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European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December. The journal publishes content in English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, case reports, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

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Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the

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

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

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

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

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

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

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

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Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Review

Hypericum's 90th Anniversary in the Laboratory

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ABSTRACT

Hypericum perforatum (HP) and its varieties are plants that have been attracting the attention of scientists since 1931. In almost every country, it is possible to encounter different HP varieties. Whereas in many countries HP is indicated as an antidepressant, its commonly used forms in our country are mainly oils for topical application due to its wound-healing properties. More than 50 substances in its composition have been well established and have been the subject of detailed scientific studies, such as those on antimicrobial, antineoplastic, and antioxidant effects. The most noteworthy point of its application in daily practice is the lack of standardization, which may lead to inadequate treatment and adverse drug interactions. Although HP's antidepressant and wound-healing properties have been traditionally accepted, its side effects and safety profile limit its use in clinical application; in addition, the HP exposure in pregnancy is an arising issue. Considering that new drug molecules are usually approved in clinical use after 10–15 years, the safety of HP application in clinics have not been established even after 90 years of rigorous studies.

Keywords: Depression, *Hypericum perforatum*, St. John's wort, wound-healing

INTRODUCTION

The development of laboratory conditions and improved knowledge in working methods have increased the synthesis of drug molecules in laboratories, and scientific studies have also accelerated the use of natural resources in drug research. *Hypericum perforatum* (HP) is a plant with approximately 400 varieties (1). It is also commonly known as St. John's wort. Its wound-healing effect was known in the 5th century, and its extract is the most consumed extract in the world today for medical purposes (2). Indeed, many of its varieties grow almost everywhere in the world, and it is well known among people. Thus, the plant was further examined in laboratories. One of the first articles on HP is, to the best of our knowledge, the one about the structure of the plant that was published in Science in 1931 (3). This shows that the plant has been right in front of us in modern science ever since.

In 1951, it was determined that the prominent active substance is hypericin (4). The new chemical substances have been found in studies over the last 60 years and are sometimes referred to the type of HP. It has also been reported that the active ingredients present in different parts of the plant, such as the root or leaves, are highly variable (2). The geographic region, methods of purification, humidity of the extract, and even exposure to light make it difficult to standardize the plant extract (5). For this reason, it can be seen that the amount of compounds in the commercial forms vary greatly. Indeed, lack of standardization of HP forms is the very important issue for human health. The components of extract are summarized below (6):

- Anthraquinone (naphthodianhrones) derivatives: *hypericin, pseudohypericin, protopseudohypericin, protopseudoacetic acid, isohypericin,* and *cyclopseudohypericin,*
- Flavonoids*:* flavonols (kaempferol*,* quercetin); flavones (luteolin); glycosides *(*hyperoside*,* isoquercitrin, quercirin, rutin); *biflavonoids* (biapigenin, amentoflavone)
- Prenylated phloro glucinols: hyperforin and adhyperforin,
- Tannins: proanthocyanidin,
- Other phenols: caffeic*,* chlorogenic, p-coumaric, ferulic, p-hydroxybenzoic, and vanillic acid,
- Essential oils: methyl-2-octane, n-nonane, methyl-2-decane, n-undecane, alpha and beta-pinene, alpha terpineol, geraniol, myrcene, limonene, caryophyllene, and humulene (sesquiterpene),
- Other ingredients: isovalerianic, nicotinic, myristic, palmitic, and stearic acid; carotenoids; choline; nicotinamide; pectin; beta-sitosterol; straight chain saturated hydrocarbons*;* and alcohols.

St. John's wort is presented in the British and European Pharmacopoeia as prepared from the dry HP tips collected at the time of flowering, and they have to contain hypericines not less than 0.08% (6).

Analyzing the results of 21 HP products sold in the United States determined that five products contained cadmium above the acceptable limits, seven of them did not fulfill even one of the quality criteria, and one product contained only 21.7% of the indicated amount of hyperphorin. In another study in the United States,

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it was reported that the content of hyperforin in eight samples varied between 0.01% and 1.89%, and only two products exceeded the recommended concentration of 1% for antidepressant activity. Similarly, when hypericin content was examined, it was found that according to the labels, the active ingredient percentage fluctuated between 57% and 130% (6). Indeed, the lack of standardization and contamination of the product with heavy metals can bring other problems into everyday practice.

Much of the work done is aimed at the treatment of depression. It is recommended to take 300 milligrams/3 times a day of standardized extract (0.3% hypericin), or 2-4 grams of dry plant, three times a day (as infusion in hot water) for antidepressant activity (6). In clinical studies on depression, the dose ranges from 240 to 1800 mg/day. In addition to the treatment of depression, the studies about anxiety, menopausal and premenstrual symptoms, and against bacterial and fungal infections are still ongoing (6).

Clinical Research Results

Depression Treatment

As of February 2017, more than 300 million people are fighting depression, and approximately 800 thousand people die from depression each year (7). The most commonly prescribed drug group in the world (with 160 million prescriptions) are antidepressants (8). Ever since the Swedish physician Paracelsus determined in 1525 that HP could be used in the treatment of psychiatric disorders, it has been used in the treatment of neuralgia, anxiety, neurosis, and depression in traditional Western medicine (9). Historically, hypericum has been used in patients who felt isolated from the community and the rest of the world. It is defined as the "wound-healing" for nerve diseases (10, 11). It is used in the short-term treatment of mild to moderate depression, and the number of studies on reliable availability in the treatment of depression is increasing. It was written in the 1800s that HP proved to be beneficial in hysteria and depressive neurological diseases (2). The extract was named LI 160 in Germany in 1990, and it is sometimes possible to see this name in the studies. A report from 1999 published that 131.5 million daily doses of HP were prescribed in 1996 for the treatment of mild to moderate depression in Germany (12).

To explain the underlying mechanisms of its antidepressant effect, many of the compounds of the extract have been subject of research. Three compounds, xanthones (1.5-dihydroxyxanthone, 5-hydroxy-1-methoxyxanthone, and 6-deoxyjacareubin), were identified by crystallography in 1994 as monoamine oxidase A and B inhibitors (MAO-A and B) (13). Hypericin 10 (-3) mol/L and hypericum total extract 10 (-4) mol/L were administered in pig liver cells, but the MAO and catechol-o-methyltransferase (COMT) inhibitory properties were not sufficient at these concentrations (14). This finding was supported by another report, which stated that the HP compound administered intraperitoneally 10 (-3) mol/L to the rats did not inhibit MAO in brain homogenates to explain depression treatment (15). On the other hand, the synthesis of serotonin receptors was found to be significantly reduced at 2, 4, 6, 8, and 10 hours after the LI 160 administration in neuroblastoma cell culture (16). In 1995, 6.2 µg/ml of LI 160 administration to neuronal cell culture showed 50% inhibition of serotonin reuptake and reported that this inhibition was responsible for its antidepressant activity (17). Another study about the astrocytic cell culture in 1999 showed that LI 160 inhibited both serotonin and norepinephrine reuptake, supporting the antidepressant activity mechanism (18). Rutin, an active ingredient of the plant, was also found have an antidepressant effect (2).

It has been suggested that daily HP use at 300-1200 mg is as active as tricyclic antidepressants or serotonin reuptake inhibitors, affects the neurotransmitter system, and activates GABA, NMDA, and serotonin receptors (19). HP was found to be significantly associated with receptor for adenosine, serotonin, GABA-A, GABA-B, benzodiazepine, inositol triphosphate, MAO-A, and MAO-B. It has been reported that the isolated pseudohypericin inhibits the enzyme of dopamine-β-hydroxylase. Flavonoids and xanthones also have a strong selective inhibitory effect on MAO-A. Flavonoid-containing fractions were found to inhibit COMT. It was determined that naftodiantronsalone generally had no effect, but only had an antidepressant effect when used in combination with flavonoids (9, 20). It is clear that the activity of each compound is different, and more studies have to be conducted for a successful stabilization and standardization of the extract.

Effects on Pathogenic Microorganisms

After the antidepressant activity, the most disputed issue was whether the plant components had a chemotherapeutic effect against microorganisms. The surgeon's wound cleaner, *oleum hyperici*, was accepted in the first official pharmacopoeia of London in 1944 (2). Sarothralen A and B (21) and saroaspidin A, B, and C were studied for antibiotic effect (22), chromene for antifungal effect (23), and hypericin and pseudohypericin (24, 25) for antiretroviral activity. In 1989, drummondins A, B, C, F compounds from *H. Drummondii* were reported to have stronger antimicrobial properties than streptomycin (26). Very effective results have been obtained against methicillin-resistant *Staphylococcus aureus* by hyperphorin. Today, clinical studies are also available. Hypericum preparations prescribed in Russia (rich in hyperphosphorins) were found to be effective against the *S. aureus* infections, additionally at three different concentrations of 30%, 40%, and 50%, has been shown to be effective against vaginal pathogenic bacteria without affecting the vaginal flora. As a result of intensive studies, the hypericum extract and its components have been found to be more effective on gram-positive bacteria than gram-negative. It should be mentioned that while the extracts prepared in July did not have an antimicrobial activity, the samples collected in August had antimicrobial properties, most probably due to the light-induced chemical reactions. Also, alcoholic extracts are more effective than water extracts (2). Additionally, 6 "-O-Acetyl Quercetin 3-O-β-D-alloside, Quercitrin, Quercetin compounds have been reported to be effective against *Plasmodium falsiparum* (2). Preclinical studies show that HP is a promising antimicrobial agent, and one of its components might be on the market after its standardization in the future. However, in a study, 30 patients with an HIV infection were applied hypericin in the Phase 1 study, and they did not show any improvement in virological markers and CD4 cell counts, developing serious phototoxicity in 1999 (6).

Wound-Healing and Immunomodulatory and Antioxidant Properties

After the 16th century, the most effective and widespread use of HP in Europe was the application of distilled oil on wounds. Experimental studies also support this well known feature of the HP varieties. The healing effect on the wounds and burns can be attributed to its antibacterial effect, increased polygonal formation of fibroblasts, and increased production of collagen. It should be emphasized that the wound-healing time is not sufficient for deciding HP; the quality of wound collagen has to be questioned for this property as well.

In a study of 24 female patients who underwent cesarean section, a calendula-hypericum oil mixture (30:70) was used, and the improvement was observed in 38% of patients, while in the control group, it was only 16% (2). Hypericin has been described as an immunomodulator due to a decreasing power of induction of NF-Kappa B by phorbol 12-myristate 13-acetate and tumor necrosis factor-alpha (TNF-alpha) in HeLa and TC10 cells (27). In addition, HP's immunomodulatory properties were observed in 18 patients with atopic dermatitis in 2003; a hypericum cream, standardized to contain 1.5% of hyperphorin and a drug-free vehicle cream were applied twice a day to the right and left side of the same patient for 4 weeks, and it was proved that hypericum was effective (28). When polymorphonuclear leukocytes were stimulated by Ca-ionophore, hyperphorin 90 nanoM concentration prevented the formation of 5-lipoxygenase (5-LO) products, and this effect was found to be nearly equivalent to zileuton; also in the same study, when platelets were stimulated by thrombin and ionophore, 0.3 and 3 μM concentrations of hyperphorin inhibited cyclooxygenase (COX)-1, and this inhibition was 3 and 18 times more potent than aspirin, respectively, but the interaction with COX-2, 12-LO, and 15-LO could not be detected (29). Alveolar A549/8 and colon DLD-1 cell lines' release of inducible nitric oxide synthase (iNOS) were inhibited due to the concentration of HP extract. Therefore, it became a promising agent in chronic inflammation (30). Glutamate-induced cell death of hippocampal HT22 cells was examined in an experimental model for neuronal diseases, and it has been reported that the administration of standardized HP extract at a concentration of 0.05% results in a reduction of calcium uptake into the cell and thus a cytoprotective effect (31). It has been shown that HP has anti-inflammatory activity by suppressing the nitric oxide release and, depending on the dose, attenuating the production and release of TNF-alpha into lipopolysaccharide-induced human monocytic cell lines (THP-1) (32). In addition to previous studies, the peroxide damage was induced for 4 hours in the PC12 pheochromocytoma cell line, whereas cells pretreated with HP were protected against the stress, and the release of lactate dehydrogenize was reduced; therefore, it has been suggested that HP may be useful in diseases with oxidative stress (33). On the other hand, beside the beneficial reports on HP, it was reported that hyperforin collapsed the mitochondrial membrane potential of cortical neurons and the released Ca and Zn from the cell, and at this point, it safety is questionable (34). The immune-modulator effects of HP require more clinical studies.

Cytotoxic and Antineoplastic Studies

Hypericin is recommended to increase the sensitivity to radiation in the photodynamic treatment of cancer, and in addition, hyperforin is frequently encountered in the literature as another active substance that is intensively studied in cancer treatment (2, 35). When applied to the mouse tumor model P388, and when the vascular effect and tumor cytotoxicity were investigated, hypericin was found to be beneficial in the reduction of tumor angiogenesis and oxygenation, which is based on the photodynamic treatment (36). When different cancer cell lines are photosensitized with hypericin, the caspase pathway participates in the apoptotic effect, and the CNE2, CCL-220.1 (colon), and bladder SD cancer series are more susceptible than nasopharyngeal carcinoma TWO-1cells (37). Hypericin accumulates in the cell endoplasmic reticulum and Golgi, in many different cell groups, such as adenocarcinoma WiDr cells, NHIK 3025 cells, and D54Mg glioblastoma; while, 10 μM hypericin is not toxic to WiDr cells in dark, 1 μM is toxic under orange light, which shows the importance of light (38). The effects of pseudohypericin and hypericin on the Jurkat cells were compared, and it was found that they decrease the cell proliferation in a dose-dependent fashion, and the possible side effects of systemic treatment were emphasized because of an increased DNA fragmentation due to drug dose (39). It is known that in vitro studies of cancer treatment do not reflect the conditions at clinics; therefore, data have to be carefully interpreted as there have not been any clinical trials so far.

Teratogenicity and Effects on Reproduction

In 1990, a series of studies was carried out on Syrian hamster embryos and Chinese hamster bone marrow cells to determine the mutagenic properties of quercetin from HP, and it was reported that this substance was not genotoxic (40). However, in another study, it was reported that when hamster oocytes were incubated for 1 hour at a HP concentration of 0.06 mg/mL, the sperm penetration to oocyte was not disturbed, but if the dose was increased to 0.6 mg/mL, the sperm penetration stopped, and DNA denaturation of spermatozoa developed (41). When HP was applied in rats 2 weeks before gestation and continued 21 days postpartum at two different doses at 100 and 1000 mg/kg, liver and kidney damage in fetuses was found (42). The safety of hypericum in pregnancy has not been determined according to the Food and Drug Administration (6). An analysis of the Danish National Birth Cohort records about the safety of maternal use of HP during pregnancy and pregnancy outcomes indicated that the prevalence of malformations in the HP exposed group was slightly higher (8.1%) than observed in the control groups (3.3%; p=0.13) (43). These authors also mentioned that the agent use was not in the prescription database, and therefore, it was hard to evaluate the real issue. Further studies have to be done on the safety of HP in pregnancy and lactation.

Other HP Characteristics

Among the studies conducted to determine the properties of hypericum varieties, those on relaxant properties of the plant on the vascular smooth muscles should also be mentioned. Melzer et al. (44) showed that prostaglandin F2-alpha and histamine-induced swelling in isolated coronary arteries were antagonized by the procanidin HP compound. In another study, phenyleph-

rine and potassium chloride aortic smooth contractions were reduced by the *H. triquetrifolium tura* extract (45). Khan et al. (1) were investigating antispasmodic properties of HP on different tissues, such as rabbit jejunum, guinea pig trachea, rabbit aorta, and guinea pig atrium, and they indicated that the extract had significant calcium antagonistic properties.

It is known that cytokine-mediated beta-cell death is the main problem in diabetes, and 1-3 μM of HP extract or hyperphorin prevent the deterioration of glucose-induced insulin release and protect the INS-1E beta-cell lines against apoptosis. Furthermore, cytokine-induced STAT-1 and NF-kappa B levels have been reduced, and the functions and lifespan of the beta cells increased (46).

For the treatment of gastric ulcer, anti-gastric, and topical antibacterial properties as well as sedative and healing properties have been reported (47, 48).

Hypericum perforatum has been also reported to be able to prevent the polymerization of p-amyloid peptide, which is responsible for the onset of Alzheimer's disease (49).

Side Effects and Drug Interactions

Gastrointestinal system disorders such as diarrhea, constipation, nausea, or many different findings such as frequent urination, mouth instability, itching of the skin, edema, fatigue, headache, anorexia, manic episodes, and anxiety can be seen with the use of HP (6). Animal poisoning was defined, and photosensitization was reported (50, 51). By using human retinal pigment epithelium cells, 10 (-7) to 10 (-5) M hypericin or fluorescence light applied separately did not show phototoxicity; however, when applied together, they showed to be phototoxic to retina due to a decreased glutathione reductase activity and increased lipid peroxidation, and it has been noted that they may lead to early retinal and macular degeneration (52). In a similar study, when 0.1-10 μM hypericin and light were applied to human lens epithelial cells together, the cells became necrotic and apoptotic. For this reason, an exposure to intense light in HP users has been shown to have catarogenic effect (53).

Although work on phototoxicity is noteworthy, adverse drug interactions are the most commonly observed clinical issues. It has been published that hyperphorin increased the CYP3A4 and CYP2C9 activities, but hypericin did not interact with the CYP1A2, CYP2C9, CYP2D6, and CYP3A4 enzyme systems on human hepatocyte culture (54). One of the valuable studies to explain the drug interactions about P-glycoprotein is from 2005. The chronic effect of HP, hyperphorin, and hypericin on the LS 180 intestinal cell line and an acute effect of HP on the LLC-GA5-COL150 cells were investigated; it was determined that in case of a long-term application of hypericum P-glycoprotein substrates, the blood level significantly decreased due to increased P glycoproteins (55). Affected drug groups especially include immunosuppressants, anticancer agents, cardiovascular drugs, oral contraceptives, and lipid-lowering agents, which caused life-threatening events in several cases (56). For this reason, herbal teas used by the patients should be well questioned in the anamnesis before any treatment. The drug interactions can change the formal treatment of the patient, or any drug can become toxic. Biggs et al. (57) has also reported an alarming issue that HP can be abused by adolescents for believing of being healthy and feeling well.

A High Dose Exposure

A 1000 mg HP extract and 2.7 mg hypericin were reported to be well tolerated, but active charcoal application and blood pressure monitoring were recommended if those were taken at very high doses (6).

CONCLUSION

The number of studies on HP has increased dramatically in the past 10 years. The efforts to determine all the properties of the plant, for example in the treatment of depression, might offer us cheaper options. Identification of the compounds obtained and the determination of their stability are promising in infectious diseases, inflammatory diseases, and cancer treatment. However, it should not be forgotten that undesirable side effects in systemic use may occur in patients and that the plant extracts used by the patients with the current treatment should be properly questioned.

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Original Research

Factors Affecting Adverse Effects after Kidney Transplantation

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ABSTRACT

Objective: The incidence of developing adverse effects in recipients after kidney transplantation (Tx) was analyzed.

Methods: A total of 206 patients (mean age was 41.40±11.88 years, 92.7% were between 46 and 59 years old, and 66.0% were men) who underwent Tx between 2011 and 2016 were evaluated retrospectively. Information regarding the sociodemographic characteristics of the patients was collected using the "Sociodemographic Characteristics Data Collection Form," which was created by the researcher.

Results: Various adverse effects were detected in 206 patients who participated in our study. The incidence of adverse effects was significantly higher in patients who had hypertension and chronic glomerulonephritis who underwent dialysis treatment during 0–12 months before Tx and who received a kidney transplant from a living donor (p=0.001). The incidence of adverse effects related to the immunosuppressive drugs used after transplantation was significantly higher in patients receiving mycophenolate mofetil (MMF)+steroid+tacrolimus and MMF+steroid+cyclosporine, and weight gain was higher in patients receiving the same group of drugs (p=0.001). There were no significant differences in terms of adverse effects that occurred in other drug combinations.

Conclusion: We found that many factors (e.g., immunosuppressive drugs) in Tx patients may be associated with the incidence of adverse effects.

Keywords: Kidney transplantation, immunosuppressive therapy, calcineurin inhibitors, side effects, dialysis

INTRODUCTION

Chronic renal failure (CRF) is an important public health problem in our country and worldwide due to its increased incidence and high treatment cost. Diabetes, hypertension, and glomerular diseases play important roles in the etiology of CRF. The most common causes of CRF in the world are these three chronic diseases (1). The options for renal replacement therapy (RRT) in patients diagnosed with end-stage renal disease (ESRD) are dialysis (hemodialysis or peritoneal dialysis) and kidney transplantation (Tx) (2, 3). RRT is a treatment that imposes a heavy burden on society and affects not only patients but also families due to its high treatment cost. In the United States in 2003, 360,000 people with ESRD were on RRT (4). Tx has been the most successful and most preferred method for patients with CRF thanks to the newly developed surgical methods and the introduction of immunosuppressive drugs (5). However, Tx has some disadvantages in addition to its advantages. Immunosuppressive drugs that are used to prevent rejection especially in patients who undergo Tx cause adverse effects (6). Giving adequate immunosuppressive therapy and providing immunity to protect infections that may occur in the recipient are proportional to the success of Tx and the survival rate of grafts (7). The immune system of the recipient after Tx should be suppressed by immunosuppressive drugs.

Sufficient immunosuppressive therapy is selected as a combination and is administered to patients (8). The age and gender of the patient, human leukocyte antigen compliance between recipient and donor, and the protocols of transplant centers are taken into account, and immunosuppressive therapy is then selected (9). The main goal in immunosuppressive therapy is to prevent the occurrence of rejection episodes (antigen recognition and costimulation proliferation) by creating a specific pharmacological tolerance against the graft with minimal adverse effects (10).

The selective properties of currently used immunosuppressive therapies are increasing. The combined use of different groups of medicines both provides a synergistic effect and avoids unwanted adverse effects by enabling dose reduction. Thus, it is possible to improve the optimal graft survival and the quality of life for transplant recipient (11).

Recently, classical triple immunosuppressive regimen started after Tx consists of mycophenolate mofetil (MMF), calcineurin

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inhibitors, and steroid hormone. MMF has been used since 1995 and is a reversible inhibitor of the enzyme inosine-5′-monophosphate dehydrogenase (12).

