective laparotomy in a state hospital due to a cystic adnexal mass located posterior to the uterus, but intraoperative observation revealed that the cyst was retroperitoneal in origin. Two months later, the patient was referred to our clinic without any further intervention.

The physical examination of the patient revealed an immobile mass of 10×10 cm in diameter with a soft consistency, which

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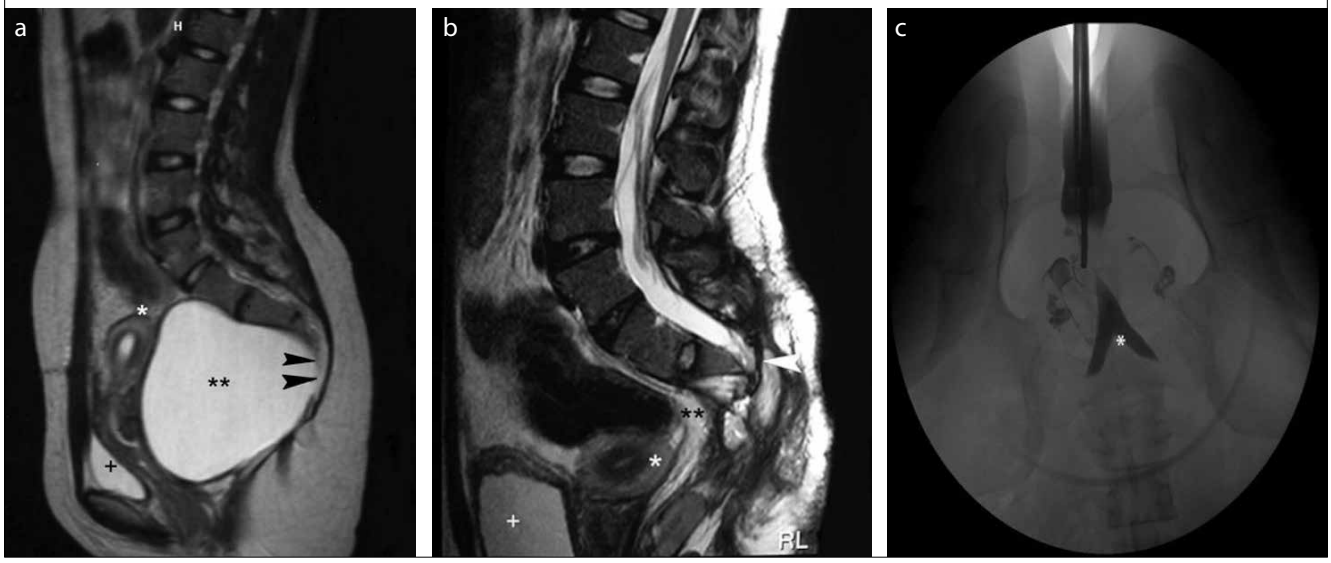
Received/Geliş Tarihi: 07.04.2017 • **Accepted/Kabul Tarihi:** 28.09.2017

Figure 1. a-c. (a) Preoperative sagittal T2-weighted magnetic resonance image demonstrating an anterior sacral meningocele (**). Note the uterus (*) compressed between the meningocele and the bladder (+). A large passage between the subarachnoid space and the meningocele (black arrowheads). (b) Postoperative sagittal magnetic resonance image showing normally positioned uterus (*) and bladder (+). The absence of meningocele (**) indirectly suggests the complete obliteration of the anterior meningocele defect with fascia substitute (white arrowhead) (c) Hysterosalphingography image demonstrating incomplete uterine septum (*).



was localized posteriorly to the uterus. The uterus was displaced more superiorly in the pelvis due to this mass, which led to difficult palpation and observation of the cervix during the speculum examination. An ultrasonography examination revealed a completely cystic mass of 11×10 cm in diameter localized posteriorly to the uterus and displacing it upwards. We also visualized an incomplete uterine septum and planned to perform hysterosalpingography (HSG) after an appropriate management of the mass. Magnetic resonance imaging (MRI) was then performed because of the possible retroperitoneal origin of the mass. MRI revealed an anterior sacral meningocele (Figure 1a). The patient was then referred to the department of neurosurgery with a preliminary diagnosis of ASM.