The most common adverse effects of MMF use are leukopenia, diarrhea, and gastrointestinal irritation. When used at higher doses, there has been an increase in invasive cytomegalovirus disease (13). Calcineurin inhibitors, such as tacrolimus and cyclosporine, are important immunosuppressive drugs used after Tx and have been found to cause adverse effects, such as hypertension and diabetes (14). Sirolimus, which is another immunosuppressive drug used after Tx, is an antibiotic with immunosuppressive properties. It inhibits the development of T cells and provides a powerful control mechanism on these cells when used with cyclosporine (15). However, it has dose-dependent adverse effects, such as hyperlipidemia, diabetes, anemia, thrombocytopenia, proteinuria, edema, impaired wound healing, and mouth ulcers (16). Corticosteroids, such as prednisolone, are drugs that have been used for many years in order to prevent rejection (17). Immediately after starting immunosuppressive drugs in all transplant patients, blood drug levels should be monitored closely. Many studies have provedn that nephrotoxicity and kidney failure rates are increased when drug levels are not adjusted well (18). In light of these data, we attempted to determine the rates of adverse effects in 206 transplant patients and the role of immunosuppressive drugs in these adverse effects.

METHODS

A total of 206 patients who underwent Tx between 2011 and 2016 were evaluated retrospectively. The mean age of the patients was 41.40±11.88 years, 92.7% were between 46 and 59 years old, and 66.0% were men. Inclusion criteria for our study were as follows: being a volunteer, receiving a kidney transplant from either a living or a deceased donor, being >18 years old, receiving immunosuppressive drugs, having no mental health illness, lack of inappropriate self-expression, and having completed at least the second month after Tx. A total of 206 patients who met the criteria were included in the study. The patients were informed about the study by the researcher. Verbal and written informed consents were obtained. Data of the study were collected by the face-to-face interview technique. The data collection period lasted 15–20 min for each individual.

The questions in the questionnaire were read out loudly and clearly by the researcher, and the answers given by the patient were marked on the forms by the researcher. The "Sociodemographic Characteristics Data Collection Form" was prepared by the researcher in order to obtain information about the characteristics of the sample patients. This form included the demographic variables, such as age, gender, marital status, educational level, family type, occupation, whether or not the patient has been informed about the use of immunosuppressive drugs related to the organ transplantation process by the health personnel, employment status after transplantation, working status, and income level, and the variables related to the disease, such as the cause of kidney failure, how many years the patient has had chronic kidney failure, whether or not the patient underwent dialysis treatment, what type of dialysis treatment the patient received, date of transplantation, donor type, whether or not the patient knew the discomforts that may occur after transplantation, immunosuppressive drugs the patient received, whether or not adverse effects occurred, what the patient did when the adverse effects occurred, whether or not the patient had rejection, and the priority ranking of drugs in the patient's life. Ethics committee approval was obtained the study Sanko University (decision no: 5, date:21.10.2016).

Statistical Analysis

Statistical analysis of the data was performed using the IBM Statistical Package for the Social Sciences Statistics version 23.0 software package (SPSS IBM Corp.; Armonk, NY, USA). The 95% confidence interval was used. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 41.40±11.88 (18–71) years. Of the study population, 92.7% were aged 46–59 years. When the distribution of the patients according to their genders was examined, 66.0% were men. Of the patients, 79.1% were married, 45.2% were literate or primary school graduates, 68.4% were core family members, and 26.7% were retired. Of these patients, 53.5% did not continue to work after transplantation, and 70.7% did not continue to work because they were retired. Among them, 48.5% had a balance between their income and expenses. Table 1 shows the distribution of patients according to their sociodemographic characteristics.

Of the patients who participated in our study, 99% were informed by the health personnel, 92.2% deemed that this informing was sufficient, 35.9% did not know the cause of chronic kidney failure, and 30.6% argued that the cause of chronic kidney failure was hypertension. The duration of CRF in 39.3% of the patients was ≥121 months. Of the transplant patients, 88.3% underwent dialysis treatment, and 29.1% had been treated for at least 10 years. Of the patients undergoing dialysis treatment, 85.7% underwent hemodialysis treatment. Of the patients, 52.4% were between the range of "12–60 months" after transplantation, and 54.4% received a kidney transplant from a living donor.

Among the patients, 61.2% knew the discomforts that can develop after organ transplantation. Table 2 shows the distribution of the patients according to the characteristics of their disease.

Of the patients, 93.1% received MMF+steroid+tacrolimus as immunosuppressive drug after transplantation. Moreover, 18% received antiviral agents, 18.4% received antifungal agents, 55.3% received antihypertensive drugs, and 14.1% received antidiabetic drugs. Among the patients, 54.9% developed adverse effects, 72% of those experiencing adverse effects gave their doctor information, 2.9% developed rejection due to incompatibility, and 94.6% reported that drugs ranked first in their life. Table 3 shows the distribution of the properties of immunosuppressive drugs used after transplantation.

Table 1. Distribution of patients according to their sociodemographic characteristics

Sociodemographic characteristics		n	%
*Age (min-max $\bar{x}$±SD), years	18-71 (41.40±11.88) years		
Gender	Male	136	66.0
	Female	70	34.0
	Total	206	100.0
Marital status	Married	163	79.1
	Single	43	20.9
	Total	206	100.0
Educational level	Illiterate	11	5.3
	Literate-primary school	93	45.2
	Secondary school-high school	82	39.8
	University and above	20	9.7
	Total	206	100.0
Family type	Core family	141	68.4
	Extended family	65	31.6
	Total	206	100.0
Occupation	Housewife	52	25.2
	Retired	55	26.7
	Self-employment	42	20.4
	Worker-officer	57	27.7
	Total	206	100.0
Employment status after transplantation	Yes	87	46.5
	No	100	53.5
	Total	187	100.0
Reason for leaving work	Changing work	2	2.5
	Leave work	22	26.8
	Being retired	58	70.7
	Total	82	100.0
Income level	High	8	3.9
	Balanced	100	48.5
	Low	98	47.6
	Total	206	100.0

n: no. of individuals
*Student's t-test was used for the analysis
Data were expressed as mean±standard deviation

Table 2. Distribution of patients according to the characteristics of their disease

Characteristics related to the disease		n	%
Informing the patients about organ transplantation	Yes	204	99.0
	No	2	1.0
	Total	206	100.0
Informing the patients sufficiently	Yes	190	92.2
	No	16	7.8
	Total	206	100.0
Cause of CRF	Hypertension	63	30.6
	Diabetes	10	4.9
	Chronic glomerulonephritis	25	12.2
	Polycystic kidney disease	4	1.9
	Chronic pyelonephritis	4	1.9
	Infections	19	9.2
	Nephrotic syndrome	1	0.5
	I do not know	74	35.9
	Hypertension and diabetes	6	2.9
	Total	206	100.0
Duration of CRF	0-12 months	30	14.6
	13-60 months	29	14.1
	61-120 months	66	32.0
	≥121 months	81	39.3
	Total	206	100.0
Dialysis status	Yes	182	88.3
	No	24	11.7
	Total	206	100.0
Duration of dialysis treatment	0-12 months	43	23.6
	13-60 months	39	21.5
	61-120 months	47	25.8
	≥121 months	53	29.1
	Total	182	100.0
Type of dialysis	Hemodialysis	156	85.7
	Peritoneal dialysis	8	4.4
	Hemodialysis-peritoneal dialysis	18	9.9
	Total	182	100.0
Time after Tx	2-12 months	57	27.7
	13-60 months	108	52.4
	61-120 months	41	19.9
	Total	206	100.0
Donor type	Living donor	112	54.4
	Cadaveric donor	94	45.6
	Total	206	100.0
Knowing the problems that can develop after Tx	Yes	126	61.2
	No	80	38.8
	Total	206	100.0

n: no. of individuals; CRF: chronic renal failure

Table 3. Distribution of properties of immunosuppressive drugs used after transplantation

Properties of immunosuppressive drugs		n	%
Immunosuppressive drugs used after transplantation	MMF+steroid+tacrolimus	192	93.1
	MMF+steroid+cyclosporine	8	3.9
	MMF+steroid+sirolimus	3	1.5
	MMF+tacrolimus	3	1.5
	Total	206	100.0
Antiviral agents used persistently	Use	37	18.0
	Not use	169	82.0
	Total	206	100.0
Antifungal agents used persistently	Use	38	18.4
	Not use	168	81.6
	Total	206	100.0
Antihypertensive drugs used persistently	Use	114	55.3
	Not use	92	44.7
	Total	206	100.0
Antidiabetic drugs used persistently	Use	29	14.1
	Not use	177	85.9
	Total	206	100.0
Development of adverse effects related to drugs	Yes	113	54.9
	No	93	45.1
	Total	206	100.0
Type of processes performed after the development of adverse effects	I stopped using the drug or I reduced its dose	5	5.4
	I called my doctor	67	72.0
	I did not do anything	21	22.6
	Total	93	100.0
Presence of rejection due to incompatibility	Yes	6	2.9
	No	200	97.1
	Total	206	100.0
Priority ranking of drugs in the patient's life	First	195	94.6
	Second	9	4.4
	Third	2	1.0
	Total	206	100.0

n: no. of individuals; MMF: mycophenolate mofetil

Various adverse effects were detected in 206 patients who participated in our study. These adverse effects were weight gain (20.08%), acne (4.9%), tremor (4.4%), diabetes (4.4%), hair loss (2.4%), fatigue (1.9%), itching (1.5%), irritability (1%), palpitation (1%), stomach pain (1%), osteoporosis (1%), eye complaints (1%), shingles (1%), nausea and vomiting (1%), hairing (0.5%), headache (0.5%), nail fungus (0.5%), lung infection (0.5%), insomnia (0.5%), drowsiness (0.5%), urinary infection (0.5%), weight loss (0.5%), ecchymosis in the skin (0.5%), blockage of the brain vessels (0.5%), tinnitus and numbness in the ear (0.5%), and redness in the body (0.5%), respectively. Table 4 shows the distribution of adverse effects after Tx according to their incidence. The incidence of adverse effects after Tx was significantly higher in patients who had hypertension and chronic glomerulonephritis (p=0.001).

Table 4. Distribution of adverse effects after Tx according to their incidence

Adverse effects	n	%
Weight gain	49	20.8
Acne	10	4.9
Tremor	9	4.4
Diabetes	9	4.4
Hair loss	5	2.4
Fatigue	4	1.9
Itching	3	1.5
Irritability	2	1
Palpitation	2	1
Stomach pain	2	1
Osteoporosis	2	1
Eye complaints	2	1
Shingles	2	1
Nausea and vomiting	2	1
Hairing	1	0.5
Headache	1	0.5
Nail fungus	1	0.5
Lung infection	1	0.5
Insomnia	1	0.5
Drowsiness	1	0.5
Urinary infection	1	0.5
Weight loss	1	0.5
Ecchymosis in the skin	1	0.5
Blockage of the brain vessels	1	0.5
Tinnitus and numbness in the ear	1	0.5
Redness in the body	1	0.5

n: no. of individuals

When the incidence of adverse effects after Tx was compared with the dialysis duration before Tx, the incidence of adverse effects (especially weight gain) was significantly higher in patients who underwent dialysis treatment for 0–12 months (p=0.001).

The incidence of adverse effects after Tx was significantly higher in patients who received a kidney transplant from a living donor than in those who received a kidney transplant from a deceased donor (p=0.001). The incidence of adverse effects related to the immunosuppressive drugs used after Tx was significantly higher in patients receiving MMF+steroid+tacrolimus and MMF+steroid+cyclosporine, and weight gain was higher in patients receiving the same group of drugs (p=0.001 and p=0.001). There were no significant differences in terms of adverse effects that occurred in other drug combinations.

DISCUSSION

Several adverse effects occurred after Tx in the patients included in the study, and that these adverse effects were mostly compatible with previous studies (19). In our study, when the incidence of adverse effects after Tx and the causes of CRF were examined, there was a significant relationship especially in patients with hypertension and chronic glomerulonephritis (p=0.001). This can be attributed to the larger number of patients with hypertension and chronic glomerulonephritis.

When the incidence of adverse effects after Tx was compared with the dialysis duration before Tx, the incidence of adverse effects was significantly higher in patients who underwent dialysis treatment for 0–12 months (p=0.001). A previous study reported that an increased dialysis duration before transplantation in patients undergoing liver transplantation affected long-term outcomes after transplantation negatively and was an independent risk factor for increased mortality (20). The results of that study are significantly different when compared with our results. This may suggest that adverse effects and negative situations that may be seen after different organ transplantations may be different. Diabetes mellitus (DM), which is present before or develops newly after Tx, increases the frequency of infection, disrupts graft function, and increases the frequency of cardiovascular diseases, which are the most important causes of mortality in transplant patients (21). Preventable risk factors, such as hepatitis C and obesity, as well as uncorrectable risk factors, such as age and family history, of newly developed DM after transplantation are gaining importance (22). Particularly, calcineurin inhibitors and corticosteroids from immunosuppressive drugs used after Tx are among the factors that facilitate the occurrence of DM after transplantation (23). Close monitoring of patients after Tx, identification of the possible risk factors, and early detection of glucose intolerance are important for preventing the development of DM and complications. Of the 206 patients included in our group, 9 (4.4%) developed DM. Since DM is a well-known risk factor, patients with DM especially in close relatives should be determined. These patients should be monitored more carefully in terms of the development of DM after transplantation, and treatments should be planned accordingly. In all solitary organ transplantations including Tx, infections are encountered especially during the first 3 months after Tx in recipients (24). Studies have shown that infections occur especially in the urinary tract, abdominal area, and chest region (25). In our study, nail fungus, lung infection, and urinary tract infection were observed in 0.5% of the 206 patients (Table 4).

In a study of the majority of Tx patients, no organ transplant rejection was found (26). In our study, 2.9% of the patients had organ rejection. In this respect, our findings are similar to the literature. Tx patients need immunosuppressive treatment throughout their lifetime. Immunosuppressive regimens used currently for this purpose are administered in combination. The majority of the Tx patients included in our study received a combined therapy of MMF+steroid+tacrolimus. Our findings are similar to the literature (27). This can be attributed to that the combination of MMF+steroid+tacrolimus is the most effective combination for immunosuppression.

When what the participants did after the development of adverse effects related to drugs was examined, it was found that the vast majority of them called their doctor. When the literature was examined, no data were found about this finding. Although it is known that immunosuppressive drugs have many adverse effects, the impacts of immunosuppressive drugs on weight gain are still unclear (28). Some studies show that there is no significant difference between them, but there are publications in the literature that report an opposite opinion (29). Many factors, such as the presence of weight gain before transplantation, sedentary life and nutritional recovery after transplantation, and immunosuppressive drugs, are thought to play a role in the development of obesity (14).

In our study, when the incidence of adverse effects related to immunosuppressive drugs was examined, adverse effects were significantly higher in patients receiving a combined therapy of steroid and tacrolimus, and weight gain was also significantly higher in the same patient group (p=0.001). Immunosuppressive drugs cause many adverse effects in the gastrointestinal tract. In a previous study, approximately 68% of the Tx patients were found to have severe gastrointestinal complaints in the first year (29).

Adverse effects, such as nausea, vomiting, and diarrhea, were frequently observed especially in patients treated with MMF (13). Studies have shown that calcineurin inhibitors, such as tacrolimus and cyclosporine, led to gastrointestinal adverse effects (14). In our study, a small proportion of Tx patients were observed with gastrointestinal adverse effects, such as nausea and vomiting. We found that the incidence of side effects was significantly higher in patients who had a living donor Tx than in those who used a cadaver donor (p=0.001). However, in literature studies, side effects occurring in recipients of cadaver and, consequently, more costs of treatment are found (30). This shows that cadaver transplantation is more effective, and that the idea is more suitable in terms of cost.

The most important limitation of the study is that it was conducted at a single center. Since the study was conducted at an organ transplant center located within a private hospital, low-income patients who need to pay extra money could not be referred to this center. Therefore, the present study cannot be generalized to all transplant patients in Turkey.

CONCLUSION

We found that many factors in Tx patients may be associated with the incidence of adverse effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Sanko University (decision no: 5, date:21.10.2016).

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

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Original Research

Is External Fixation Valid Option for Pertrochanteric Fractures in High-Risk Patients?

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ABSTRACT

Objective: The objective of the present study was to evaluate whether surgical treatment of the pertrochanteric fractures of the femur with external fixator could reduce the pre- and postoperative length of hospital stay, with low complications and mortality and with satisfactory functional results to achieve rehabilitation and incorporation into the daily life in high-risk patients.

Methods: Twenty-six patients who had pertrochanteric fractures were treated using the Orthofix Pertrochanteric Fixator (Bussolengo Verona, Italy). There were 14 male and 12 female patients. The mean age of the patients was 73 (37–93) years. The fractures were classified according to the modified Evans classification. Of the fractures, 19 were unstable, and 7 were stable. Patients were evaluated on the day the fixators were removed according to the Foster criteria.

Results: The mean operative time was 24 (20–65) min. The average hospitalization was 12.7 (3–43) days. The average union time of the 16 patients who were alive and whose fixators could be removed was 5.2 (3–11) months. Stable fractures healed at approximately 4.1 months, whereas unstable fractures healed at 5.9 months. Six patients developed pin tract infection and five of them were superficial. During the 12-month follow-up period, 10 patients died from causes unrelated to the operation. The mortality rates of the 26 patients who had intertrochanteric fractures treated with pertrochanteric fixator in our retrospective study were 23.07% within the first 30 days and 42.3% within 1 year.

Conclusion: In conclusion the use of external fixation for the management of pertrochanteric fractures in elderly patients of poor health is a valuable and valid alternative surgical method.

Keywords: Pertrochanteric fracture, external fixation, elderly

INTRODUCTION

In the 20th century, there has been a significant increase in the average life span with the parallel improvement of the scientific development of living conditions. The elderly population develop osteoporosis in proportion to malnutrition and inactivity. As a result, pertrochanteric femur fractures can occur with a simple trauma. Several treatments have been tested in the treatment of fractures of this region, and the advantages and disadvantages of each method have been reported over time.

Most hip fractures are seen in elderly patients with osteoporosis who have prior problems and functional limitations. Owing to the good blood supply in intertrochanteric femur fractures, conservative treatment is possible because of the low incidence of non-union and avascular necrosis, but the complications of immobilization in elderly patients lead to increased mortality and morbidity up to 60% with conservative treatment (1, 2).

This elderly patient population often has cardiac, pulmonary, and genitourinary system disorders and metabolic and neurological problems, and the timing and planning of treatment are difficult (3). The purpose of surgical treatment is to improve the quality of life by providing early mobilization and to restore the prefracture status as soon as possible (4). The quality of surgery depends on the selected osteosynthesis method, surgical technique, bone quality, and reduction quality.

Treatment options include internal fixation, hemiarthroplasty, and external fixation. These methods have advantages and disadvantages. Plates and intramedullary nails are used in the internal fixation method. The disadvantage of the internal fixation method is the necessity to open the fracture area for fixation with plates. If close reduction could not be made during fixation with an intramedullary nail, open surgery must be performed. However, in both methods, the operation time is long, and it is a hemorrhagic surgical method that may require blood transfusion during the operation. In both methods, there is a risk of failure in the screws inserted into the femoral neck, but they provide a rigid fixation. Reduction loss and non-union are rarely seen in the postoperative period, especially in patients with unstable fractures. The disadvantages of hemiarthroplasty include a more bleeding method, serious complications due to cement, long operation time, dislocation of the postoperative hip, and revisions due to cement. The advantage is that the patient can be allowed full weight bearing postoperatively. The disadvantages of hemiarthroplasty are intraoperative blood loss, serious complications due to cement, long operation time, dislocation of the hip, and revision difficulties due to cement. However, hemiarthroplasty patients can be allowed full

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weight bearing significantly earlier than internal fixation patients. External fixation has several advantages, such as short operation time, minimal bleeding, and short residence time, but also disadvantages, such as loss of reduction especially in unstable fractures, pin tract infection, and pin loosening.

The objective of the present study was to evaluate whether surgical treatment of the pertrochanteric fractures of the femur with external fixator could reduce the pre- and postoperative length of hospital stay, with low complications and mortality and with satisfactory functional results to achieve rehabilitation and incorporation into the daily life in high-risk patients.

METHODS

Between 2007 and 2013, 26 (10%) of the 270 patients with pertrochanteric fractures who were admitted to our department were classified by the anesthetist as American Society of Anesthesiologists (ASA) grade 3 or 4 and considered not suitable for conventional fracture fixation. Table 1 shows the medical conditions causing the patients to be considered as high risk.

Written informed consent was obtained from all the patients who participated in the study. Ethics committee approval was obtained from Gaziantep University (date: 2013/decision no: 328).

Twenty-six patients who had pertrochanteric fractures were treated using the Orthofix Pertrochanteric Fixator (Bussolengo Verona, Italy). There were 14 male and 12 female patients. The mean age of the patients was 73 (37–93) years. The right hip was involved in 12 cases, and fracture occurred in the left hip in the remaining 14. Two of the fractures occurred in traffic accidents, and the remaining 24 were caused by simple in-house fall. The fractures were classified according to the modified Evans classification (5). Of the fractures, 19 were unstable, and 7 were stable (Table 2).

Of the patient's operations, 10 were performed under general anesthesia, 13 were under regional spinal anesthesia, and 3 were under sedoanalgesia. The patient was placed on a fracture table, and a closed reduction of the fracture was performed under image intensification in all cases. A guide wire was inserted percutaneously at a 125°–130° angle approximately into the center of the femoral neck and head. Two long, 6.5 mm, self-drilling and self-tapping pins were inserted manually on each side of the guide wire within the confines of the femoral neck. The pins were advanced to approximately 10 mm from the subchondral bone of the head. The device attached to the proximal pins acted as a guide for the insertion of the two distal pins. When the implantation of the two proximal pins is complete, the posterior clamp-locking screws are tightened, leaving a distance of 1 to 2 cm between the skin and the posterior clamp. The mean operative time was 24 (20–65) min. Parenteral cephalosporin was given for 2 days after the operation, and low-molecular-weight heparin was administered until discharge.

On postoperative day 1, full weight bearing with a walker is allowed as tolerated. Only four very senile patients who were non-ambulatory before the occurrence of the fracture were not able to walk postoperatively. Pin site care was performed every day, and the patients' families were given instructions on continuing the pin site care after discharge from the clinic. The average hospitalization was 12.7 (3–43) days. Outpatient visits were arranged every month until the fracture was united, and the fixator was removed. Only 16 patients were evaluated according to fracture union and function because 10 patients died within the first 1 to 120 days after surgery before fracture healing was completed. Patients were evaluated on the day the fixators were removed according to the Foster criteria (6). Table 3 shows the Foster criteria.

Table 1. Medical conditions of high–risk patients

Medical conditions increasing surgical risk	Patients (n)
Chronic renal failure	4
Chronic renal failure and insulin–dependent diabetes mellitus	5
Cardiovascular disease	2
Cardiovascular and pulmonary diseases	3
Total	14

Table 2. Classification of our cases according to the fracture types

Type of fractures according to the modified Evans classification		Patients operated (n)	Patients can be evaluated (n)
Stable	Type 1	7	6
Unstable	Type 2	10	5
	Type 3	9	5
Total		26	16

Table 3. Foster's criteria

	Functional grading	Anatomical grading
Excellent	Walks as well as before the operation. No limp or pain	Union in perfect position
Good	Walks well, uses stick to go out	<10° varus and minimal shortening
Fair	Requires stick, considerable limp or pain	10°–25° of varus and 0.5 to 1 in of shortening
Poor	Bedridden or confined to chair	Severe malunion, varus deformity of ≥25° or >1 in of shortening

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 statistical package for Windows (SPSS Inc.; Chicago, IL, USA). Continuous data were expressed as mean, whereas categorical data were presented as percentage (%).

Table 4. Postoperative complications

Postoperative complications	Patients (n)	Treatment
Superficial pin tract infection	5	Oral antibiotic therapy and dressing
Deep pin tract infection	1	Parenteral antibiotic therapy
Refracture	1	Hemiarthroplasty
Anemia	2	Blood transfusion

Table 5. Functional and anatomical grading of cases according to their fracture types

	Functional grading		Anatomical grading	
	Stable fractures	Unstable fractures	Stable fractures	Unstable fractures
Excellent	4	6	3	4
Good	1	3	3	4
Fair	–	1	–	1
Poor	1	–	–	1
Total	6	10	6	10

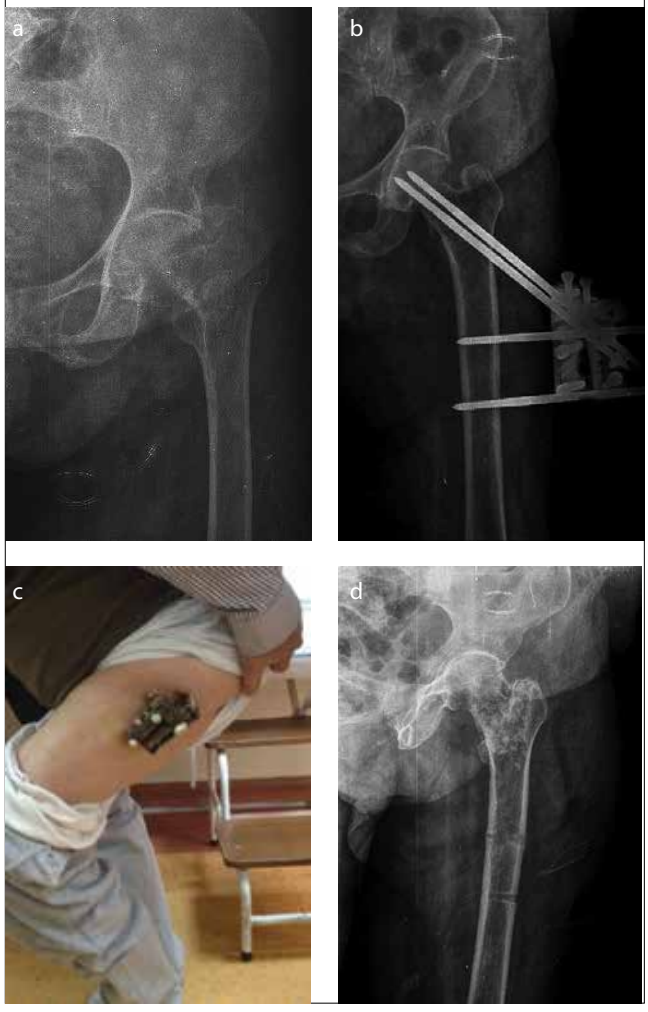
RESULTS

The analysis of the results showed that in relation to the most affected gender, there were 14 men and 12 women. The average age of the patients was 73 (37–93) years. Two patients required blood transfusion postoperatively. The fixator did not interfere with sitting or lying, and there was no restriction of knee movements. The predominant etiology was by fall during walking at home with 92% (24/26). The mean operative time was 24 (20–65) min. The average hospitalization was 12.7 (3–43) days. The average union time of the 16 patients who were alive and whose fixators could be removed was 5.2 (3–11) months. Stable fractures (Evans–Jensen type 1) healed at approximately 4.1 months, whereas unstable fractures (Evans–Jensen types 2 and 3) healed at 5.9 months. Figure 1 shows an 82-year-old patient who had unstable pertrochanteric fracture treated with external fixation and healed with satisfactory functional result.

There were no cases of pin loosening, breakage, or penetration of the femoral head. Twelve patients had an average limb shortening of 18 mm. With respect to the femoral varus compared with the contralateral side, an average of 126.7° (118°–139°) collodiaphyseal angle in the fractured side was calculated (non-fractured side collodiaphyseal angle was 135.5°).

Several complications were seen in eight cases (Table 4). Five patients developed superficial pin tract infection. This involved the proximal pins in all cases. The infections were successfully treated with oral antibiotics and daily cleansing with antiseptic solutions. One developed deep pin tract infection, and intravenous antibiotics were administered for 1 week. There was no osteomyelitis, and none of the pins have to be removed before completion of the treatment in any patient. The patient who developed refracture and treated with hemiarthroplasty was not excluded from the evaluation because he had fracture 3 months after removal of the fixator. There were no cases of pin loosening, breakage, or penetration of the femoral head.

Figure 1. a-d. (a). Preoperative X-ray of left intertrochanteric Evans–Jensen type 2 fracture of an 82-year-old m an. (b) Postoperative X-ray of the patient with external fixator. (c) Full weight bearing and knee flexed position of the patient at postoperative week 1. (d) After removal of external fixator and excellent healing anatomically at 4 months



During the 12-month follow-up period, 10 patients died from causes unrelated to the operation. The mortality rates of the 26 patients who had intertrochanteric fractures treated with pertrochanteric fixator in our retrospective study were 23.07% within the first 30 days and 42.3% within 1 year. When the alive patients were evaluated according to the Foster criteria, anatomically, 7 patients were excellent (3 stable and 4 unstable), 7 were good (3 stable and 4 unstable), 1 was fair (unstable), and 1 was poor (unstable). Functionally, 10 patients were excellent (4 stable and 6 unstable), 4 were good (1 stable and 3 unstable), 1 was fair (unstable), and 1 was poor (stable) (Table 5).

DISCUSSION

Improvements in health services have resulted in a significant increase in survival and pertrochanteric fracture incidence, which mainly occur in the elderly population. Intertrochanteric femur fractures constitute approximately 8%–10% of all fractures in the body. They usually occur as a result of low-energy traumas in older ages and high-energy trauma in young people. Age and other factors increase the tendency to fall. These are visual loss, loss of muscle strength, blood pressure variability, vascular diseases, and musculoskeletal system pathologies. These fractures are seen at the third frequency after distal radius fracture and femur neck fracture in the elderly (7). More than 200,000 patients with intertrochanteric femur fractures are seen annually in the United States. The overall mortality has been reported as high as 10% at 30 days and 30% at 1 year post-injury (8, 9). The mortality risk increases along with the presence of several factors, including increasing age, male gender, number of comorbidities, low mini-mental test score on admission, low hemoglobin concentration on admission, residence in an institution, and the presence of malignant disease (10, 11). When the mortality rates of the 26 patients who had intertrochanteric fractures treated with pertrochanteric fixator in our retrospective study were analyzed, the mortality rates were 23.07% within the first 30 days and 42.3% within 1 year. These results support the study by Moran et al. (12).

Conservative treatment is an unacceptable alternative since it has been associated with mortality of up to 60% (1, 2). The purpose of surgical treatment is to improve the quality of life by providing early mobilization and to restore the prefracture status as soon as possible (4). The quality of surgery depends on the selected osteosynthesis method, surgical technique, bone quality, and reduction quality.

Over the years, several surgical fixation techniques have been proposed. The most widely used implants are the sliding hip screw and the intramedullary hip screw. Internal fixation has several potential disadvantages: patient preparation is difficult and is related to a higher surgical risk intraoperatively and postoperatively, such as potential blood loss, soft tissue manipulation, difficulties of patient positioning, and fracture reduction and obligation of traction table (13).

The biomechanical advantages of the intramedullary hip screw over the sliding hip screw include increased stability and better loading of the proximal part of the femur (14). Furthermore, with intramedullary fixation, a buttress is created that minimizes the amount of translation, helping to control fracture impaction. Another advantage of the intramedullary device is that insertion requires a less invasive surgical approach. However, even with intramedullary fixation, the lateral cortex may be damaged during implantation. Both techniques are associated with high rates of implant failure (ranging from 5% to 20%), including lag screw cut-out and cortical screw pull-out, particularly when the devices are used to treat unstable fractures (15, 16).

Several complications are also described related to intramedullary implants, including malalignment, cut-out, infection, false drilling, wrong lag screw length and drill bit breakage during the interlocking procedure, external or internal malrotation (≥20°) of the femoral diaphysis, elongation of the femur (up to 2 cm), impaired bone healing, periprosthetic fracture distal to the tip of the nail, fracture collapse, implant failure, lag screw intrapelvic migration, neurovascular injury, secondary varus deviation, complications after implant removal, trochanteric pain, and refracture (17).

Vossinakis and Badras compared sliding nail with external fixators in a prospective randomized study of 100 patients with pertrochanteric fractures (18). After 6 months of follow-up, patients with external fixator were found to have less blood loss, shorter operation time, less postoperative pain, shorter hospital stay, earlier mobilization, and less mechanical complication rate.

Cochrane reviewed three published studies and found a shorter operative time, less surgical trauma, less postoperative pain, earlier mobilization, and shorter in-hospital duration for a pertrochanteric external fixation compared with a sliding hip screw (19).

Shortening because of collapse and varisation of the femoral neck is a well-recognized complication of both internal and external fixation in unstable fractures or in the presence of severe osteoporosis (20-22). In our study, 12 (46%) patients had an average limb shortening of 18 mm. With respect to the femoral varus compared with the contralateral side, an average of 126.7° (118°–139°) collodiaphyseal angle in the fractured side was calculated (non-fractured side collodiaphyseal angle was 135.5°), but these varus and shortening complications were not associated with implant failure or cut-out. The Orthofix Pertrochanteric Fixator device used in our study offers enough stability to allow full weight bearing without compromising fracture healing. Lack of mechanical complication has been attributed to the large contact surface between the pins and the bone and to a degree of controlled sliding (23). Although the proximal pins are not free, smooth shafts of pins could slide in the lateral cortex, allowing minimal impaction at the fracture. It has also been suggested that the elasticity of the fixation due to the increased distance of the fixation device from the femur promotes early, florid callus formation that allows the early participation of the bone in load bearing, thus reducing the stresses on the fixation (24). However, these theories require documentation by appropriate biomechanical studies.

The main disadvantage of external fixation is the tendency to superficial pin tract infection. In the treatment of hip fractures with external fixators, the risk of pin track infection varies 0%–30% (24-26). In our study, superficial pin tract infection was observed in 5 (19%) patients and deep pin tract infection in 1 (4%). In the literature, deep infection that required pin removal or repositioning has been reported (1, 20, 27). However, superficial and deep pin tract infections did not require reoperation and did not affect the functional results of our patients.

Another well-described disadvantage of external fixation in the pertrochanteric fractures is postoperative knee stiffness caused by fixation of the fascia lata and vastus lateralis by the distal pins (20). This problem was not seen in our study due to the use of

short pertrochanteric fixator, which did not allow the placement of the distal pins distally in the femur.

Petsatodis at al. (28) compared the stable intertrochanteric fractures and unstable intertrochanteric fractures with other valid surgical options and revealed that external fixation reduces operative time and minimizes blood loss. Their study also suggested that when external fixation is used in unstable pertrochanteric fractures, a high incidence of technique-related complications (pin migration, pin loosening, non-union, varus malunion, and infection) is found (28). External fixation in unstable fractures resulted in prolonged union time, increased incidence of the varus position of the fracture site, and worse functional outcome compared with stable fractures also reported in this study, and Petsatodis et al. (28) suggested that external fixators should be used with caution in the geriatric population in unstable pertrochanteric fractures. However, in our study, there were no cases of pin loosening, breakage, or penetration of the femoral head, and there was no any significant difference between the stable and unstable fractures according to the complications and functional–anatomical criteria of Foster. Only union time criteria was bad in the unstable cases compared with stable ones. Stable fractures (Evans–Jensen type 1) healed at approximately 4.1 months, whereas unstable fractures (Evans–Jensen types 2 and 3) healed at 5.9 months. Andruszkow et al. (29) suggested the external fixation as an alternative to commonly applied implants in patients with multimorbid geriatric trauma.

The external fixation method is minimally invasive and fast. In elderly patients of high-risk (ASA 3 or 4) who have often comorbidities, stable fixation without surgical trauma could be vital for a faster recovery and mobilization and reduced morbidity and mortality (30).

CONCLUSION

The use of external fixation for the management of pertrochanteric fractures in elderly patients of poor health is a valuable and valid alternative surgical method.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (Date: 2013/Decision no: 328).

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

Peer-review: Externally peer-reviewed.

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

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Original Research

Changes in Choroidal Thickness Following Energy Drink Consumption in Healthy Subjects

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ABSTRACT

Objective: This study aims to investigate the effects of consumption of energy drink (ED) on subfoveal choroidal thickness (CT) using enhanced depth imaging spectral domain optical coherence tomography (EDI-OCT).

Methods: In this study, 40 healthy volunteers who consumed 250 mL ED and 40 healthy subjects who consumed 250 mL water were enrolled. All volunteers underwent EDI-OCT scanning for subfoveal CT measurement at baseline and following time periods after ED or spring water consumption. The OCT scannings were performed by the same physician, and all subfoveal CT measurements were manually taken by two independent masked physicians. All subfoveal CT measurements for both groups were analyzed by repeated measure analysis.

Results: Our results showed no significant difference in baseline and following subfoveal CT measurements between the groups ($p>0.05$, for all). The difference in mean values among the following seven measurement periods was not statistically significant in the study and control groups ($p=0.417$ and $p=0.856$, respectively).

Conclusion: The ED in our study did not significantly change subfoveal CT in spite of the caffein content. This may be because of the interactions of caffein with other ingredients of the ED.

Keywords: Energy drinks, choroid, optical coherence tomography

INTRODUCTION

Energy drinks (EDs) are popular among young people worldwide (1, 2). Main consumers are students and athletes in the second and third decades of age (3). The most common ingredients of EDs are caffeine, taurine, various vitamins, glucose, and herbal extracts (4). Caffeine is the stimulatory effective ingredient of EDs (5). However, researchers observed a synergistic effect among the ED ingredients. They also showed that the EDs improved performance more than that by the caffeine content alone (6, 7).

Caffeine is the most commonly consumed psychoactive alkoloid in the world (8). It reaches maximum plasma concentration between 20 and 120 min with a half-life of 3-6 h. Blood pressure changes develop in 30 min, peak in 1-2 h, and may persist for over 4 h (9). Caffeine may significantly reduce macular circulation and choroidal thickness (CT) (10-12). It may also cause transient increase in intraocular pressure and changes in retrobulbar blood flow (13-15).

We aimed to assess the effects of ED consumption on subfoveal CT using enhanced depth imaging spectral domain optical coherence tomography (EDI-OCT) in healthy subjects. To best of our knowledge, this study is the first report that specifically assessed the effect of ED consumption on subfoveal CT.

METHODS

In this prospective observational study, 40 eyes of 40 healthy participants for study group and 40 eyes of 40 healthy participants for control group were included. All participants gave informed consent, and approval of the ethics committee was received from the Gaziantep University. The study followed the principles of the Declaration of Helsinki.

Participants

The participants underwent complete ophthalmic examination. Those who had best-corrected visual acuity of at least 20/20 without any ocular pathology were included in this study. Participants who had intraocular pressure readings >20 mmHg, metabolic diseases, systemic diseases, smokers, pregnants, drug usage, and alcohol abuse were excluded from the study. Additionally, participants who consumed any beverage with caffein or chocolate in the last 24 h were excluded. They were randomly assigned to study or control groups. The participants in study group received a 250 mL can of ED (including 150 mg/l caffeine, 200 mg taurine, B-group vitamins, glucose, sucrose, and water), and those in control group received 250 mL spring water. Only right eye of each participant was examined. The axial length, spherical equivalent, weight, height, and body mass index (BMI) values of each participant were noted. The measurements were

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Table 1. Demographic and clinical characteristics of study and control groups

	Study Group	Control Group	p*
Number			
Eyes/Patients	40/40	40/40	–
Sex			
F/M	20/20	20/20	–
Age, years			
Mean±SD	26.6±4.8	25.2±3.4	0.108
Range	(19–40)	(19–39)	
SE			
Mean±SD	–0.90±1.4	–1.13±1.5	0.478
Range	(–4.00–+4.00)	(–4.00–+3.75)	
AL, mm			
Mean±SD	2420±0.74	24.17±0.90	0.901
Range	(22.83–25.85)	(22.17–25.99)	
Weight, kg			
Mean±SD	71.1±13.9	71.3±15.2	
Range	(50–100)	(51–113)	0.951
Height, cm			
Mean±SD	171.2±8.9	172.3±8.4	0.580
Range	(158–190)	(157–191)	
BMI, kg/m^2			
Mean±SD	24.1±3.6	23.8±3.2	0.695
Range	(18.6–32.6)	(18.3–32.5)	

* Independent student's t–test
F: female; M: male; SD: standart deviation; SE: spherical equivalent; AL: axial length; BMI: body mass index

performed between 9:00 am and 03:00 pm to eliminate any possible diurnal choroidal variation. Measurements were performed at 5 and 30 min as well as at 1, 2, 3, 4, and 6 h following ED or spring water consumption.

Subfoveal CT Measurement

The OCT scans were performed by an experienced clinician using Heidelberg® Spectralis® SD-OCT (Heidelberg Engineering, version:1.8.6.0, Heidelberg, Germany) with EDI modality. A line scan of 30° consisting of 768 A-scans per frame was used. This image was averaged for 100 scans using the automatic averaging and eye-tracking features (16). The subfoveal CT was defined as the vertical distance from the outer surface of the retinal pigment epithelium to the inner surface of the sclera at the fovea. Subfoveal CT values were measured independently by two masked ophthalmologists (S.A.Y and I.E.Y). Measurement differences of >10% between the interpreters were excluded from the study.

Table 2. The mean subfoveal CT measurements of participants at baseline, 5 min, 30 min, 1, 2, 3, 4, and 6 h

	Study Group (Mean±SD)	Control Group (Mean±SD)	p*
Baseline	350.7±72.2	367.7±55.4	0.240
5 min	352.1±72.1	367.9±56.6	0.278
30 min	352.7±72.2	368.4±55.2	0.280
1 h	351.0±72.2	368.6±55.5	0.226
2 h	351.6±72.3	369.7±54.8	0.210
3 h	351.4±71.7	368.9±54.6	0.223
4 h	349.7±70.1	368.6±53.9	0.180
6 h	350.5±71.7	368.2±53.5	0.214

All measurements are in mm
*Independent student's t–test; SD: standart deviation

Statistical Analysis

We used Statistical Package for the Social Sciences 16.0 (SPSS Inc.; Chicago, IL, USA) to analyze outcomes. Kolmogorov-Smirnov test was used to check normality for each continuous variable. Independent student's t-test was used to analyze the categorical variables and subfoveal CT values between the groups. Subfoveal CT values for both groups were analyzed by repeated measure analysis. A p value of <0.05 was considered to be statistically significant.

RESULTS

We enrolled 40 eyes of 40 participants in the study group, and 40 eyes of 40 participants in the control group. Clinical and demographic properties are shown in Table 1. Age, spherical equivalent, axial length, weight, height, and BMI did not significantly differ between the groups (p>0.05 for all).

The mean subfoveal CT measurements of participants at baseline and following periods are shown in Table 2. No statistically significant difference between the groups in mean subfoveal CT measurements at baseline and following periods (p>0.05 for all) was observed.

The difference in mean subfoveal CT among the following six measurement periods was not statistically significant in the study and control groups (p=0.417, F=0.417; p=0.856, F=0.470; respectively).

DISCUSSION

The consumption of EDs, especially in young adults and athletes, has become a worldwide phenomenon. The EDs are frequently consumed to increase performance, counteract sleepiness, and maintain alertness (1). They contain stimulants like caffeine, taurine, herbal extracts, and B-vitamins. The amount of caffeine in

EDs per can varies between 75 and 150 mg (17). Adenosine has a potent vasodilatory effect on multiple vascular beds. Researchers showed that in animal studies, adenosine causes an increase in cerebral blood flow and retinal vessel diameter (18). The exact mechanism of caffeine is still debated, but it is believed that caffeine inhibits vasodilation by competing with adenosine for its receptor (19). Kerrison et al. (20) reported five heavy caffeine consumers who developed central ring scotomas without visual loss. They explained the responsible pathophysiological mechanism by vasoconstriction and transient ischemia of macula. Lotfi and Grunwald (10) reported 200 mg of caffeine reduced retinal blood flow by approximately 13% using blue field stimulation technique. Okuno et al. (11) measured choroid-retina blood flow using laser speckle tissue analyzer and showed that blood flow decreased by 6% in the first hour after an oral administration of 100 mg caffeine. They thought that caffeine might reduce blood flow in the optic nerve head and choroid by increasing vessel resistance. Ozkan et al. (13) reported that caffeine (300 mg) affects retrobulbar blood flow by increasing the resistive index of the ophthalmic, central retinal, and nasal posterior ciliary arteries. Vural et al. (12) reported that drinking 100 mL Turkish coffee (57 mg caffeine) causes a significant reduction in subfoveal CT for at least 4 h (12). In a recent study, Zengin et al. (21) reported similar results. Contrary to previous reports, we observed no statistically significant change in subfoveal CT in the study group. Other synergistic vasoactive and non-vasoactive agents in ED somewhat limit the temporary vasoconstrictive effect of caffeine on choroidal vessels. We showed only the short-term effect of a single-type ED's ingredients combination on CT. The ingredients were not individually evaluated. Therefore, it is impossible to specify whether the effects were the result of an interaction among ingredients. The combination of caffeine and taurine in EDs has been known to have synergic effect on cognitive performance (22). Cardiovascular effects of taurine are similar to those of caffeine (23). To the best our knowledge, acute effects of isolated taurine or caffeine-taurine combination on choroid is unknown.

Despite advances in imaging technology, adequate imaging of the choroid is still lacking. Other imaging techniques, such as B-scan ultrasonography and ICG, are limited in image resolution and measurement accuracy. The EDI-OCT provides evaluation of the choroid, and facilitates understanding of the chorioretinal abnormalities and diseases (24). Osmanbasoglu et al. showed that the mean diurnal variation of central CT was not significiant between 9:00 am and 4:00 pm (25). In our study, we performed all measurements between 9:00 am and 3:00 pm. We did not observe any significiant variation among the measurement times in participants.