The neurosurgeons have preferred a posterior surgical approach. A mid-sagittal skin incision was made between L5-S4 levels. The closure of this area was impossible without dural substitute. First, the arachnoid membrane around the nerves was secured. Then, the communication between the ASM and the dura mater space was disconnected by tethering the neck of the meningocele. Postoperative control with MRI revealed that the uterus and bladder were returned to their normal position (Figure 1b). Two months after surgery, the planned HSG that revealed incomplete uterine septum was performed (Figure 1c). The patient had undergone hysteroscopic resection.

DISCUSSION

Retroperitoneal masses should almost always be considered in differential diagnosis of pelvic masses. One of the very rare types of these masses is ASM. ASM is a unilocular or multilocular enlargement of the meninges from the sacral spinal canal to the retroperitoneal presacral space through sacral bony defects and is characterized by a communication with the subarachnoid space (3, 4). Congenital and acquired are the major types of ASM in literature (5). Congenital ASM is usually accompanied by urological and gynecological pathologies; however, it can rarely occur alone (6). In our case, we detected an incomplete uterine septum, and this is as far as we know, the first report of ASM with uterine septum in an infertile woman.

Currarino syndrome is a well-known autosomal-dominant disease, which includes sacral bony defect, anorectal malformation, and presacral mass. This syndrome is most often presented with congenital ASM (7). Acquired ASM develops due to proceeding enlargement of the dura mater and arachnoid membrane that can or cannot result from connective tissue disorders (8).

In two-thirds of all cases, localized symptoms emerge (7). These symptoms occur as a result of pressure on the sacral nerve roots, rectum, bladder, or genitalia. Lower back and pelvic pain, constipation, difficulties in defecation, dysmenorrhea, dyspareunia, and urinary incontinence are the most common symptoms. In the differential diagnosis of retroperitoneal masses, ASMs should always be considered (6, 9). A fixed pelvic mass located posteriorly to the uterus, which is not mobile during a bimanual pelvic examination, should also give the clinician a suspicion of a retroperitoneal pathology and a need for more definitive imaging techniques, such as MRI, other than pelvic ultrasonography. Because of the poor visualization resolution, such as revealing connection between the sacral spinal canal and the pathology, ultrasonography should not be considered primarily (8). MRI is the gold standard for the diagnosis of ASM, which allows for the most accurate preoperative imaging to determine the surgical course (3, 10). ASMs can be misdiagnosed as an adnexal mass in gynecological practice; however, it is usually located posteriorly and both ovaries may be visualized separately (11). Due to the

retroperitoneal location of the ASM, diagnosis may also be made during the surgery (6, 12). Preoperative diagnosis is important to prevent major neurological deficits during surgery. A retroperitoneal mass, which is found unexpectedly at an operation due to the other pelvic diseases, should not be resected (2). Also, any diagnostic intervention, such as transrectal or transvaginal aspiration or biopsy, should be avoided to prevent meningitis, which can result from rectal injuries during the course of anterior sacral meningocele. If it occurs, it may lead to severe morbidity and mortality (13).

Anterior sacral meningomyelocele can be symptomatic or asymptomatic. When it is symptomatic, surgical approach is necessary for relieving the patient's complaints. Traditionally, neurosurgeons intend to extirpate the relation between the subarachnoid space and the meningocele (14). Anterior, posterior, and endoscopic approaches are the surgical choices. Easy ligation of the neck of lesion can be achieved and any associated spinal cord problem can be determined by the posterior approach (10).