Our study has some limitations. Firstly, the concentration of caffeine and other ingredients vary among different EDs. In the US market alone, >300 different EDs are available (17). The fact that this study only compared a single-type ED (150 mg/l caffeine, 200 mg taurine, B-group vitamins, glucose, sucrose, and water) with spring water as a control provides limited information on the relative contribution of these ingredients. Thus, these results cannot be generalized to other EDs. Secondly, the CT was not directly measured in this study.

CONCLUSION

The ED we used in our study did not change subfoveal CT despite the fact that it had caffein as a main ingredient. The effect of caffein on the CT may be limited by the interactions with other ingredients of the ED. To the best our knowledge, this is the first report evaluating the acute effect of EDs on subfoveal CT using EDI-OCT. Further studies are required to investigate the effects of EDs on CT.

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

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

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

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Original Research

The Effects of Intravenously Administered Tramadol, Dexketoprofen Trometamol, and Midazolam in the Management of Renal Colic Pain; A Prospective Randomized Study

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ABSTRACT
Objective: This study aims to assess the effects of analgesic treatment combinations on ultrasonography findings and pain scales in patients with renal colic pain who were admitted to the emergency department of Gaziantep University Medical Faculty.
Methods: This prospective randomized clinical study was conducted in 100 patients with renal colic pain who were admitted to the emergency department of Gaziantep University Medical Faculty between September 2013 and September 2014. The patients were divided into four groups: the first group received tramadol, the second received dexketoprofen trometamol, the third received a tramadol-midazolam combination, and the fourth group received a dexketoprofen trometamol-midazolam combination. Blood pressure, pulse, and bedside renal ultrasonography (USG) findings were evaluated. Pain severity levels were assessed using the visual analog scale (VAS) and the renal colic symptom score (RCSS), and were recorded as pre-treatment (0 min) and post-treatment (30 min) scores. These values were then statistically compared.
Results: There was no statistically significant difference among the four groups in terms of gender and age (p=0.951 and p=0.890, respectively). A significant decrease was detected in the pre-treatment (0 min) and post-treatment (30 min) VAS and RCSS scores of all groups. The largest decrease was observed in the tramadol-midazolam group in the between-group comparison. In the evaluation of the alterations of the bedside USG findings, the largest change in renal parenchymal diameter of painful kidney was also observed in the tramadol-midazolam group.
Conclusion: The efficacy and safety of a tramadol-midazolam combination as an analgesic in management of renal colic may be used as an alternative, or add-on, therapy to currently available options.
Keywords: Renal colic, bedside ultrasonography, analgesic

INTRODUCTION

Pain is the symptom for which people usually consult their physicians. Renal colic is an emergency that usually develops secondary to renal stone disease, presents as acute and severe pain, and is primarily diagnosed and treated in emergency departments (EDs). The incidence and prevalence of renal stone disease is reportedly increasing worldwide, and acute renal colic episodes, typically described by patients as "coming out of the blue", cause severe distress and warrant emergency medical attention. These patients are treated with opioids and non-steroidal anti-inflammatory drugs (NSAIDs) to relieve pain in the acute setting (1).

Tramadol is a centrally acting synthetic opioid analgesic that binds to specific opioid receptors. It is used to treat moderate to moderately severe pain. Onset of action is dose dependent, but it generally occurs within 5–10 min of intravenous (IV) dosing (2). Dexketoprofen trometamol is a newly developed NSAID that is used in treatment of moderate pain. Itproducesan analgesic effect within 30 min of administration (3). Midazolam is a short-acting central nervous system (CNS) depressant of the benzodiazepine class. Intravenous midazolam is indicated for procedural sedation (often in combination with an opioid), for preoperative sedation, for the induction of general anesthesia. Light intravenous sedation with midazolam is used to make anxious patients more comfortable before medical procedures (4).

Multimodal analgesic techniques provide potent and synergistic effects. Therefore, pain control can be achieved with balanced and effective analgesia. Concomitant use of anxiolytic and sedative drugs with analgesic agents may reduce anxiety and increase early mobilization and early discharge from the emergency services.

The primary objective of this study was to measure the severity of pain by using appropriate assessments in patients admitted to the ED with renal colic, and to determine renal parenchymal di-

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ameters by ultrasonography (USG). The secondary objective was to compare the efficacy of tramadol, dexketoprofen trometamol, tramadol-midazolam, and dexketoprofen trometamol-midazolam combinations in relieving pain associated with acute renal colic.

METHODS

This prospective, randomized, single-blind study was performed in the ED of the Gaziantep University Medical Faculty. The study protocol conformed to the principles of the Declaration of Helsinki, and was approved by the Gaziantep University Ethics Committee (Ethical committee resolution no: 06-2009/264, date 18.06.2009). The study was funded by the Commission of Scientific Research Projects, Gaziantep University (Project no: TF.12.31). All participants were given details of the study protocol, and written consents were obtained from them.

This study was conducted between September 2013 and September 2014 in 100 patients who were admitted to the ED and diagnosed with renal colic, met the study criteria, and gave approval voluntarily to participate in the study. Patients who were diagnosed with acute renal colic based on their chief complaint, history, and physical examination, and, hematuria in urine analysis and, or past medical history of renal stone, were enrolled in the study. In all participants, kidney or urinary tract stones were confirmed by ultrasound, plus kidney-ureter-bladder (KUB) X-ray or CT scan. The participants (all aged over 16 years) were randomly allocated, without gender discrimination, using computer-generated random numbers to four groups receiving differing medications: tramadol (Group 1, 100 mg), dexketoprofen trometamol (Group 2, 50 mg), tramadol-midazolam (Group 3, 100 mg to 0.01mg/kg), and dexketoprofen trometamol-midazolam (Group 4, 50 mg to 0.01 mg/kg). A detailed medical history was taken, and a thorough physical examination was performed for each participant. Vascular access was established in each participant, and complete blood count, urinalysis, urea, and creatinine level measurements were conducted. In addition, blood pressure and pulse were measured. Diagnosis, USG, and treatment efficacy were all evaluated by the same physician. The relevant physician had been certificated after 8 h of theoretical and practical training in a basic emergency USG course. Patients for whom ultrasonographic measurements could not be performed for technical and anatomical reasons, such as obesity and excessive abdominal gas, were excluded from the study. The participants who had received an analgesic medication during the previous 24 h, had an NSAID allergy, had a history of peptic ulcer or gastrointestinal bleeding, or were receiving anticoagulant treatment, as well as those in whom a solitary kidney or bilateral urinary obstruction was detected, were also excluded, as were those with a serum creatinine level above 2 mg/dL, visual and hearing defects, and female patients in menstruation. Pregnant and nursing females were also excluded.

All participants were taken into the intervention room, and were laid on stretchers and monitored. Then, 500 cc 0.9% NaCl was administered via the left antecubital vein to each individual. Medications were administered via the same intravenous route. Pain severity was evaluated in each participant, using the visual analog scale (VAS) and renal colic symptom score (RCSS), immediately before administering medications and after 30 min (Figure 1). Pre-treatment and post-treatment renal and parenchymal sizes were measured in the supine position using the Logiq P6 (GE Healthcare, 2008) device and a 3.5 MHz convex probe to obtain longitudinal and axial images. The participants were examined for nephrolithiasis, hydronephrosis, and pelvicalyceal dilatation. Pre-treatment and post-treatment anteroposterior diameters were measured in those with detected pelvicalyceal dilatation.

Statistical Analysis

Statistical Package for the Social Sciences for Windows version 18.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical evaluation. The distribution of the permanent data that were obtained in this study was examined graphically and using a Kolmogorov–Smirnov test. An analysis of variance test was used in an intra-group comparison of independent and normally distributed data. As the data were independent and normally distributed, groups were compared using an independent-sample t test. As the data were normally distributed and dependent, groups were compared using a paired-sample t test. A Kruskal–Wallis test was used in intra-group comparison of independent and not normally distributed data, while a Mann–Whitney U test was used for paired comparison. The relationship between variables was analyzed using the Pearson correlation test. All data were expressed as mean±standard deviation. In all comparisons, $p<0.05$ was considered statistically significant**.**

RESULTS

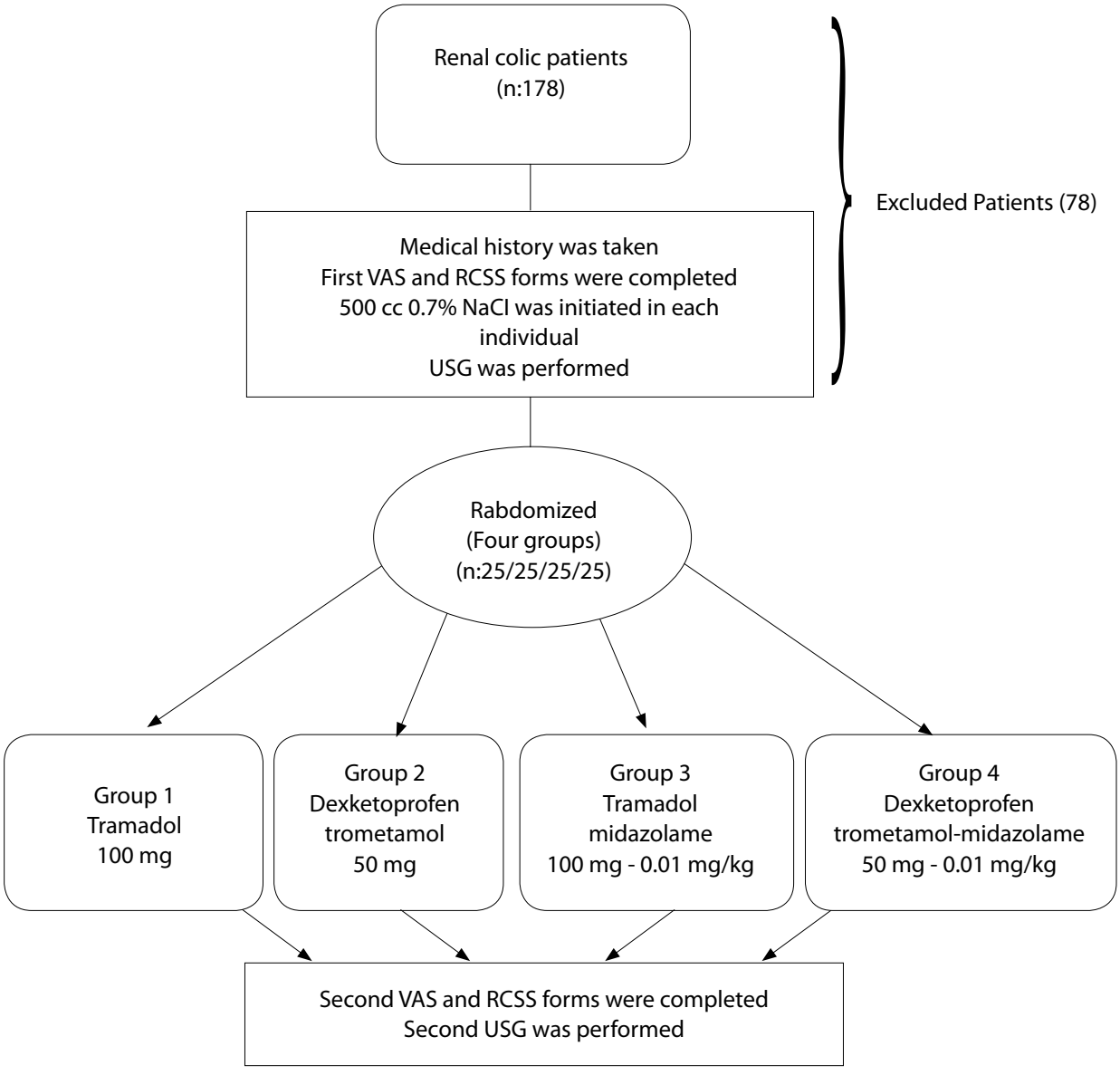
In a year, approximately 100,000 patients (over 16 years old) are referred to our ED for diagnosis and treatment. Of these patients, approximately 200 are admitted due to renal colic. This study involved 100 participants who had been admitted to the ED with renal colic, with the numbers of enrolled females and males being 36 (36%) and 64 (64%), respectively. The mean age of the participants was 34.6±13.3 years. Pre-treatment urea, creatinine, and WBC values were measured, recorded, and compared between the groups. Between the groups,there was no statistical difference in the mean ages, gender, and laboratory results (Table 1), and there was no statistically significant difference in terms of pre-treatment and post-treatment blood pressure and pulse values (Table 2).

A significant decrease was detected in post-treatment VAS and RCSS scores when compared to pre-treatment values (Table 3). In addition, there was a significant difference between the groups with regard to pre-treatment VAS and RCSS scores (p=0.000 and p=0.001, respectively), while no significant difference was observed for post-treatment values (p=0.286 and p=0.937) (Table 3).

The highest decrease between pre-treatment (0 min) and post-treatment (30 min) VAS scores was observed in Group 3, as 75.3%±26.7%. A statistically significant difference was found between the groups in decrease in pre-treatment (0 min) and post-treatment (30 min) VAS scores (p=0.025) (Table 4).

There was no statistically significant difference between the groups in pre-treatment and post-treatment renal long axis and short axis (Table 5).

Figure 1. Flow chart of the study design
VAS: visual analog scala; RCSS: renal colic symptom score; USG: ultrasonography



DISCUSSION

Renal colic is a common worldwide disease. It often leads to ED visits, and frequently requires imaging evaluation (1, 5). Acute renal colic is one of the most painful events that an individual can experience, and relief of this pain becomes an urgent and daunting task for the ED physicians. Different drug groups used for pain relief in acute renal colic have been studied and described (1, 6). Although morphine and pethidine were formerly used as first-line treatment agents for this disorder, NSAIDs have been used as medications with proven efficacy since the 1970s (6, 7). Current medical treatment of acute renal colic includes the use of calcium channel blockers, steroids, NSAIDs, and α blockers. The European Association of Urology guidelines suggest the use of NSAIDs, such as diclofenac, indomethacin, or ibuprofen, as first-choice treatment when renal colic is initially diagnosed. Opioids, such as hydromorphine and tramadol, are suggested as the second-choice options (7). Some previous studies have assessed the use of NSAIDs and opioid combinations; however, there are no available studies on the concomitant use of anxiolytic and sedative drugs with analgesic agents (1, 6, 8).

In previous studies, comparisons of vital signs obtained during renal colic have been performed in participants receiving different groups of drugs (9, 10), and these have revealed differing results. In our study, inter-group comparison of systole-diastole and pulse data demonstrated no differences (Table 2). In the pre-treatment and post-treatment in-group comparison, we found that systolic-diastolic pressure significantly decreased in

Table 1. Comparison of demographic data, laboratory, and urine analysis results

	Group 1	Group 2	Group 3	Group 4	p
Male (n)	15	16	17	16	0,951[α]
Female (n)	10	9	8	9	
Age (year)	34.8±16.1	33±13.9	34.8±11.7	35.9±11.9	0.89[β]
Urea (mg/dL)	28.7±7.1	33.6±18.8	29.9±7.5	28.8±9.1	0.403[β]
Creatinine (mg/dL)	0.8±0.2	0.9±0.3	0.9±0.1	1.03±0.3	0.261[β]
WBC (uL)	9579±2298	9268±3460	10171±4057	99.5±2516	0.780[β]
Urine leukocytes					
Positive	5	14	14	12	0.032[α]
Negative	20	11	11	13	
Urine erythrocytes					
Positive	12	17	22	19	0.020[α]
Negative	13	8	3	6	

[β]: analysis of variance; [α]: Chi–square test; WBC: white blood cell

Table 2. Comparison of measured parameters

	Group 1	Group 2	Group 3	Group 4	p[α]
Pre–treatment					
Systole	118±15	116±22	122±20	122±23	0.679
Diastole (mmHg)	67±12	71.8±14	77±11	72.2±17	0.105
Post–treatment					
Systole	110±13	114±13	114±14	111±18	0.625
Diastole (mmHg)	66±12	72.7±10	71±10	72.1±15	0.215
Pre–treatment					
Pulse (Pulse/min)	87±9	83±14	84±14	81.2±11	0.611
Post–treatment					
Pulse (Pulse/min)	78.56±8	79.52±8.8	80±11	78.1±12	0.734
Pre–Post P[β] (Systole)	0.003	0.491	0.043	0.010	
(Diastole)	0.681	0.720	0.034	0.965	
(Pulse)	<0.001	0.167	0.189	0.968	

[α]: analysis of variance; [β]: paired simple test

Group 3. We believe that the anxiolytic and cardio depressive effects of midazolam might have caused it.

As in other painful conditions, pain-scoring systems are used to grade pain severity in acute renal colic. In this study, we utilized VAS and RCSS, and we used four drug groups to relieve pain and decrease pain-related anxiety. We detected a significant decrease in post-treatment VAS and RCSS scores in all groups (Table 3, 4), with this being most prominent in Group 3, which shows that addition of midazolam to tramadol increases treatment efficacy. No information on the concomitant use of midazolam and tramadol is currently available, and few previous studies have investigated the use of tramadol as a single agent (11, 12). In our study, we found a statistically significant decrease in VAS and RCSS scores because of the concomitant use of tramadol and midazolam when compared to other combinations.

Table 3. Comparative analysis of changes in the VAS and RCSS levels

	Group 1	Group 2	Group 3	Group 4	p[α]
VAS					
Pre-treatment	7.28±1.4[a]	7.72±1.5[b]	8.7±1.2[c]	8.6±1.3[d]	0.000
Post-treatment	3.1±1.8	2.1±1.5	2.2±2.5	2.5±2.2	0.286
RCSS					
Pre-treatment	3.8±1.4[e]	4.7±2.2[f]	6.4±2.3[g]	5±2.6[h]	0.001
Post-treatment	1.5±1.3	1.4±1	1.3±0.8	1.3±0.1	0.937
Pre-Post P[β]					
VAS	<0.001	<0.001	<0.001	<0.001	<0.001
RCSS	<0.001	<0.001	<0.001	<0.001	<0.001

[α]: analysis of variance; [β]: paired simple test, Mann-Whitney U test (avs c, avsd, bvsc, bvsd, evsg, evsh, fvs g for p<0.05); VAS: visual analog scale; RCSS: renal colic symptom score

Table 4. Comparison of percentage reduction of VAS and RCSS levels

	Group 1	Group 2	Group 3	Group 4	p[α]
VAS Decrease (%)	57.6±25[a]	73.2±17.7[b]	75.3±26.7[c]	70.5±25.2[d]	0.025
RCSS Decrease (%)	63.4±25.4	70±19	77±15.6	72±22.8	0.095

[α]: Kruskal-Wallis test, Mann-Whitney U test (avsb, c, d for p<0.05); VAS: visual analog scale; RCSS: renal colic symptom score

Table 5. Comparison of renal sizes

Aching side	Group 1	Group 2	Group 3	Group 4	p[α]
Pre-treatment					
Long axis	10.7±1.1	10.6±1.2	11.3±1.2	10.84±0.9	0.161
Short axis	5±0.7	5.2±1	5±0.97	5.1±1	0.402
Parenchyma	1.35±0.2	1.4±0.3	1.3±0.27	1.33±0.1	0.304
Post-treatment					
Long axis	10.7±1.1	10.6±1.3	11.2±0.9	10.80±0.7	0.161
Short axis	5±0.8	5.3±0.9	5.3±0.9	5±0.9	0.402
Parenchyma	1.33±0.1[e]	1.3±0.3[f]	1.1±0.25[g]	1.31±0.2[h]	0.014
Pre-treatment					
Anteroposterior	1.322±0.21	1.1±0.6	1.3±0.54	1.104±0.9	0.831
Post-treatment					
Anteroposterior	1.327±0.23	1.2±0.5	1.4±0.52	1.1±0.8	0.553
P[β] for Long axis	0.804	0.832	0.793	0.702	
P[β] for Short axis	0.539	0.446	0.673	0.186	
P[β] for Parenchyma	0.595	0.367	0.066	0.374	
P[β] for Anteroposterior	0.604	0.410	0.152	0.863	

[α]: Analysis of variance; [β]: paired simple test, *Mann-Whitney U test (gvse, f, h for p<0.05)

This may be due to a possible additive effect obtained by the concomitant use of these agents. Another possible explanation is that decreasing anxiety in patients who are admitted to the ED may decrease anxiety-induced pain.

Although no previous studies have shown the relationship between renal diameters and analgesics, there have been several investigations of the correlation between hematuria and the presence of hydronephrosis (13, 14). A total of 70% of our study sample had hematuria, bedside USG revealed hydronephrosis in 21% of the cases, and there was no statistically significant difference between these patients in terms of measured pre-treatment (0 min) and post-treatment (30 min) anteroposterior diameter values (Table 5). In addition, we detected no in-group differences with regard to pre-treatment and post-treatment long axis, short axis, and parenchymal diameters (Table 1, 5). Inter-group comparison revealed a difference in post-treatment parenchymal diameters, which was related to the largest decrease being detected in Group 3. It remains unclear as to why the tramadol-midazolam combination led to a statistically significant decrease in renal parenchymal diameters.

The main limitation of the present study was its monocentric, single-blinded design, and relatively small sample size. A double-blinded design could have improved the investigation.

CONCLUSION

Renal colic treatment modalities have been generally evaluated for their efficacy within 60 min of analgesia application and using only VAS. This study evaluated the analgesic effects of four different renal colic treatment modalities for 30 min using both VAS and the RCSS, and also with renal diameters. This fact differentiates this study from others of the same genre. Tramadol-midazolame combination may represent an alternative or add-on analgesic to currently available options for renal colic.

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

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Z., G.K.; Design – S.Z.; Supervision – S.Z.; Materials – G.K.; Data Collection and/or Processing – G.K.; Analysis and/or Interpretation – S.Z.; Literature Search – B.A.; Writing Manuscript – S.Z., B.A.; Critical Review – C.Y.; Other – C.Y.

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Original Research

Effects of Nutrition and Exercise Habits in Patients with Type 2 Diabetes

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ABSTRACT
Objective: Diet and exercise therapy form the basis of treatment of type 2 diabetes mellitus (T2DM). The objective of the present study was to evaluate the effects of diet and physical activity interventions for patients with T2DM.
Methods: We assessed the prospective association between levels of physical activity, diet, and quality of life (QOL) in patients with T2DM. We measured body mass index (BMI), waist-to-hip ratio, and QOL index (36-item Short Form Health Survey). A total of 300 patients (169 women and 131 men) were enrolled in the study.
Results: The mean age and BMI of the patients were 53.50±8.58 years, 30.39±3.97 kg/m^2 in women and 56.32±8.80 years, 30.28±1.79 kg/m^2 in men, respectively. QOL was significantly increased in patients with T2DM with regular exercise and diet (p=0.001, 0.024, and 0.012).
Conclusion: Our findings show that combined diet and physical activity interventions achieved clinically meaningful increase in the QOL. Especially, aerobic exercise program improved the QOL in women with T2DM.
Keywords: Type 2 diabetes mellitus, exercise, nutrition

INTRODUCTION

Diabetes is a chronic condition that occurs when the pancreas does not produce sufficient amounts of insulin or when the body cannot effectively use the insulin it produces. If endocrine disease is the origin, metabolic disease is seen as the main finding. It is chronic and progressive. Diabetes is a common disease, and this frequency is increasing dramatically worldwide. According to the World Health Organization, in 2000, 171 million individuals with diabetes were reported to be >2 times more likely to have diabetes in 2030. Diabetes is an endocrine disorder that is accompanied by hyperglycemia, which is life-threatening and can be seen at any age, increasing in incidence in developing countries and in our country. If uncontrolled, it is an important health problem that will increase mortality and morbidity due to microvascular and macrovascular complications.

Non-insulin-dependent diabetes is frequently encountered due to type 2 diabetes mellitus (T2DM) obesity and physical inactivity, also called adult diabetes. It covers 90%–95% of all individuals with diabetes (1).

There is an increasing incidence of diabetes today. Nutrition and exercise are two very important components to control and prevent possible complications. Three components of an effective diabetes treatment are defined as exercise, diet, and medication. Exercise is considered as the main building block of T2DM treatment (2).

The purpose of the present study was to evaluate the nutritional and exercise habits of patients with T2DM and how they affect their quality of life (QOL).

METHODS

This was a survey of 300 patients with T2DM conducted in Florence Nightingale Hospital Internal Medicine and Physical Medicine and Rehabilitation departments. In the study, quota sampling method was used as a possibility sampling method. Patients with T2DM aged 25–65 years were included in the study. Exclusion criteria include gestational diabetes, prediabetes, paralysis, patients with cancer, physical handicaps, and pregnant women. The ethics committee of İstanbul Bilim University approved the study.

Data regarding patients were given a regular diet, whether they were doing physical activity or not (mild, moderate, and severe), age, height, weight, body mass index (BMI), marital status, educational levels, measurements of waist/hip circumference, and accompanied chronic illness were noted. The 36-item Short Form Health Survey (SF-36) questionnaire was completed to assess the QOL.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 22.0 program (SPSS IBM Corp.; Armonk, NY, USA). Mann–Whitney U and Chi-square tests were used for non-parametric tests, and Spearman correlation test was used for correlation analysis. A p value <0.05 was considered significant.

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RESULTS

The demographic characteristics of the patients are shown in Table 1. Of the patients, 141 were high school graduates, 254 were married, and 165 were working. Of the participating patients, 158 use insulin and antidiabetic drugs, 135 use only antidiabetic drugs, and seven do not use insulin or antidiabetic drugs. Of the patients, 128 were cigarette smokers, nine were using alcohol, and 139 were hypertensive. Among our patients, 140 reported regular exercise. Of those, 125 reported mild aerobic exercise for 30 to 90 min per week, and 15 for 2 to 4 h per week for mild aerobic exercise.

Compared with the SF-36 health profile parameters of our patients who did or did not exercise, physical function, general health perception, energy level, social functioning, and emotional role difficulties were found to be statistically higher than those who did not exercise (Table 2).

Table 1. Demographic characteristics of the patients

	Women (n=169) Mean±SD (min–max)	Men (n=131) Mean±SD (min–max)	z	p
Age (year)	53.50±8.58 (33–65)	56.32±8.80 (33–65)	–1.707	0.088
BMI	30.39±3.97 (20.40–38.59)	30.28±1.79 (26.51–34.72)	–0.652	0.514

Mann–Whitney U test
BMI: body mass index; SD: standard deviation

Table 2. Comparison of SF–36 health profile parameters of exercising and non–exercising patients

SF–36 parameters	Exercising Mean±SD (min–max)	Non–exercising Mean±SD (min–max)	z	p
Physical function	81.62±11.00 (50–100)	58.08±20.62 (25–100)	–5.451	0.000**
Physical role limitation	79.37±24.60 (25–100)	69.58±33.85 (0–100)	–1.240	0.215
Pain	71.87±18.22 (32.50–100)	75.79±35.05 (32.50–100)	–0.064	0.949
General medical health	53.62±9.19 (35–75)	48.91±9.74 (30–70)	–2.253	0.011*
Vitality	52.90±13.96 (30–85)	45.91±12.16 (20–75)	–2.253	0.024*
Social functioning	69.56±20.51 (25–100)	60.37±15.76 (10–87.50)	–2.124	0.034*
Emotional role limitation	74.04±25.38 (33–100)	56.25±34.50 (0–100)	–2.507	0.012*
Mental health	62.85±16.05 (28–92)	62.60±18.93 (28–140)	–0.629	0.529

*p<0.05; **p<0.001; Mann–Whitney U test

Compared with the SF-36 health profile parameters of patients who did not apply regular diet, emotional role and pain parameters were found to be statistically significantly higher than those who did not regularly administer the diet. The physical function parameter was found to be higher in patients who regularly administered the diet than in those who did not (Table 3).

When the correlation analysis of the waist and hip measurements with the QOL were examined, it was found that the correlation between waist circumference and physical function, energy level, and emotional role strength parameters was a negative correlation (p=0.001, 0.018, and 0.000). According to this result, as the waist circumference decreases, the physical function, energy level, and emotional role of the patients increase. The hip circumference was also found to correlate negatively with the physical function and the emotional role strong parameters (p=0.026 and 0.000). As a result, it has been found that as the hip circumference decreases, the physical function and emotional role of the patients increase (Table 4).

DISCUSSION

Diabetes continues to be the most important health problem in our country and in the world every year. In the long term, it affects the QOL because of its complications. According to the atlas of diabetes, approximately half of adults with diabetes are in the 40–59 age range.

This number is expected to increase in the following years. In 2013, the number of men with diabetes is 14 million more than women, and in 2035, the difference is expected to increase to 15

Table 3. Comparison of SF–36 health profile parameters of patients who do and do not practice regular diet

SF–36 parameters	Applying regular diet Mean±SD (min–max)	Not applicable regular diet Mean±SD (min–max)	z	p
Physical function	70.47±19.20 (25–100)	59.44±23.34 (30–100)	–2.257	0.024*
Physical role limitation	69.17±33.46 (0–100)	85.18±17.34 (50–100)	–1.915	0.056
Pain	72.73±33.20 (32.50–100)	78.24±15.02 (55–100)	–2.122	0.034*
General medical health	50.20±9.84 (30–75)	52.40±9.54 (35–70)	–1.153	0.249
Vitality	49.05±12.67 (25–85)	47.77±15.08 (20–75)	–0.020	0.984
Social functioning	63.76±19.07 (10–100)	64.81±16.27 (25–100)	–0.556	0.578
Emotional role limitation	59.29±33.79 (0–100)	74.38±24.99 (33–100)	–1.966	0.049*
Mental health	62.60±19.31 (28–140)	62.96±12.91 (44–88)	–0.246	0.806

*p<0.05; **p<0.001; Mann–Whitney U test

Table 4. Correlation of SF-36 parameters with waist and hip circumference

SF-36 parameters	Spearman	Waist circumference (cm)	Hip circumference (cm)
Physical function	r	−0.336	−0.223
	p	0.001**	0.026*
Physical role limitation	r	−0.100	−0.097
	p	0.320	0.339
Pain	r	−0.179	−0.180
	p	0.075	0.073
General medical health	r	−0.004	0.114
	p	0.968	0.260
Vitality	r	−0.237	−0.126
	p	0.018*	0.212
Social functioning	r	−0.018	0.069
	p	0.856	0.493
Emotional role limitation	r	−0.361	−0.389
	p	0.000**	0.000**
Mental health	r	0.096	0.075
	p	0.344	0.457

*p<0.05; **p<0.001; Spearman's correlation

million (3). Of the patients who participated in our study, 56.3% were female, and 43.7% were male.

Studies have shown that low levels of education are effective in the development of T2DM.

Although the level of education is not directly related to the incidence of T2DM, it is an effective factor in terms of good diabetes management (4). When we look at the level of education of the individuals participating in our study, it is seen that 47% of them have graduated from high school.

Smoking is another risk factor for the development of T2DM. The risk of diabetes in smokers and females is approximately 50%. Patients with diabetes are at risk for many microvascular and macrovascular diseases. Smoking increases this risk through diabetic nephropathy, increased inflammation for retinopathy and neuropathy, and metabolic effects along with endothelial dysfunction. T2DM is very important in terms of quitting smoking, facilitating glycemic control, and limiting the development of diabetic complications (5). Of the patients in our study, 42.66% were using diabetes to trigger diabetes.

Studies conducted on alcohol use have shown that moderate alcohol consumption may reduce the risk of T2DM. Studies have shown that alcohol increases insulin sensitivity. On the other hand, excessive alcohol consumption increases the risk of T2DM in women (6, 7). In the population we examined, a small number of patients (3%) reported using alcohol. Diabetes often accompanies chronic disease hypertension. Hypertension risk was 1.5–2 times higher in people with diabetes than in those without diabetes (8). In the present study, 46.33% of the patients also had hypertension at the same time.

In a planned and conducted study to evaluate eating behavior disorders, QOL, nutritional status, biochemical findings, and anthropometric measurements of patients with T2DM, 112 patients aged between 35 and 87 years with a diagnosis of T2DM were studied. When the QOL was compared according to the BMI values, it was found that there was no significant difference in the QOL among patients with normal BMI and patients with high BMI. There was a negative correlation between duration of diabetes and physical function, physical role limitation, energy, social functioning, and mental health scores. Some studies using the SF-36 QOL scale have shown that fat individuals have lower physical function scores than normal individuals. In a study of patients with T2DM, patients with T2DM who were second-degree obese were found to have lower QOL than those who were overweight and obese at first (9). In our study, patients with high BMI were found to have lower energy levels, emotional role, and social functioning.

Another study of patients with T2DM found that patients with attention to their diet had higher physical functions, energy levels, and emotional role (10). In our study, patients' physical function and emotional role difficulties were found to be higher, and pain levels were lower. The benefits of exercise have been proven in studies (11). Exercise with insulin therapy has been reported to lower blood glucose levels, decrease insulin requirement, and increase glucose tolerance (12). For individuals with T2DM, combined exercise with exercise should be applied together with an appropriate diet program. This treatment approach provides optimal blood glucose control with other positive health effects. Regular exercise appears to improve glucose tolerance; increase muscle and liver insulin sensitivity; decrease glycated hemoglobin levels; cardiovascular risk factors, such as lipid profile, blood pressure, and body weight; and functional capacity in patients with T2DM (13, 14). In the present study, we also found that patients who exercise regularly have higher QOL similar to the literature.

In a study of physical activity and QOL in patients with T2DM, sedentary patients were found to have lower functional capacity, physical limitations, pain, general health status, and emotional limitation. In a study conducted, 39% of adults with diabetes were reported to be physically active, and 59% of those without diabetes were active. It has been found that being physically active is related to the level of income, physical function limitations, depression, and obesity (15). It is not known why individuals with diabetes are less active, but it is assumed to be due to a lack of interest. It is also thought that people with diabetes frequently have decreased exercise capacities and are uncomfortable during exercise (15). Another researcher investigated the effect

of different exercise programs on functional performance and QOL in patients with T2DM (16). We found that the 12-week exercise program affected the QOL, depression level, energy consumption, fatigue, and balance in a positive way (16). In parallel to the literature, we also found that exercise patients had better physical functions, energy levels, emotional states, and general health perceptions than non-exercise patients. In a planned study with the aim of evaluating the effects of an exercise program consisting of aerobic and refractory exercises on metabolic control, depression, and QOL in patients with diabetes, 36 patients with T2DM were included in the study. Resistive exercises, calisthenic exercises, and walk-in supervised exercise programs were found to have positive effects on metabolic control, QOL, and depression in patients with T2DM (17).

Smutok and colleagues compared the effects of augmentation and aerobic exercise program for 5 months in controlled trials involving T2DM and impaired glucose tolerance patients. Positive changes in insulin function were more pronounced in the group receiving boosting training (18). In our study, 40% of the patients were also found to have regular aerobic exercise, and those who exercise had higher QOL.

The limitations of our study are that the number of patients is low, the nutritional consumption is not recorded, and the laboratory analysis results are unknown.

CONCLUSION

As a result, it has been found that patients with T2DM who regularly exercise have higher QOL. It is emphasized that patients with diabetes for this result are effective in regularly implementing aerobic exercise as well as regular practice of diet programs in reducing blood glucose levels.

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

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflict of interest to declare.

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Original Research

Investigation of the Protective Effects of Nigella Sativa Oil and Thymoquinone in Radiation Exposed Rats

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ABSTRACT
Objective: It is not always possible to treat early and late side effects due to radiotherapy. In this study, the effects of free radicals on the oxidant antioxidant system were investigated in comparison with the clinical use of WR-2721 in the prevention and treatment of side effects caused by free radicals.
Methods: According to the experimental protocol, rats were randomly assigned to five groups: Control Group (K; n=10), Radiotherapy Group (R; n=10), Nigella sativa oil Group (NSO; n=10; 2.4 g/kg/day), Nigella sativa oil+Radiotherapy Group (R+NSO; n=10; 60 min; 2.4 g/kg/day), Radiotherapy+Amifostine Group (R+WR-2721; n=10; 200 mg / kg / day; 60 min before 60 min. Radiotherapy was applied to the rats using radioactive cobalt-60 teletherapy machine in a single dose of 8 Gy to the whole body area as SSD 40 cm. The study was completed in 72 h following radiation application, and the rats were sacrificed by decapitation. Oxidative Stress Index (OSİ) Total Oxidative Stress (TOS) Total Antioxidant Status(TAS) malondialdehyde (MDA), nitric oxide (NO), myeloperoxidase (MPO), superoxide dismutase (SOD), glutathione (GSH), and catalase (CAT) parameters were measured.
Results: According to these results, WR has more positive effects on MPO and CAT values when NSO on MDA values. There was no statistically significant difference in TOS, OSI, NO, TAS, SOD, CAT values between the R + NSO and K Groups. Compared to the R Group, TOS, OSI, NO, MDA levels significantly decreased and TAS, SOD, GSH, CAT levels significantly increased in the R+NSO Group.
Conclusion: In this study, we have shown that Nigella sativa oil is effective in radiation-induced damage on the liver oxidative stress and nitrosative stress. Further studies should be conducted to investigate different tissues, with different radiation intensities and different concentrations of Nigella sativa oil.
Keywords: Nigella sativa oil, cancer, radiation

INTRODUCTION

Cancer is the second highest cause of death in Turkey following cardiovascular diseases. Even though no concrete solution has been found for the disease, it is important to improve the effects of the progress of the disease, and increase, or at least improve, the quality of life (1).

Radiotherapy (RT) has been commonly and effectively used in the treatment of cancer for over a century. RT is mostly administered by using high energy photon rays and electron rays such as X rays or gamma rays. The objective of this treatment method is the elimination of tumor tissue, as well as the protection of normal tissue. Damage in the normal tissues is related to the sensitivity of that tissue to radiation, and it may not always be possible to treat it. The risk of complications increases as the dose is increased in RT. Besides this, the risk increases more as the critical organ volume within the treatment site increases. Each organ's resistance to radiation is different (2, 3).

The biological effects of radiation occur directly or indirectly in normal tissues. Direct effect is the effect of radiation directly on the target molecule DNA in the cell. Indirect effect, on the other hand, causes the formation of free radicals with the radiolysis of water molecules due to the effect of radiation. Anti-oxidants are the most effective components against free radicals (3, 4).

It may not always be possible to treat the early and late adverse effects that emerge as a result of radiotherapy. Researchers have used various agents that reduce the cellular toxicity of ionized radiation in normal tissues to prevent early and late complications caused by ionized radiation in organs such as the peripheral nerves, heart, bladder and kidney (5). It has been reported that compounds containing sulfur have the most protective effect. The most commonly investigated agent is aminothiol (cysteine, cystamine, WR-2721, glutathione) compounds. Amifostine demonstrates its effect by converting into WR-1065, which is its metabolite. It is pointed out in the literature that WR-2721 and

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WR-1065, which are claimed to have selective cytoprotective effects in normal cells compared to cancer cells (6), are the most feasible radio-protectors for humans and have started to be used in the clinical setting (7).

Commonly known as black seed, Nigella sativa L. belongs to the Ranunculaceae family, and is an annually flowering plant that is grown commonly in many countries, mostly Eastern Mediterranean ones (8). Nigella sativa seeds consist of 0.4-0.45% essential oils, and more than 30% fixed oils. Thymoquinone (TQ) accounts for 18.4-24% of the essential oils. TQ's structure is 2-isopropyl-5-methyl-1.4-benzoquinone, and its molecular formula is $C_{10}H_{12}O_2$. It has been determined that Nigella sativa is made up of 22.6-26.7% protein, and 32.7-40.0% carbohydrates (9). In a study focused on articles written in English between 2000-2016 which was conducted on some popular search engines such as PubMed, Science Direct, Scopus and Web of Science, Nigella sativa (NS) and Trigonella foenum-graecum were the most frequently mentioned plants in the treatment of cancer (10).

In a review on the anti-oxidant, anti-inflammatory, anti-cancer, anti-diabetic, gastro-protective, hepato-protective, antimicrobial and antihistaminic effects of TQ, the main chemical compounds of the NS plant, a set of therapeutic benefits were emphasized under different *in vitro* and *in vivo* conditions (11).

Anti-cancer effects of TQ were observed in several preclinical studies where it was used for the diverse pharmacologic effects of NS (12). TQ prevents a wide range of tumorigenic processes, as well as carcinogenesis, malignant growth, invasion, migration and angiogenesis, due to its versatile nature (13).

Cisplatin (CP) is an effective anti-cancer drug that causes significant toxicity in the kidneys, the proximal tubules in particular, by producing reactive oxygen derivatives. It has an excellent content for use as functional food or combinatorial nutraceuticals in the CP chemotherapy to cure nephropathy accompanied by long-term NS and TQ cancer chemotherapy (12). In another study, it was shown to suppress metastatic phenotype, and reverse the epithelial mesenchymal transition (EMT) of the prostate cancer cells. These findings give rise to the idea that thymoquinone is a potential therapeutic substance against prostate cancer that acts by targeting the transforming growth factor-β (TGF-β) (14).

In this study, the effects of nigella sativa oil on the oxidant/anti-oxidant system have been examined, which have antitumoral, anti-inflammatory, anti-oxidant characteristics in the prevention and treatment of adverse effects created by free radicals. For this purpose, the potential protective effects of the nigella sativa oil were examined from oxidant parameters Oxidative Stress Index (OSİ) Total Oxidative Stress (TOS) malondialdehyde (MDA), nitric oxide (NO), myeloperoxidase (MPO) and anti-oxidant parameters superoxide dismutase (SOD), glutathione (GSH), catalase (CAT) and Total Antioxidant Status (TAS) in rats exposed to single dose of 8 Gy ionized radiation.

METHODS

Ethics committee approval was received for this study from the ethics committee of Gaziantep University Animal Experiments Local Ethics Committee with the decision no. 4/4 dated 06.02.2012.

The study was performed at the Gaziantep University Faculty of Medicine; Department Biophysics, Department of Physiology, Department of Biochemistry and Clinical Biochemistry and Oncology Hospital, Department of Radiation Physics.

Sprague Dawley 50 female rats weighing about 150-250 gr were used in this study, and divided into 5 groups.

Radiotherapy was administered to the whole body of these rats in a single dose at 8 Gy fraction with a Co 60 teletherapy device so that SSD was 40 cm.

Rats were quarantined at least one week before the radiotherapy. The care and feeding of rats were performed under 21±2°C ambient temperature, 55-60% moisture and 12:12 hours of light-darkness cycle conditions. The weight of the animals was 200±50 gr, and they were fed with standard rat food. In the examination conducted before the study, rats in a poor condition of health were excluded from the study.

In accordance with the study protocol, rats were randomized into a total of 5 groups, namely: Control Group (C; n=10), Radiotherapy Group (R; n=10), Nigella Sativa Oil Group (NSO; n=10), Nigella Sativa Oil+Radiotherapy Group (R+NSO; n=10), Radiotheapy+Amifostine (R+WR-2721; n=10).

The 1st Group (Control Group I): This control group was fed with normal feed and water for 72 hours.

The 2nd Group (Radiotherapy Group): Throughout Day 1, 0.25 mL normal saline was administered to these rats in this group intraperitoneally 30 minutes before a single dose of 8 Gray (Gy) radiotherapy. Then they were fed with normal feed and water for 3 days. At the end of Day 3, their blood and liver tissues were collected.

The 3rd Group (Nigella Sativa Oil Group): The rats in this group received 2.4 g/kg/day nigella sativa oil on Day 1 by means of gavage. They were fed with normal feed and water for 3 days. At the end of Day 3, their blood and liver tissues were collected.

The 4th Group (Nigella Sativa Oil + Radiotherapy Group): On Day 1, 2.4 g/kg/day nigella sativa oil was given to the rats in this group by means of gavage 60 minutes before a single dose of 8 Gy radiotherapy. Then they were fed with normal feed and water for 3 days, and at the end of Day 3, their blood and liver tissues were collected.

The 5th Group (Radiation+Amifostine Group) 200 mg/kg WR-2721 was administered intraperitoneally 30 minutes before a single dose therapy. Then they were fed with normal feed and water for 3 days. At the end of Day 3, their blood and liver tissues were collected.

Except for the control group, rats in other groups were anesthetized with 50 mg/kg/ip of ketamine and put on the radiotherapy

equipment in face down position. Radiotherapy was administered to the whole body of these rats in a single dose at 8 Gy fraction with a Co 60 teletherapy device so that SSD was 40 cm. The study was completed within 72 hours following radiotherapy, and then the rats were decapitated.

Surgical procedures of the study were carried out under sterile conditions and deep anesthesia. At the end of hour 72, 50 mg/kg/ip. Ketamine HCL (Ketalar) and 10 mg/kg Xylazin HCl (Rompun) mixture was administered intraperitoneally for anesthesia. Half of the liver tissue samples were spared for pathologic examination in a 10% neutral buffered formalin solution, and the remaining part was stored at -85°C for biochemical measurements.

The blood's 1000 g that was collected in the tubes without anti-coagulants was centrifuged at $^{+}4^{0}$C for 10 minutes after keeping at room temperature for 30 minutes. 1000g of blood samples collected in the tubes with heparin was centrifuged at $^{+}4^{0}$C for 10 minutes. Erythrocyte packages were prepared and portioned after separating the plasma, and kept at -85°C until the time of analysis.