CONCLUSION

As in our case, a large retroperitoneal mass may contribute to the pathogenesis of infertility by distorting the utero-tuboovarian relation. Gynecologists have to take into account that gynecologic anomalies may accompany ASMs and consider further evaluation in these patients. An MRI performed to determine the origin of retroperitoneally fixated masses helps direct the patient to the right consultant department and may avoid an inappropriate surgical approach, which can lead to a failure. Also, a multidisciplinary surgical approach with a neurosurgeon to such patients will help to prevent possible complications.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.K.; Design - M.A.; Supervision - İ.E.; Data Collection and/or Processing - B.K.U.; Analysis and/or Interpretation - H.Ç.Ö.; Writing Manuscript - H.Ç.Ö.; Critical Review - M.G.U.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastadan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - İ.K.; Tasarım - M.A.; Denetleme - İ.E.; Veri Toplanması ve/veya İşlemesi - B.K.U.; Analiz ve/veya Yorum - H.Ç.Ö.; Yazıyı Yazan - H.Ç.Ö.; Eleştirel İnceleme - M.G.U.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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How to cite:

Özcan HÇ, Alptekin M, Kaya Uğur B, Uğur MG, Erkutlu İ, Kutlar İ. Anterior sacral meningocele mimicking an adnexal mass in an infertile woman: a report of an extremely unusual case. Eur J Ther 2017; 23: 184–6.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.213

Original Image / Orijinal Görüntü

A Coronary–cameral fistula leading to angina pectoris

Anjina pektorise yol açan koroner–kameral fistül

Örsan Deniz Urgun, Mustafa Topuz

Clinic of Cardiology, University of Healthy Science Adana Numune Training and Research Hospital, Adana, Turkey

A 77-year-old male with well-controlled hypertension presented to our clinic with angina pectoris on exertion. Five year ago, he had undergone diagnostic coronary angiography due to chest pain and he was reported to have normal coronary arteries. His physical and laboratory findings were normal. Baseline electrocardiography revealed sinus rhythm and negative T waves in V3-V6 leads with left axis deviation (Figure 1). During transthoracic echocardiography, there segmental wall motion abnormality and the patient diastolic dysfunction [left ventricular (LV) wall thickness was increased, E/A ratio was blunted, and left atrial diameter was increased]. Due to the patient's symptoms and our treadmill exercise stress test results, he underwent diagnostic coronary angiography. The angiogram excluded hemodynamically relevant stenosis of the coronary arteries. However, there was a fistula network from the end of the left anterior descending artery and circumflex arteries to the LV cavity during end-diastole similarly a ventriculography pose (Figure 2).

Figure 1. Patient's electrocardiogram revealed sinus rhythm and negative T waves in V3–V6 leads with left axis deviation.

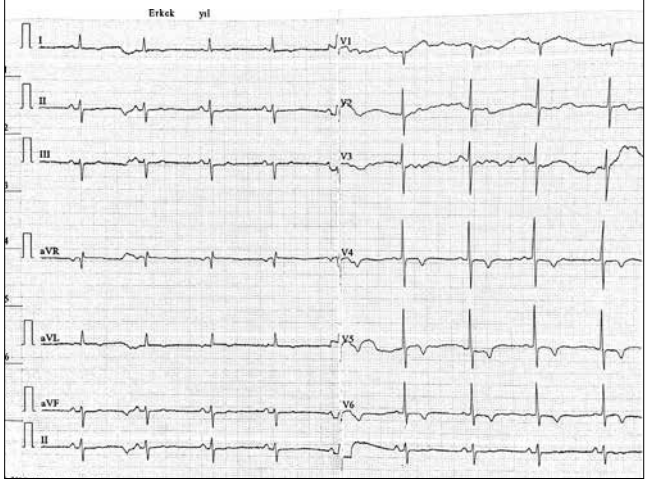
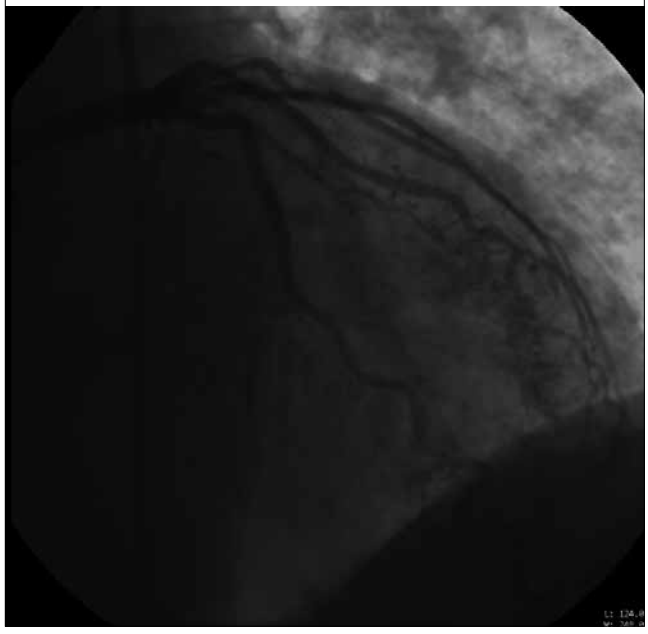