Total antioxidant status, TOS, OSI, MDA, NO, MPO, SOD, CAT and GSH parameters were measured. Tests were performed on serum samples using the myeloperoxidase ELISA method. Glutathione, Superoxide Dismutase, Malondialdehyde, Nitrate, and Catalase were analyzed in the liver tissue on an ELISA reader using the colorimetric method. Total oxidant level was tested in the auto-analyzer device using spectrophotometric method. TAS and TOS were measured using the Rel Assay commercial kits. OSI which is considered as an indicator of Oxidative Stress is expressed in percentage ratio of TOS and TAS. MDA was measured with colorimetric method at 532 nm using Cayman commercial kit (item no: 10009055). Results were expressed in nmol/mL. SOD was measured with colorimetric method at 450 nm using Cayman commercial kit (item no: 706002). Results were expressed in U/mL. Nitrate was measured with colorimetric method at 540 nm using Cayman commercial kit (item no: 780001). The results were expressed in μM. Myeloperoxidase was determined with ELISA method at 405 nm using the Immundiagnostik (REF K 6631B) commercial kit. The results were expressed in ng/mL.

RESULTS

In the comparison of R and C groups, it was seen that TOS, OSI, NO, MDA, and MPO parameters increased in a statistically significant manner, whereas TAS, SOD, GSH, CAT levels decreased.

In the NSO group, MPO levels increased, creating a significant difference as compared to the C group. SOD decreased in the R+WR group in a statistically significant manner as compared to the C group.

Total antioxidant status, GSH and OSI a value was observed between the C and R groups in NSO, R+NSO and R+WR groups, respectively. This value shows a statistically significant difference between the two groups. Similar MDA results were obtained in NSO, R+NSO, R+WR groups.

According to the comparison with R+NSO group, there was a decrease in CAT values in NSO and R+WR groups. When compared to the R+NSO group, MDA was higher and MPO was lower in the R+WR group. However, MDA and OSI parameters were lower and TAS parameter was higher in the NSO group as compared to the R+NSO group. These changes show a statistically significant difference.

In the comparison between R+NSO and C groups, GSH was lower in R+NSO whereas MPO and MDA were lower in C group. These values show a statistically significant difference. TOS, OSI, NO, TAS, SOD, and CAT values did not demonstrate a statistically significant difference in the R+NSO group compared to the C group.

In the comparison between R+NSO and R groups, it was seen that TOS, OSI, NO, MDA parameters decreased in a statistically significant manner whereas TAS, SOD, GSH, CAT levels increased in the R+NSO group. No statistically significant difference was seen in MPO value in the R+NSO group as compared to the R group (Table 1).

Table 1. Mean TAS, TOS, OSI, NO, MPO, CAT, GSH, SOD, MDA levels in experiment and control groups (Mean±SD)

	C	R	NSO	R+NSO	R+WR
TAS	1.15±0.09	0.81±.04[a,c]	1.31±0.15[a,b,c]	1.04±0.14	1.02±0.18
TOS	24.79±1.73	37.87±3.6[a,c]	24.97±1.35	25.37±1.43	27.38±1.11
OSI	21.67±2.22	46.82±4.49[a,c]	19.24±3.03[c]	24.78±4.48	27.62±5.41[a,b]
SOD	0.73±0.01	0.67±0.01[a,c]	0.73±0.008	0.72±0.02	0.7±0.02a
NO	1.05±0.13	1.39±0.12[a,c]	1.03±0.12	1.14±0.07	1.19±0.21
GSH	57.53±1.49[c]	45.81±1.53[a,c]	57.06±2.78	52.83±4.86[a,b]	56.69±4.6
MPO	0.77±0.13[c]	1.43±0.52[a]	1.14±0.17a	1.32±0.19[a]	0.92±0.06[c]
CAT	228.74±5.81	192.66±3.64[a,c]	230.96±1.74[c]	223.55±6.11	234.84±1.73[a,b,c]
MDA	32.74±1.04[c]	48.1±1.5[a,c]	28.68±0.75[a,b,c]	35.7±1.91[a,b]	44.28±1.43[a,b,c]

[a]p<0.05: In comparison to C group, [b]p<0.05: In comparison to R group, [c]p<0.05: In comparison to R+NSO group
TAS: total antioxidant status; TOS: total oxidative stress; OSI: oxidative stress index; NO: nitric oxide; MPO: myeloperoxidase; CAT: catalase; GSH: glutathione; SOD: superoxide dismutase; MDA: malondialdehyde

DISCUSSION

Various agents that reduce the cellular toxicity of ionized radiation in normal tissues have been used before application to prevent early and late complications caused by ionized radiation in organs such as peripheral nerves, heart, bladder and kidneys (15).

WR-1065 is an aminothiol that has selective cyto-protective effects in normal cells as compared to cancer cells, and used for protection of tissues against the harmful effect of chemotherapy drugs (8).

In a study, radiation-related harmful effects of 2- (3-aminopropylamino) ethylsulphonyl phosphonic acid (WR-2721) and peptidoglycan (PGN) on the intestines and bone marrow peptidoglycan both as a single agent or a combination therapies. WR-2721 was given in a dose of 3 mg per rat 30 minutes after the 10 Gy radiation, and 30 ug PGN per rat was injected intraperitoneally 24 hours after radiation. Application of WR-2721 with PGN had both a re-increasing effect in hematopoietic and intestinal cells, and a synergistic effect on survival in rats exposed to radiation, however it caused a certain degree of disorder in immunity (16).

The studies conducted showed the antibacterial, anti-inflammatory immunomodulator, gastroprotective antiviral (11), antiasthmatic (17), antidiabetic (18), antihelminthic (19), antifungal (20), antitumoral (21), antihistaminic (22) effects of the nigella sativa.

As the main bioactive compound of nigella sativa, Thymoquinone shows an anti-cancer activity via various mechanisms of action by intervening with the DNA structure that shows a selective antioxidant and oxidant activity, and affecting the carcinogenic signal molecules/pathways, paths and immunomodulation. In vitro activity of thymoquinone was affected more in animal cancer models; however there has not been any proven clinical practice yet (23).

In our study, MDA and CAT values rose in a statistically significant manner in the R+WR group as compared to the R+NSO group. MPO value, on the other hand, decreased in a statistically significant manner. According to these results, in the comparison of NSO and WR, NSO was effective on the MDA value, but WR created more positive effects on the MPO and CAT values.

In a study, antioxidant, blood pressure-decreasing diuretic characteristics of NS and its active compounds were investigated (24).

In some models, it led to a hepatoprotective effect on liver toxicity. Effects of NSO were investigated on rats infected with Schistosomiasis Mansoni in a study. Two doses of oil was given (2.5 and 5 mL, two weeks, oral / kg) in a single dose or combination with Praziquantel (PZQ) which is preferred in the treatment of schistosomiasis.

The role of nigella sativa against the changes caused by S. mansoni infection is thought to be partly due to its antioxidant effect, and the improvement of immunologic main system (25).

Additionally, nigella sativa has been shown to have antioxidant, anti-inflammatory and anti-ulcer activity under various conditions. In a study, the effects of an extract containing nigella sativa fluid on gastric acid secretion were investigated in isolated rat stomachs. It was supported that nigella sativa has a gastroprotective effect since it decreases the gastric acid secretion (26).

In a study on the antioxidant effects of nigella sativa against the effects of radiation on rat tongues, oxidative stress index, total oxidant state and lipid hydroperoxide levels were statistically higher in R group, C, CN (sham) and RN groups. It has also been emphasized that NS oil might be a beneficial substance in the protection against isolated radiation therapy-induced tissue damage (27).

In a study, rats were orally given NSO at a dose of 1 g/kg/day 1 hour before the 5 gray radiation for 10 days, and NSO was concluded to have antioxidant effects that increase the antioxidant capacity in the liver tissue of rats, and to be effective on reduction of oxidative stress indicators (28).

In our study, 2.4 g/kg/day nigella sativa oil was given to the R+NSO group by means of gavage 60 minutes before a single dose of 8 Gy radiotherapy on Day 1. In the comparison of R and C groups, it was seen that oxidative stress indicators, TOS, OSI, NO, MDA, MPO parameters increased in a statistically significant manner whereas levels of antioxidant parameters TAS, SOD, GSH, CAT decreased in R group.

In an article on the effects of nigella sativa on the treatment and complications of diabetes, it was stated that nigella sativa and its compounds decrease the oxidative and nitrosative stress, increase the antioxidant capacity, and thus reduced the diabetic complication risks (29).

A single dose was administered in our study at a fraction of 8 Gy. While NO levels increase remarkably in the RO group as compared to the C group, there was some decrease in the R group as compared to R+NSO group; however, no statistically significant difference was seen.

In a study on rats investigating the effects of NSO pre-treatment on the ethanol-related hepatoxicity, hepatic MDA levels were observed to have decreased, but an increase was seen in GSH levels (30).

Similar to the study mentioned, GSH was lower and MDA was higher in a manner to demonstrate a statistically significant difference in the R group as compared to the R+NSO group in our study. According to the comparison with R+NSO group, CAT and TAS values were higher in the NSO group. However, MDA and OSI parameters decreased in the NSO group. These changes show a statistically significant difference.

Besides, TOS, OSI, NO, TAS, SOD, CAT values did not demonstrate a statistically significant difference in the R+NSO group in our study as compared to the C group. In the comparison of R+NSO and R groups, it was seen that TOS, OSI, NO, and MDA parameters decreased in a statistically significant manner whereas TAS, SOD, GSH, and CAT levels increased in the R+NSO group.

Nigella sativa was observed to create clear changes in GSH and MDA parameters. According to our overall results, we think that nigella sativa is effective on TAS, TOS, NO, MPO and SOD parameters by decreasing the oxidative stress and supporting the increase in antioxidants.

CONCLUSION

Damaging and eliminating the tumor tissue are the main problems in treating common diseases such as cancer. The main factor that accompanies this problem and makes the treatment process difficult is the protection of healthy tissue against the damages of radiation. This study showed that nigella sativa oil is effective on the radiation-induced damage in the liver in case of oxidative stress and nitrosative stress. It would be worth conducting further studies with different tissues, different radiation severities, and different Nigella sativa oil doses.

Ethics Committee Approval: Ethics committee approval was received for this study from Gaziantep University Animal Experiments Local Ethics Committee with the decision no. 4/4 dated 06.02.2012.

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Original Research

Investigating the Most Commonly Applied Lactate Recovery Method According to the Positions in Football

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ABSTRACT
Objective: This study aimed to investigate the most suitable recovery method that can be applied for eliminating blood lactate accumulated in the blood of football players after training or a match. Furthermore, the effectiveness of the soccer player's role in these recovery methods was determined.
Methods: Herein, 36 professional or professional candidate football players, which included 12 defenses, 12 midfielders, and 12 attackers, were included. Athletes were asked to warm up before the field workout started and then they were subjected to a maximal field test on an 800-m course. The blood samples taken from the athletes after the field test were evaluated for blood lactate. Then, each athlete was rested with either active, passive, or massage recovery methods, and the blood analyses were repeated and recorded. Each athlete was evaluated and recorded for 48 h after the same field test by other recovery method.
Results: According to the obtained statistics, it was found that the most appropriate method for lactate recovery after maximal exercise was active recovery ($p<0.05$). Massage recovery was found to be more effective than passive recovery but significantly less effective than active recovery ($p<0.05$). We determined that the football player positions do not affect the effectiveness of the recovery methods used ($p>0.05$).
Conclusion: The most effective recovery method was determined as active recovery, and the effect was proven even in a 15-min application.
Keywords: Football, lactate recovery, massage, lactic acid

INTRODUCTION

Today, sports is defined in a more extensive manner as "the activities that improve a person's state of health and that maintain the improved health status". Being engaged in sports has become necessary in order to be healthy and maintain this state of health (1). Football is probably the most popular sports branch and the most widespread one with the most crowded audience group and more than 200 million certified players throughout the world. Like in all sports branches, being successful in football is also based on increasing performance and maintaining this performance level for a long time. Today's football, although it seems like a sports activity, has become an industry due to the developing economic conditions and gains. Football players, technical directors and clubs have been making great efforts to reach required performance levels, minimize fatigue after matches and training, avoid injuries and achieve maximum performance within the shortest time possible in order to obtain the highest efficiency from this industry.

In sports branches that require maintaining long-term performance, fatigue is one of the reasons for not being able to achieve the required level of performance. Fatigue was previously considered to be important only in individual sports. However, conducted studies revealed the importance of fatigue also for team sports. This is because the required force is not individual but joint (2).

According to the literature review, studies on lactate recovery include recovery analysis after any sort of maximal effort exerted by randomly selected athletes rather than focusing on any specific sports branch. Although there are some studies specifically focusing on football, there were not any studies investigating the effectiveness of a recovery method from the positional aspect (3, 4). Recovery applications in these studies have varying durations but they generally include time periods of 20 minutes or longer (5). In football, although lactate recovery after a match or training is important, lactate recovery during the 15-minute half-time in matches is also highly important (3, 4, 6).

Akgül et al. (3) conducted a study to investigate the effectiveness of hydrotherapy in lactate recovery in football players. In this study, football players were subjected to a shuttle run test and then blood lactate levels were tested after the players were rested actively in the sports hall, actively in the pool and passively in the pool. This study has shown that active lactate recovery both in the hall and in the pool were significantly superior in comparison to passive recovery.

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In a study conducted on football players by Baldari et al. (7), it was reported that aerobic active resting under the threshold was more effective in lactate recovery in comparison to active resting over the threshold after exercise, and it was emphasized that 3-5 minutes would not be sufficient and this time period should be longer, whereas in literature it is stated that this time period should be between 10 and 30 minutes (8).

A study conducted by Monedero et al. (9) on 18 cyclists has shown that the most effective method for eliminating lactic acid accumulating in the blood after 5 km bicycle riding was active exercise together with massage and that active recovery was more effective than massage and passive recovery.

Our main objective in this study is to investigate the effectiveness of active recovery, passive recovery and massage recovery methods in blood lactic acid recovery, which is highly important for the next exercise or match for football players, to compare this effectiveness according to the football player's position in the games, to determine whether the football player's position provides him an advantage in terms of lactate recovery, to identify which recovery method is more effective in which position, and to create recovery programs specific to the player's position according to obtained results and prepare him for the next effort in the best way possible. Our secondary objective is to determine the effectiveness of 15-minute recovery methods that can be practiced during half-time in order to reduce lactate accumulation in the player's blood and to investigate ways to enable the football player to start the second half of the match in his fittest form.

METHODS

The approval no. 2017/383 of the Clinical Trials Ethics Committee of Gaziantep University was obtained and 26 players between the ages of 16-20 including the professional players of the Gaziantepspor team in the A league and professional candidates in the A2 league. The players were divided into three groups; defense (n=12), midfield (n=12) and attack players (n=12). Informed consent forms were obtained from each player.

Method of the Study

A program consisting of an 800 meter run, at the maximum exercise intensity with the field exercise protocol, was applied on athletes that participated voluntarily in our study. The athletes ran the first 400 meters of the 800-meter course at a heart rate equivalent to 80% of the maximum heart rate (220- age) and the remaining 400 meters as fast as they could together with audible instructions (10). During the entire run, their heart rate was monitored using polar (Polar RS 400, POLAR, Oulu, Finland) watches in order to monitor complications and changes in heart rate. After the exercise, athletes were rested at the pitch-side for 3 minutes and then the lactate levels were measured from capillary blood samples obtained from the fingertip (Lactate Scout Analyzer, EKF Diagnostic, Lepzig, Germany). Then, any of the massage, active recovery or passive recovery methods was applied on each tested player followed by blood lactate level measurement once more. The same player was rested using another method after the same field protocol 48 hours later and blood analyses were repeated. This application was repeated for every player participating in the study.

The Lactate Recovery Methods Applied

Athletes that were subjected to the maximal running course with the field protocol were rested for 3 minutes at the pitch-side, followed by;

Active recovery; they were subjected to a 15-minute run with a heart rate equivalent to 40% of maximal oxygen uptake ($VO_{2\ max}$) and blood analyses were repeated and recorded after the run (11).

Passive recovery; Lower extremities were elevated to a level above the heart level and athletes were rested passively for 15 minutes on a massage bed and blood analyses were repeated and recorded after the rest.

Massage recovery; They were subjected to a classic massage application including the lower extremities for 15 minutes on a massage bed. Massage application was performed by the same person for 7.5 minutes on both lower extremities of the athlete including both the anterior and posterior muscle groups. Blood analyses were repeated and recorded after massage application.

Statistical Analysis

Normal distribution of the data obtained in this study was tested using the Shapiro Wilk test. Variation between methods was tested using repeated measures analysis of variance. Mean±standard deviation values were given for the numerical variables as the descriptive statistics. Statistical Package for the Social Sciences for Windows version 24.0 (IBM SPSS Corp.; Armonk, NY, USA) software package was used for statistical analyses, and $p<0.05$ was considered statistically significant. Sample size was determined by power analysis.

RESULTS

Age, body height and weight of the football players included in the study have similar mean values and exhibit no significant differences ($p>0.05$) (Table 1).

Blood lactate levels of football players who ran at maximal exercise intensity were measured and then passive, active and massage recovery methods were applied in order to evaluate blood lactate levels in millimole/liters (mmol/L) as mean plus minus standard deviation (±SD) (Table 2). Considering the daily lactate changes since measurements were performed in each player with 48-hour intervals, the maximal exercise

Table 1. Mean demographic characteristics of football players

	Age (years)±SD	Height (meters)±SD	Weight (kg)±SD
Position			
Defense	17.25±1.13	177.58±5.17	68.91±5.69
Midfield	17.16±0.93	172.25±3.33	65.58±4.81
Attack	17.58±1.31	177.25±6.18	70.66±6.90

SD: standard deviation

Table 2. The average blood lactate levels before (at the end of maximal exercise) and after recovery

	Passive Recovery (mmol/L)			Active Recovery (mmol/L)			Massage Recovery (mmol/L)		
Position	**Before**	**After**	**% Change**	**Before**	**After**	**% Change**	**Before**	**After**	**% Change**
Defense (n=12)	14.31	10.32	26.85	11.32	3.83	64.25	11.36	5.77	45.99
Midfield (n=12)	12.53	7.81	37.21	10.92	4.23	57.14	9.95	5.20	48.58
Attack (n=12)	12.05	8.29	31.34	11.65	5.66	50.29	10.79	6.55	37.98
Mean±SD (n=36)	31.80±16.89			57.23±17.20			44.18±15.19		

Before: Mean blood lactate measured from football players after applying maximal exercise protocol. After: Mean blood lactate measured from football players after applying recovery method. Change %: Decrease in blood lactate level in percentage from values measured before and after.

Figure 1. Recovery methods versus change % in blood lactate
*Significant difference in comparison to passive recovery (p<0.05)
**Significant difference in comparison to passive recovery and massage (p<0.05)

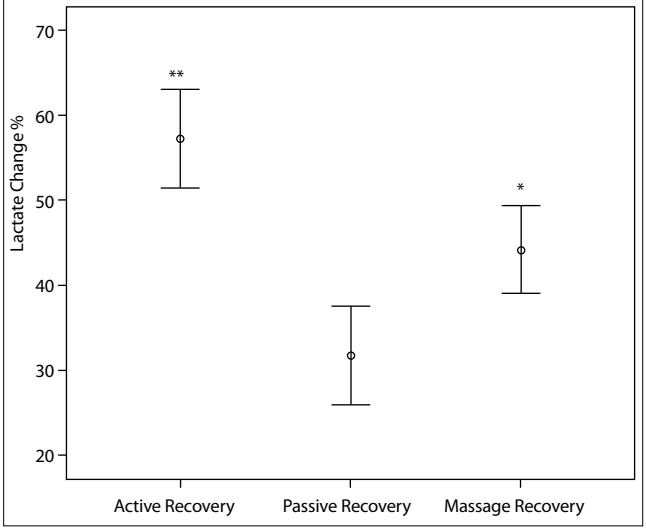
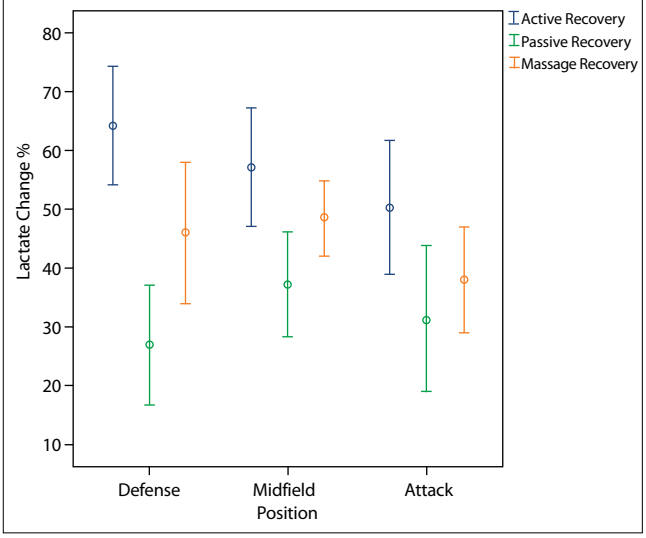


Figure 2. Comparison of the recovery methods by positions
*Significant difference in comparison to passive recovery (p<0.05)
**Significant difference in comparison to passive recovery and massage (p<0.05)



protocol was repeated before applying each recovery method and the decrease in blood lactate level in percentage (change %) was recorded after the application of the recovery method (Table 2).

Comparing the change percentage of blood lactate and the recovery method applied, it was found that active recovery decreases blood lactate at a higher rate as compared to passive recovery and massage (p<0.05) (Figure 1). Moreover, it was understood that massage was significantly more effective than passive recovery but less effective than active recovery (p<0.05) (Figure 1).

There was no significant difference in evaluating recovery methods by football player positions (p>0.05) (Figure 2).

DISCUSSION

As a result of this study, some of the most commonly used lactate recovery methods in football, i.e. active recovery, passive recovery and massage recovery, were compared and it was shown that the most effective recovery method in football players is active recovery. In addition, lactate variance between attack, defense and midfield players, who have different types of exercise activities during the game, was analyzed and which recovery method provided advantages for which positions was investigated. The main findings were that active recovery was the most effective method for all positions and massage was more effective than passive recovery.

Baldari et al. (7) found in their study that the active recovery performed under the anaerobic threshold was more effective in lactate elimination in comparison to the recovery performed above threshold. The study also provided evidence on how long active recovery should last and it was emphasized that recovery periods lasting 3-5 minutes would not be enough and recovery should last for a longer period of time. According to the literature review, active recovery methods should be applied for 10-30 minutes and at an intensity lower than the threshold value (8). In our study, active recovery period was determined as 15 minutes and the intensity of the recovery run was kept under the threshold value. The results of our study also support the importance of active recovery in eliminating lactic acid from the blood.