Figure 2. Right coronary oblique view demonstrated an intensive coronary–cameral fistula such as ventriculography pose during diastole.



Coronary artery fistulas are rare and have an incidence of 0.2% to 0.6% in angiographic series. A coronary-cameral fistula involve a sizable communication between a coronary artery bypassing the myocardial capillary bed and entering either chamber of the heart. Although patients with coronary artery fistulas are frequently asymptomatic, it must be keep in mind that the fistulas can cause ischemic chest pain secondary to coronary steal as well as LV hypertrophy caused by volume overload and increased oxygen consumption.

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

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Received/Geliş Tarihi: 20.09.2017 • **Accepted/Kabul Tarihi:** 04.10.2017

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.T.; Design - M.T.; Supervision - Ö.D.U.; Resources - Ö.D.U.; Materials - Ö.D.U.; Data Collection and/or Processing - Ö.D.U.; Analysis and/or Interpretation - M.T.; Literature Search - M.T.; Writing Manuscript - M.T.; Critical Review - M.T.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - M.T.; Tasarım - M.T.; Denetleme - Ö.D.U.; Kaynaklar - Ö.D.U.; Malzemeler - Ö.D.U.; Veri Toplanması ve/veya İşlemesi - Ö.D.U.; Analiz ve/veya Yorum - M.T.; Literatür Taraması - M.T.; Yazıyı Yazan - M.T.; Eleştirel İnceleme - M.T.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

How to cite:

Urgun ÖD, Topuz M. A Coronary–cameral fistula leading to angina pectoris. Eur J Ther 2017; 23: 187–8.

European Journal of Therapeutics DOI: 10.5152/EurJTher.2017.301117

Author's Reply / Yazara Yanıt

Importance of neutrophil-to-lymphocyte ratio in coronary artery disease

Koroner arter hastalığında nötrofil-lenfosit oranının önemi

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Department of Cardiology, Gaziantep University School of Medicine, Gaziantep, Turkey

Dear Editor,

We very much appreciate and thank Dr. İnanoğlu for his interest in our article, importance of neutrophil-to-lymphocyte ratio in coronary artery disease (1).

It has been shown that inflammation plays a major role in the initiation and progression of atherosclerotic cardiovascular diseases. The inflammation mediated by neutrophils leads to further tissue damage via several biochemical mechanisms (2). The neutrophil-to-lymphocyte ratio is an inflammatory marker that has been demonstrated to correlate with severity of coronary artery disease in acute coronary syndromes (3-5). However, independent studies may have resulted either in favor of or opposite of previous researchers therefore, despite our inconsistent results with literature we have rather preferred to publish our study in order to be free from bias.

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How to cite:
Yılmaz Coşkun F. Importance of neutrophil-to-lymphocyte ratio in coronary artery disease. Eur J Ther 2017; 23: 189.

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Received/Geliş Tarihi: 14.10.2017 • **Accepted/Kabul Tarihi:** 15.10.2017