Another most commonly investigated method among lactic acid recovery methods is massage. One of the reasons for using massage in recovery studies is the opinions supporting that massage accelerates lactic acid elimination in athletes. Ph decreases with the formation of lactate leading to a slow down in glycolysis and therefore the release of energy-providing substances decreases, which limits muscle contraction. Lactic acid accumulating in muscles and in the blood leads to fatigue. In a study conducted on professional swimmers regarding the elimination of this fatigue-causing substance from the blood and muscles, it was reported that massage was more effective than passive recovery in blood lactate elimination but active recovery was significantly more effective than massage (12). In another study conducted on cyclists, it was reported that active recovery was significantly more effective in comparison to massage and passive recovery, however there was no difference between massage and passive recovery (13). In a study conducted by Robertson et al. (4) on athletes engaged in different sports branches, subjects exercised on a bicycle ergometer with 6 repeats of 30 seconds each and then they were passively rested in supine position for 20 minutes or subjected to massage for 20 minutes. It was reported that there was no significant difference between these applications in terms of lactate recovery. However, our study revealed that massage recovery was statistically more significant in all positions in comparison to passive recovery.

In the study of Menzies et al. (14) conducted on 10 male participants who were moderately trained, subjects ran for 5 minutes at 90% of VO_{2max} and then rested in passive recovery and under active recovery conditions at various levels of lactate threshold. As a result of this study, it was found that active recovery was significantly better than passive recovery in terms of lactate recovery, whereas this effect of active recovery was only possible when runs were performed at a level close to high lactate thresholds and that runs performed at 40% of the maximal lactate threshold even yielded results similar to passive resting. In parallel to this data, our study demonstrated that active recovery was significantly better than passive recovery, but unlike the aforementioned study, our results were obtained by keeping the intensity of recovery constant at a heart rate between 40-60% of $VO_{2\,max}$. It was thought that the possible differences between Menzies' study and our study could stem from the fact that the run had an intensity and duration that increase blood lactate nearly to 4 mmol/l and that the subjects were moderately trained amateur athletes. In contrast, maximal blood lactic acid level of the subjects in our study occasionally got even higher than 20 mmol/l after the field protocol.

In a study conducted by Harbili et al. (15) on 22 male athletes, the subjects were actively rested for 10 minutes on a bicycle ergometer with a load equivalent to 35% of VO_{2max} or passively rested for 10 minutes by sitting on a chair after Wingate test followed by blood lactic acid measurements from venous blood. According to the obtained results, it was reported that there was no significant difference between lactic acid levels of the athletes that had certain lactate accumulations with the Wingate test in terms of the two recovery methods, and yet active recovery was more effective (15). The reasons why the effect of active recovery could not be proven to be significant include short resting periods or athletes not reaching a sufficient level of fatigue due to a submaximal exercise. In our study, active recovery application was found to be significantly more effective than the other two methods in terms of lactic acid elimination. However, variation of this effect by positions could not be proven.

In a study conducted by Lane and Wenger (16), subjects exercised for 18 minutes and then they were subjected to methods such as active resting by cycling at an intensity equivalent to 30% of $VO_{2\,max}$ for 15 minutes, massage of the legs for 15 minutes, immersion of legs for 15 minutes in a 15 degrees C water bath or sitting for 15 minutes. Superiority of any of these methods over the others could not be statistically proven. However, it was reported that active recovery and recovery in water were more effective than massage. In our study, the effectiveness of active recovery was proven for all positions and it was found to be more effective than massage and passive recovery. It was seen that massage recovery was more effective in lactic acid elimination as compared to passive recovery.

A similar study conducted by Monedero et al. (9) on 18 professional cyclists investigated the effectiveness of active recovery, passive recovery, massage recovery and combined (active and massage) recovery methods in lactate elimination after a 5 km cycling exercise and consequently, it was reported that the most effective method for eliminating lactic acid in the blood was the combined recovery method and this was statistically more significant than the other applications. In the same study, they reported that active recovery was more effective than the rest of the methods in the 9th minute of a 20-minute recovery period. However, contrary to our study, they also reported that massage recovery did not have any superiority over passive recovery (9). This might possibly stem from the variability of massage application for each person or how much the person, who is getting the massage, likes or dislikes massage.

The study has some limitations. Limitations of the study include the sample size not being larger, not including groups on which the recovery methods evaluated in this study were applied in a combined manner (for example, a group that has massage and active recovery at the same time) and not including goalkeepers while investigating football player positions. Future studies might be planned accordingly.

CONCLUSION

Thirty-six football players were evaluated in this study, which was conducted in order to investigate the most effective method in eliminating lactic acid that accumulates in the blood after maximal exercise in professional or professional candidate football players and to assess whether positions provide an advantage for players in this respect. The results of our study are as follows:

In this study, there are differences between methods for eliminating lactate accumulating in a football player's blood after a maximal run.

The most effective recovery method was determined as the active recovery and its effect was proven even in a 15-minute ap-

plication. Therefore, it was thought that football players can get ready for the second half of the game in an active manner in the resting halls during half-time in football games.

Massage recovery was found to be significantly more effective than passive recovery; however, it was less effective than active recovery.

It was found that the effectiveness of lactic acid recovery methods did not exhibit any differences in terms of position.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (Approval no. 2017/383).

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

Peer-review: Externally peer-reviewed.

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

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Original Research

Retrospective Analysis of Total Laparoscopic Hysterectomy Experience in a Single Center for Five Years

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ABSTRACT
Objective: To analyze the indications, complications, and clinical outcomes of total laparoscopic hysterectomies (LH) for benign diseases in a tertiary health care hospital over a period of five years.
Methods: This retrospective cohort study includes 151 patients that underwent total laparoscopic hysterectomy (TLH) for benign indications at a university hospital between 2013 and 2017.
Results: Abnormal uterine bleeding (44.4%) was the most common indication. The mean hospital stay, estimated blood loss, and operative time were 2.3±1.2 days, 159.5±87.8 mL, and 69.5±16.9 minutes. The learning curve in terms of average operative time during five years decreased from 82±18.5 minutes to 57.8±5.2 minutes. Total complication rate was 10.6% including 7.9% intraoperative and 2.6% postoperative. Total complication rate decreased from 20% in 2013 to 2.2% in 2017. Most ureteral injuries were diagnosed postoperatively. Especially we observed no ureteral injury between 2015 and 2017 and there was 5.9% and 13.3% ureteral injury rate in 2014 and in 2013; respectively. Conversion rate to laparotomy was 3.3%.
Conclusion: LH is a good alternative to abdominal hysterectomy wherever an advanced laparoscopic skilled surgeon can safely perform this procedure. Lower complication (especially urinary) rates can be expected with better handling of the uterus via manipulators, consideration of anatomical proximities, and always following safe dissection rules.
Keywords: Complication, total laparoscopic hysterectomy, urinary injury, benign indication, learning curve

INTRODUCTION

Laparoscopic hysterectomy (LH) was first introduced in 1989 by Reich et al. (1). The most common indications for a hysterectomy include adenomyosis, abnormal uterine bleeding, symptomatic leiomyoma, endometriosis, and prolapse of the uterus (2), and the major determinants for the route of hysterectomy are the patient's choice, body mass index (BMI), weight and volume of the uterus, history of surgical intervention, and the surgeon's skill (3). For the treatment of benign diseases, LH is considered as an alternative to abdominal hysterectomy in cases for which vaginal surgery is contraindicated (4, 5). LH has numerous advantages, including shorter duration of hospital stay, earlier return to normal activity, less pain, low rate of infection or ileus, and magnified exposure of uterine vessels or ureter (6, 7); however, compared to the transabdominal route, it is generally associated with a longer operative time (8) and a higher rate of urinary tract complications (9-11).

The aim of this study was to analyze the indications, complications, and clinical outcomes of total laparoscopic hysterectomies (TLHs) for benign diseases in a tertiary health care hospital over 5 years.

METHODS

This retrospective cohort study included patients who underwent TLH for benign indications at Department of Obstetrics and Gynecology of Gaziantep University Hospital between 2013 and 2017. The institutional review board of the hospital approved the study (approval number: 2017/415), and the written informed consent was obtained from all study participants. Demographic and clinical data were obtained for all patients. The indications for hysterectomy included abnormal uterine bleeding, leiomyoma uteri, endometrial hyperplasia, uterine prolapse, cervical intraepithelial neoplasia, benign adnexal mass, hermaphroditism, and chronic pelvic pain. Malignant cases were excluded from the study. Age, parity, menopausal status, and BMI were recorded in a scope of maternal characteristics. The type of surgery (TLH-bilateral salpingo-oophorectomy [TLH-BSO], TLH-unilateral salpingooophorectomy, or TLH), suture type used in the vaginal cuff, duration of hospital stay, uterine volume (depending on pathological reports), intraoperative blood loss (the level of blood remaining in the suction tube after subtracting the amount of the washes), need for blood transfusion, the date of surgery, operative time (time interval between umbilical incision and closure), difference between preoperative and postoperative hemoglobin

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levels, conversion to laparotomy, and intraoperative or postoperative complications were analyzed. The same gynecologic team performed all the operations included in the study. After a transumbilical vertical incision, the abdomen was accessed using the closed Veress needle entry technique, and insufflation of carbon dioxide gas up to 20 mmHg pressures was preferred for adequate pneumoperitoneum. We inserted a primary 12 mm trocar at the umbilical incision, in addition to 2 ipsilateral 5 mm and one contralateral 5-mm trocars (diamond-shaped) for surgery. A 10mm 0^0 laparoscope and operating instruments were inserted through the trocars. We determined the site of the vaginal cuff incision by using different types of uterine manipulators (Clermont-Ferrand®, Karl Storz, Tuttlingen, Germany and VCare®, Conmed, New York, United States) and circumferentially incised the vaginal tissue using the monopolar needle diathermy or harmonic scalpel, Ethicon®. Surgical specimens were extracted from the vaginal cuff. All the patients were intravenously administered with cefazolin sodium 2 g as perioperative antimicrobial prophylaxis. Complications included ureter injury, bladder injury, hemorrhage requiring blood transfusion, vault infection, and conversion to laparotomy due to miscellaneous complications. In the last 2 years, we modified our routine practice and performed cystoscopy to ensure the patency of ureters at the end of the operation for all patients. All bladder injuries were intraoperatively restored by laparoscopic suturing. We placed a 16 F Foley catheter into the bladder for 10 days in the cases with a bladder injury. We evaluated patients with suspected ureteral injuries with a computed tomography (CT) scan if there was acute pelvic pain, abnormal distension, or an inflammatory reaction in the serum (elevated C-reactive protein and leukocytosis). In addition, we evaluated the presence and extent of the ureteral injury with intravenous pyelography unless kidney function tests were abnormal. Suspected ureteral injuries were intraoperatively or postoperatively repaired, and involved JJ stent placement, ureteroureterostomy, and ureteroneocystostomy.

Statistical Analysis

The Shapiro-Wilk test was used to test the normality of distribution of continuous variables. The Student-T test and the Mann-Whitney U test were used for the comparison of 2 independent groups of variables with normal and non-normal distributions, respectively; whereas the ANOVA test and the Kruskal-Wallis test were used for the comparison of 3 independent groups of variables with normal and non-normal distributions, respectively. The Pearson test was used to assess the relation between parametric variables and Chi-square test for the relation between categorical variables. Descriptive statistic parameters were presented as frequency, percentage (%), and mean±standard deviation (mean±SD). Statistical analysis was performed using the Statistical Package for Social Sciences for Windows version 22.0 (IBM SPSS Corp.; Armonk, NY, USA), and a $p<0.05$ was considered statistically significant.

RESULTS

A total of 151 patients were included in the study. General and surgical characteristics of patients are presented in Table 1. Conversion to laparotomy was required only in 5 cases (conversion rate 3.3%), which included partial ureteral injury, dense adhesion, intra-abdominal bleeding due to uterine artery injury, and manipulator discordance in a huge myoma uteri case. Furthermore, laparotomy had to be performed in only one case because of intra-abdominal hematoma in the early postoperative period. We observed a total of 16 (10.5%) complications during the intraoperative (12 [7.9%]) and postoperative (4 [2.6%]) period. Complications and their corresponding recognition times are summarized

Table 1. General characteristics and surgical outcomes of patients

Age (years) *	50±7.7
Gravidity*	5.2±2.4
Parity*	4.3±2
BMI (kg/m^2)*	30.3±3.5
Uterine volume (mL)*	211.4±123.5
Duration of hospital stay (days)*	2.3±1.2
Operative time (minutes)*	69.5±16.9
Need for erythrocyte suspension (IU)**	26 (17.2)
Blood loss (mL)*	159.5±87.8
Decrease in hemoglobin level (g/dL) *	1±0.9
Menopausal status**	
Premenopausal	83 (55)
Postmenopausal	68 (45)
Type of vaginal cuff suture**	
Polyglactin	104 (68.9)
Barbed	47 (31.1)
Type of surgery*	
TLH–BSO	124 (82.1)
TLH	16 (10.6)
TLH–USO	11 (7.3)
Indications**	
Abnormal uterine bleeding resistant to medical therapy	67 (44.4)
Endometrial hyperplasia	31 (20.5)
Myoma uteri	19 (12.6)
Cervical intraepithelial neoplasia	14 (9.3)
Benign adnexal mass	12 (7.9)
Decensus uteri	5 (3.3)
Hermaphroditism	2 (1.3)
Chronic pelvic pain	1 (0.7)

*Mean±standard deviation, **n (%). BMI: body mass index; TLH: total laparoscopic hysterectomy; BSO: bilateral salpingo–oophorectomy; USO: unilateral salpingo–oophorectomy; IU: international unit

Table 2. Characteristics of complications with their recognition time

	Recognition time of complication (postoperative day)	Number of patients (%)
Intraoperative		12 (7.9)
Urinary tract injury		10 (6.6)
Bladder injury	0	3 (2)
Ureter injury		7 (4.6)
Thermal injury	0 and 30	2 (1.3)
Complete transection	2, 4, and 45	3 (2)
Partial transection	0	1 (0.7)
Ureteral kinking	15	1 (0.7)
Uterine artery bleeding	0	2 (1.3)
Postoperative		4 (2.6)
Respiratory distress	2	1 (0.7)
Umbilical hernia	45	1 (0.7)
Intra-abdominal hematoma	1	1 (0.7)
Vaginal cuff cellulite	45	1 (0.7)

0 defines the intraoperative recognized complication

in Table 2. Ureteral injuries were restored through the abdominal route using ureteroureterostomy and ureteroneocystostomy in one and 2 cases, respectively. Ureteral stent application was required in three cases of ureteral injuries, including 2 thermal injuries and one ureteral kinking. All bladder injuries were at the dome and were restored intraoperatively through laparoscopic suturing. The data analyses of premenopausal and postmenopausal patients are shown in Table 3. The comparison of patients with and without complications is shown in Table 4. The operational data including operative time, estimated blood loss, and complications regarding the year of surgery are summarized in Figures 1 and 2, respectively. The total (intraoperative and postoperative) complication rate was 20% (9/45), 17.6% (3/17), 7.1% (1/14), 3.4% (1/29), and 2.2% (1/46) in 2013, 2014, 2015, 2016, and 2017, respectively. There were a total of 7 ureteral injuries, including one case in 2014 and 6 cases in 2013. Mean BMI of 5 patients who had and had not undergone conversion to laparotomy was 32.58±2.71 and 30.24±3.53, respectively (p=0.054). There was a positive correlation between decreased hemoglobin level or blood loss and operative time (r=0.171, p=0.036 and r=0.196, p=0.016, respectively).

DISCUSSION

For benign diseases, the vaginal or laparoscopic route of hysterectomy is generally recommended in literature (4) and by the guidelines of American College of Obstetricians and Gynecologists or the American Association of Gynecologic Laparoscopists (AAGL) (12, 13). LH has become more popular with the development of

Table 3. Comparison of patients with respect to menopausal status

	Premenopausal (n=83)	Postmenopausal (n=68)	p
Age (years)*	45.24±5.67	55.9±5.65	0.001†
Gravidity*	4.58±2.23	6.04±2.46	0.000†
Parity*	3.88±1.78	4.87±2.15	0.002†
BMI (kg/m²)*	30.52±3.7	30.08±3.32	0.443
Uterine volume (mL)*	235.08±126.7	182.56±113.97	0.009†
Hospital stay (days)*	2.28±1.09	2.4±1.48	0.567
Operative time (minutes)*	67.4±16.45	72.22±17.32	0.082
Need for erythrocyte suspension (IU)**	19 (22.9%)	7 (10.3%)	0.041†
Blood loss (mL)*	171.19±102.37	145.29±63.85	0.060
Hemoglobin drop (g/dL) *	0.97±0.8	1.14±0.92	0.247
Type of surgery*			0.001†
TLH-BSO	57 (68.7%)	67 (98.5%)	
TLH	16 (19.3%)	0 (0.0%)	
TLH-USO	10 (12.0%)	1 (1.5%)	
Complication**	9 (10.8%)	6 (8.8%)	0.680
Conversion to laparotomy**	5 (6.0%)	0 (0.0%)	0.013†

*Mean±standard deviation, **n (%), †p<0.05. BMI: body mass index; TLH: total laparoscopic hysterectomy; BSO: bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy; IU: international unit

Table 4. Comparison of patients with respect to presence or absence of complications

	Complication n=15	Without complication n=136	p
Age (years)*	49.6±9.64	50.09±7.56	0.380
Gravidity*	5.07±2.02	5.26±2.49	0.811
Parity*	4.33±1.63	4.32±2.05	0.990
BMI (kg/m^2)*	32.25±4.94	30.11±3.29	0.028†
Uterine volume (mL)*	245.67±121.91	207.65±123.59	0.200
Hospital stay (days)*	4±2.75	2.15±0.82	0.001†
Operative time (minutes)*	89±23.86	67.43±14.64	0.001†
Need for erythrocyte suspension (IU)**	8 (53.3%)	18 (13.2%)	0.001†
Blood loss (mL)*	245.53±138.81	150.04±75.26	0.004†
Hemoglobin drop (g/dL)*	1.31±092	1.02±0.85	0.132
Type of surgery*			0.311
TLH-BSO	10 (66.7%)	114 (83.8%)	
TLH	3 (20.0%)	13 (9.6%)	
TLH-USO	2 (13.3%)	9 (6.6%)	
Menopausal status**			0.680
Premenopausal	9 (60.0%)	74 (54.4%)	
Postmenopausal	6 (40.0%)	62 (45.6%)	
Conversion to laparotomy**	3 (20.0%)	2 (1.5%)	0.005†

*Mean±standard deviation, **n (%), †p<0.05. BMI: body mass index; TLH: total laparoscopic hysterectomy; BSO: bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy; IU: international unit

laparoscopic procedures in different countries, including 12% of all hysterectomies in the United States (US) in 2003 (14) and 36% in the Netherlands in 2012 (15). A nationwide study in the US regarding LH demonstrated that abnormal bleeding was the most common indication (53%), and the average duration of hospital stay was 1.65 days (16). Candiani et al. (17) and Morelli et al. (18) reported the average duration of hospital stay as 2.7 and 2.9 days, respectively. According to a recent meta-analysis, the average duration of hospital stay was 2.5 days shorter for TLH compared to total abdominal hysterectomy (19). Similarly, in the present study, abnormal uterine bleeding (44.4%) was the most common indication, and the average duration of hospital stay was found to be 2.3 days. The median range of estimated blood loss reported in randomized controlled trials for LH is between 156 and 568 mL (4), and that in the present study is 159 mL. However, lower amounts of blood loss between 84 and 119 mL have also been previously reported (17-19). One of the primary disadvantages of LH is the relatively long operative time. The mean operative time of TLH in 3 randomized controlled trials (17, 20, 21) was reported to be 112 minutes. Our institutional learning curve in terms of average operative time during 5 years is encouraging, as the mean operative time gradually decreased from 82 minutes to 58 minutes (average, 69.5 minutes; Figure 1). We believe that the advancement in the development of instruments (availability of different types of manipulators or bipolar technologies), standardization of operative techniques, more appropriate patient selection, and enhanced surgical experience may contribute to the shortening of operative time. Although LH is recommended for benign disease in obese patients (22), we demonstrated an association between BMI (average 30.2 kg/m^2) and operative time (p=0.028) or complications (p=0.028), which is similar to the data reported in another study (23). In contrast, previous studies have stated that there is no difference between the operative time among normal BMI, overweight, and obese patients (24). In our study, the mean BMI of the 5 patients who required conversion to laparotomy was higher than the mean BMI of those who did not require the conversion, but this effect was not statistically significant. BSO is crucial in perimenopausal and postmenopausal women because the removal of prophylactic adnexectomy precludes adnexal torsion, ovarian cancer, benign ovarian pathologies, and prolapsed salpinx (7.91%) (25, 26). We performed BSO in 82.1% (124/151) of all cases in the present study and up to 98.5% in postmenopausal patients. We demonstrated a significant difference between premenopausal and postmenopausal groups when age, gravidity, parity, uterine volume, need for erythrocyte suspension, type of surgery, and conversion to laparotomy were compared. As expected, we observed a greater decrease in hemoglobin level and more blood loss with increasing operative time.

Figure 1. Operational outcomes including the operative time and estimated blood loss over 5 years

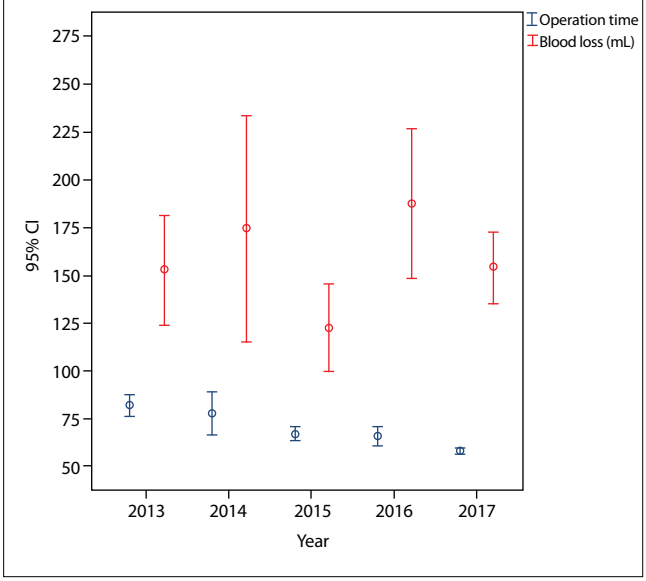
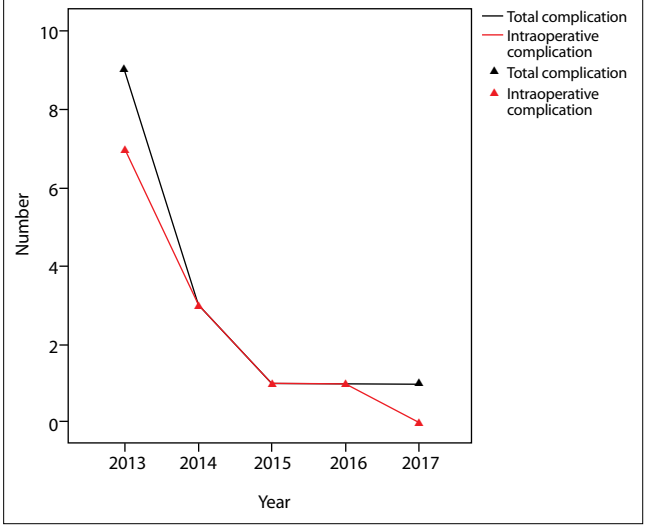


Figure 2. Total and intraoperative complications between 2013 and 2017



Other disadvantages of LH are the long learning curve and more frequent ureteric and hemorrhagic complications (8). However, there was no statistically significant difference in pooled urinary tract injury rates for LH compared with those for vaginal hysterectomy (27). A lower complication rate and shorter operative time can be accomplished by experienced surgeons (28). A large proportion of the major complications occur during the learning curve (29). Wattiez et al. (30) and Makinen et al. (31) suggested that the learning curve threshold should be at least 21 and 30 procedures, respectively.

Although there are low complication rates (between 0 and 1.4%) regarding LH have been reported (32, 33), high complication rates (between 9.8% and 11.1%) have also been reported by some authors (9-11). In the present study, the total complication rate (intraoperative and postoperative) was 10.6%. There was a significant difference between 2 groups (with or without complications) when we compared the BMI, duration of hospital stay, operative time, need for erythrocyte suspension, blood loss, and conversion to laparotomy. All of these parameters were found to be higher in the patients with complications. There was one patient with vaginal cuff cellulitis concurrent with ureteral injury diagnosed on the 45th day of TLH. Vault infection can be a result of a high-energy application during colpotomy, which induces thermal injury and decreases vascular blood flow to the vaginal cuff, ultimately hampering postoperative healing.

The anatomic relationship between ureters and pelvic genital organs may lead to unintentional ureteral injury during hysterectomy. The upward traction of the cervix with a uterine manipulator is an important step in moving the uterine artery away to avoid ureteral injury (30). In a recent systematic review, the incidence of lower urinary tract injury, primarily of the bladder and ureters, associated with LH for benign disease was 0.35 (416 patients among 117982 operations) (34). Studies have reported that urinary tract lesions occur more frequently during LH (3, 4, 28). If the patients who underwent LH present with fever, flank pain, or hematuria, the ureteral injury can occur. A CT scan with contrast medium may reveal the presence of urine in the peritoneal cavity (34). In our study, most ureteral injuries were diagnosed postoperatively (50%, 5/10), whereas all the bladder injuries were diagnosed intraoperatively.

Although the intraoperative diagnosis of urinary tract injuries is crucial to decrease the morbidity and AAGL recommended routine cystoscopy after laparoscopic hysterectomies in 2012 (35), there is no evidence that routine cystoscopy significantly increases the diagnosis rate of postoperative urinary tract injury ($p<0.054$ for ureter injury) (36). Ureteral transection and complete occlusion can be efficiently diagnosed by an experienced laparascopic surgeon on cystoscopy, unless the injury is partial (37). We performed cystoscopy to check bilateral ureteral efflux in suspected cases of ureteral injuries and to perform ureteral surgery in the early postoperative period in parallel with this finding. The ureter should be cautiously distinguished from the uterine vessels before the safe coagulation of the uterine vessels. In our study, we demonstrated that thermal diathermy led to ureteral injury in 2 patients. A multicenter Finnish retrospective study regarding LH (38) found that the rate of urinary tract injuries decreased from 1.4% to 0.7% and that of ureteral injuries decreased from 0.9% to 0.3% over 5 years. Our complication rate is an excellent reflection of the learning curve. The total (intraoperative and postoperative) complication rate decreased from 20% (9/45) in 2013 to 2.2% (1/46) in 2017. Particularly, we observed no ureteral injury between 2015 and 2017, and the rate of ureteral injury was 13.3% (6/45) and 5.9% (1/17) in 2013 and 2014, respectively. We can attribute this dramatic decrease in complications to the more effective utilization of uterine manipulators directed toward an upward fashion regardless of the assistant surgeon, use of better bipolar hemostasis instruments, and awareness of the possibility of such injuries.

A Finnish study reported that the rate of bladder injury was 6.9% in patients with LH (39). A recent review regarding urinary tract injuries in LH found that the rate of bladder injury (0.24%) was 3 times higher than that of ureteral injury (0.08%) (34). Bladder injuries most frequently result during the dissection of the vesicouterine peritoneum. Underreporting of the cases with urinary tract injuries may limit the real rate of urinary tract complications. In our study, all bladder injuries (3/151, 2%) were at the dome and restored intraoperatively by laparoscopic suturing. There was no bowel injury, and ureterovaginal or vesicovaginal fistula formation in our study.

The conversion rate to laparotomy varied as 2.7%-3.9% in previously reported studies (37). However, David-Montefiore et al. (40) reported the rate as 19%, which was related to surgical inexperience. The conversion rate to laparotomy was 3.3% in our study, which is consistent with other studies. The limitations of our study are its retrospective nature, small size, and lack of evaluation of the long-term effects, including vaginal vault prolapse, urinary incontinence, and sexual function.

CONCLUSION

Laparoscopic hysterectomy has numerous beneficial advantages, including short postoperative time interval, limited loss of blood, relatively fewer complications, and good cosmetic view and is a suitable alternative to abdominal hysterectomy when it can be successfully performed by an advanced laparoscopy skilled surgeon. Lower complication (especially urinary) rates can be expected with better handling of the uterus via manipulators during surgery, consideration of anatomical proximities, and following safe dissection rules at all times.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gaziantep University (Approval number: 2017/415).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.Ç.Ö.; Design - M.G.U., N.B.T.; Supervision - H.Ç.Ö.; Resources - S.S., Ö.K.K., T.G.K.; Data Collection and/or Processing - S.S., N.B.T., Ö.K.K.; Analysis and/or Interpretation - T.G.K., S.S.; Literature Search - Ö.K.K.; Writing Manuscript - H.Ç.Ö., M.G.U.; Critical Review - M.G.U., T.G.K., N.B.T.

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Original Research

Evaluation of Patients Presenting to the Emergency Service with Shoulder Dislocation

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ABSTRACT

Objective: Glenohumeral joint dislocation is the most common major joint dislocation in the entire body. This study is an epidemiologic and demographic investigation of dislocated shoulder cases presenting to the emergency room of a public hospital.

Methods: This study includes patients that presented to the emergency room of Sivas public hospital with a dislocated shoulder between the dates 01/02/2015-01/01/2018. Patients that were admitted to the emergency room and diagnosed with shoulder dislocation were informed about the study.

Results: Five hundred and eighty one patients presenting to Sivas public hospital and diagnosed with shoulder dislocation were included in the study. The average age of patients was 43±18.59, with the youngest patient 19 years old and the oldest 88 years old. 537 (92.4%) patients had anterior, 32 (5.5%) patients had posterior and 12 (2.1%) patients had inferior dislocations.

Conclusion: Shoulder dislocation cases are commonly seen in emergency rooms. It is more commonly seen in males and the most frequently seen type is anterior dislocation. This condition concerning individuals of all age groups develops mainly due to trauma.Despite the fact that shoulder dislocations can be diagnosed and treated easily in emergency rooms, prevention of shoulder dislocations can only be achieved by means of preventive measures and informative meetings.

Keywords: Emergency service, shoulder dislocation, orthopedics

INTRODUCTION

Among major joint dislocations in the entire body, glenohumeral joint dislocation is the most common (1).

Anterior dislocations (95%), posterior dislocations (2-5%), and inferior dislocations (luxation erecta) secondary to arm hyper-abduction injury (0.5%) constitute the majority of shoulder dislocations (2-6).

Anterior dislocations occur mostly due to indirect trauma when the upper extremity is positioned in abduction, extension, and external rotation. Convulsion, direct impact to the back, and electric shock can also result in anterior shoulder dislocation. Posterior dislocations occur mostly due to indirect trauma when the upper extremity is positioned in adduction, flexion, and internal rotation (4, 7).

Inferior shoulder dislocation is very rare. It is mainly seen in older patients. Superior glenohumeral dislocation is a very rare presentation that is seen less frequently than inferior shoulder dislocations (4, 8).

After shoulder dislocation, patients tend not to move their arm due to muscle spasm and pain. In cases of anterior shoulder dislocation, the shoulder is typically in slight abduction and external rotation. Fullness in the posterior region of the shoulder joint is decreased, and the humeral head cannot be felt by palpating the posterior edge of the acromion. Since patients with posterior shoulder dislocation do not exhibit a marked deformity, they should be examined very carefully. The arm on the affected side is typically in adduction and internal rotation. The humeral head can be palpated on the posterior and coracoid process on the anterior. Pain is significantly severe in inferior shoulder dislocation. In a typical clinical presentation, the patient's arm is in 110°-160° abduction, the elbow is in flexion, the forearm is in pronation, and the hand is above the head level. This position can also be defined as the salute position. The humeral head can be palpated on the lateral chest wall and axilla. The humeral shaft is directed to the superior. Pain is significantly severe in superior shoulder dislocation. In a typical clinical presentation, the patient's arm is in adduction, and the upper extremity affected by the migration of humeral head to the superior is shortened. The humeral head can be palpated above the acromion. Neurologic pressure symptoms often coexist, and are alleviated after reduction (4, 7, 8).

Anteroposterior, scapular Y, and axillary graphs of the shoulder should be obtained in radiologic imaging. Direct graphs, espe-

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cially in posterior dislocations, can sometimes be unhelpful. In this case, computerized tomography should be used (2, 4).
Shoulder dislocation is treated by reduction with traction and counter-traction maneuvers under sedation and/or analgesia. The arm should be immobilized in a sling for 3-6 weeks after reduction. Severely painful shoulder dislocations should be treated under general anesthesia (4, 7).

The most commonly used and known methods are the Hippocratic technique and the Kocher technique. In addition, there is the Stimson technique, Milch technique, and combined techniques involving both these methods. The front flexion-adduction-external rotation (FAD rotation) method has also been commonly used in recent years (1, 7, 8).

Neurologic complications are common during the reduction of shoulder dislocation. However, the probability of these complications cannot be predicted before the reduction procedure. Apraxia is generally completely healed. Nerve laceration is significantly rare (less than 4% of cases). Axillary and suprascapular nerves carry the highest risk of laceration (1, 4, 7).

This study is an epidemiologic and demographic investigation of dislocated shoulder cases presenting to the emergency room of a public hospital.

METHODS

This study includes patients who presented to the emergency room of Sivas Numune Public Hospital with a dislocated shoulder between the dates 01/02/2015 and 01/01/2018. This hospital provides services for 1 million people on average, and the number of patients admitted to the emergency room per day is around 1200-1400. Ethics committee approval was received for this study. Ethical approval was obtained from the Non-interventional Clinical Research Ethical Committee of Cumhuriyet University (2017-20836).

Patients admitted to the emergency room and diagnosed with shoulder dislocation were informed about this study. Patient consents were obtained, and patient information was filled in previously prepared reports. Emergency medicine specialists and orthopedists treated patients, and evaluated their radiologic imaging. During treatment, the emergency trauma room was used. Patients with polytrauma, hemodynamic instability, and accompanying two- and more-part proximal humerus fracture were not included in the same group as patients with intraarticular fracture.

RESULTS

A total of 581 patients presenting to Sivas Numune Public Hospital and diagnosed with shoulder dislocation were included in the study.

The average age of patients was 43±18.59 years, with the youngest patient aged 19 years, and the oldest 88 years. The study included 242 (41.7%) females and 339 (58.3%) male. A total of 537 (92.4%) patients had anterior, 32 (5.5%) patients had posterior, and 12 (2.1%) patients had inferior dislocations. In addition, bilateral shoulder dislocation was observed in 12 (2.1%) patients, and superior dislocation in none. A total of 497 (85.5%) of shoulder dislocation cases were associated with trauma, whereas 84 (14.5%) of the cases were due to spontaneous and low-energy events (coughing, sneezing etc.).

Table1. Demographic information of shoulder dislocation

Demographic Variable	Case cohort	%
Age (year)		
Mean	43±18.59	
Range	69	
Min–Max	19–88	
Sex		
Male	339	58.3
Female	242	41.7
Shoulder dislocation type		
Anterior	537	92.4
Posterior	32	5.5
Inferior	12	2.1
Bilateral	12	2.1
Injury mechanism		
Traumatic	497	85.5
Nontraumatic	84	14.5
Method		
FAD	183	31.5
Cunningham	164	28.2
FAD+Cunningham	177	30.5
Others	57	9.8
Sedation		
Yes	480	82.6
No	101	17.4
Type of dislocation occurred		
Primary	473	81.4
Recurrent	108	18.6

Reduction of dislocations was performed by FAD rotation in 183 patients, Cunningham in 164 patients, and both methods in 177 patients. One of the other methods, that is, Hippocratic, Kocher, or Stimson, was applied for dislocations that could not be reduced with the previously mentioned methods. The remaining 57 dislocations were reduced using these methods.

A total of 480 (82.6%) patients were sedated, and 101 (17.4%) patients were not sedated. A total of 23 (3.9%) patients were hospitalized, and 558 (86.1%) patients were discharged after a short monitoring period in the emergency room.

The average duration of hospital stay was 9.12±5.50 days with the longest hospitalization period of 33 days.

In the first attempt, 455 (78.3%) dislocations were reduced, whereas in the second, 126 (21.7%) dislocations were reduced.

Furthermore, 473 (81.4%) cases presented with a dislocated shoulder for the first time, whereas 108 (18.6%) cases presented with recurrent shoulder dislocation to the emergency room (Table 1).

DISCUSSION

This study was conducted with data obtained from a public hospital that address a large population, and showed the incidence and demographic characteristics of shoulder dislocation cases. Sadly, there are not many extensive studies showing these characteristics of shoulder dislocation in Turkey. The studies conducted indicate that the prevalence of shoulder dislocation is higher throughout the world as compared to that in Turkey. For instance, studies conducted in the United States and Europe report rates that are three to four fold higher in comparison to the rates of the studies conducted in Turkey (9-12). This might stem from the sociodemographic structure of people living in this region. Another reason might be the fact that people living in Sivas and its vicinity choose a more sedentary lifestyle due to long and harsh winter conditions.

Leroux et al. (13) found that the average age of patients presenting to hospitals with shoulder dislocation was 37.39±16.62 years, whereas Tas et al. (14) found it to be 37.2±21.3 years, and Abbasi et al. (15) found it to be 31.63±15.88 years in their studies encompassing Turkey. In our study, the average patient age was 43±18.59 years. Sivas is a city that is not strong in terms of industry with especially limited employment opportunities and harsh winter conditions. The highest rate of immigration to another city in Turkey is seen in Sivas. In fact, most of the immigrants in Istanbul are from Sivas. The high average age of the patients with dislocated shoulders in our study is associated with the fact that the employed young population is low in Sivas.

The majority of cases in our study were males, whereas females constituted only 42%. In literature, males constitute the majority of shoulder dislocation cases (13-15). Our study is in compliance with the literature inthis respect.

In the study, 537 (92.4%) patients had anterior, 32 (5.5%) patients had posterior, and 12 (2.1%) patients had inferior dislocations. In addition, bilateral shoulder dislocation was observed in 12 (2.1%) patients, and superior dislocation in none. In this aspect, our study complies with other studies examining this subject (13-16).

The initial diagnosis and treatment of shoulder dislocation is performed in emergency departments throughout the world (17). Emergency medicine physicians should have sufficient knowledge for the initial diagnosis of shoulder dislocation. In Turkey, emergency medicine physicians in many clinics are sufficiently trained for diagnosing shoulder dislocation. In fact, in our study, almost all shoulder dislocations were diagnosed by emergency medicine physicians. Orthopedists provided support during the reduction operation.

Shoulder dislocation mainly occurs due to various types of trauma. Falls, car accidents, and sports injuries are some examples. A minority of shoulder dislocations occur due to epileptic seizures, mild strain, and contraction (4, 7). Tas et al. (14) found that shoulder dislocation injuries resulted from falls in 74.5%, simple trauma in 12.5%, motor vehicle accidents in 8.7%, physical assault in 2.9%, and epileptic seizures in only 1.4% of cases. Abbasi et al. (15) classified causes of shoulder dislocation as traumatic and a traumatic, and reported that traumatic causes were encountered more frequently with 63.8%. The most common traumatic causes included fights and falls, whereas the majority of atraumatic causes occurred during sleep and arm movement (15). In our study, 497 (85.5%) of shoulder dislocation cases were associated with trauma, whereas 84 (14.5%) of the cases were due to spontaneous and low-energy (coughing, sneezing etc.) events.

There are many conventional methods for the reduction of shoulder dislocation. The most commonly used methods are the Hippocratic technique and the Kocher technique. In addition, there is the Stimson technique, Milch technique, or combined techniques involving both these methods; the Cunningham technique and the FAD rotation method (7, 16). Reduction was performed by FAD rotation in 183 patients, Cunningham in 164 patients, and both methods in 177 patients. The Hippocratic, Kocher or Stimson method was applied for 57 dislocations that could not be reduced through the previously mentioned methods.

In a study conducted in Turkey, it was stated that FADR rotation method is a simple, nontraumatic, and effective method that requires only one practitioner to reduce shoulder dislocations. It was suggested that the method can be easily applied by orthopedic assistants and emergency physicians since it is practical and has a low learning curve (16).

Gul et al. (16) did not sedate their patients during the reduction procedure, in which they used the FAD rotation method, because there was not much pain. Tas et al. (14), on the other hand, sedated all their patients during the reduction procedure. In Canada, all patients were sedated during the reduction of shoulder dislocations in a study investigating younger cases (13). In our study, 480 (82.6%) patients were sedated during reduction, whereas sedation was not needed in 101 (17.4%) patients. Sedation was performed by emergency physicians in the emergency room.

The average duration of hospital stay was 9.12±5.50 days with the longest hospitalization period of 33 days. A total of 455 dislocations were reduced in the first attempt, whereas 126 dislocations were reduced in the second attempt.

Furthermore, 473 (81.4%) cases presented with a dislocated shoulder for the first time, whereas 108 (18.6%) cases presented with recurrent shoulder dislocation to the emergency room. Considering the studies conducted in Turkey, Gul et al. (16) reported that recurrent shoulder dislocation was seen in 28.1% of

the cases, whereas Tas et al. (14) reported the same in 17.3% of the cases. Our study is similar to the ones in the literature.

CONCLUSION

Shoulder dislocation cases are commonly seen in emergency rooms. The incidence of shoulder dislocation is around 4.09% in Public Hospital. It is more commonly seen in males, and the most frequently seen type is anterior dislocation. This condition concernsindividuals of all age groups, and develops mainly due to trauma. Although there are many methods for treating shoulder dislocation, a majority of shoulder dislocations were reduced using mainly FAD rotation and Cunningham methods in our study. Despite the fact that shoulder dislocations can be diagnosed and treated easily in emergency rooms, prevention of shoulder dislocations can only be achieved by means of preventive measures and informative meetings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Cumhuriyet University (2017-20836).

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

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Original Research

Evaluation of Cornea and Anterior Chamber Results of Patients with Obstructive Sleep Apnea Syndrome

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ABSTRACT

Objective: To evaluate the anterior segment findings measured via corneal topography of patients with obstructive sleep apnea syndrome (OSAS) and to compare the findings with normal subjects.

Methods: A total of 43 eyes from 43 patients with OSAS and 43 eyes from 43 healthy persons who were referred to eye clinics from 2012 to 2016 were randomly selected and included in this retrospective study. Routine eye examination and anterior segment findings measured via corneal topography were recorded for both groups. Central corneal thickness (CCT), keratometry values (K1, K2, and Kmax), corneal volume (CV), anterior chamber depth (ACD), anterior chamber volume (ACV), and anterior chamber angle (ACA) of the two groups were compared.

Results: The mean CCT values of the control and OSAS groups were 567.23±31.17 and 544.4±36.44 (p=0.002), respectively. The mean CV (HR) was found to be 60.51±8.44 in the control group and 59.78±3.47 in the OSAS group (p=0.04). There was no statistically significant difference between the OSAS and control groups in terms of mean age, K1, K2, Kmax, ACV, ACD, and ACA (p>0.05). The mean apnea/hypopnea index (AHI) score of the OSAS group was found to be 21.82±12.79. There was no negative or positive correlation between the AHI score and age, CCT, K1, K2, Km, SCL, SCL, SCA, and CV.

Conclusion: Central corneal thickness and CV are lower in OSAS patients than in normal people.

Keywords: Obstructive, sleep apnea, anterior segment of the eye, topography

INTRODUCTION

Briefly put, obstructive sleep apnea is the partial or complete occlusion of the upper respiratory tract at regular intervals and recurrently during sleep. These periods of obstruction are a significant cause of disruption of patient comfort. These periods can cause chronic fatigue and cognitive impairment in daytime hours in patients (1). It is thought to affect between 3-7% of the population with varying frequency (2). Polysomnography, which calculates the number of apneas that occur during the night, is the most important diagnostic test for obstructive sleep apnea (3). Obstructive sleep apnea is thought to be a risk factor for various eye disorders due to hypoxia caused by the periods of apnea in the body. These include glaucoma, flexible eyelid syndrome, optic neuropathy, and keratoconus (4-6).

In previous studies, the frequency of clinical conditions such as papilledema and optic neuropathy (7), retinal vascular tortuosity, and congestion increase (8) have been investigated in patients with obstructive sleep apnea syndrome (OSAS). In a study conducted, 69 patients with obstructive sleep apnea had a glaucoma incidence of 7.2% (9). In another study, it was shown that the incidence of primary open-angle glaucoma was higher in patients with sleep apnea syndrome (10).

On the other hand, in another study, sleep apnea patients and healthy subjects were compared and there was no significant difference between the two groups in terms of anterior chamber findings such as anterior chamber depth, anterior chamber volume, and anterior chamber angle (11). Patients with severe sleep apnea have been shown to have increased eyelid laxity, higher Schirmer test scores, and reduced tear breakup time compared to healthy subjects (12).

Obstructive sleep apnea syndrome is associated with many eye diseases as mentioned above. We are of the opinion that anterior segment parameters may be affected by mechanisms such as hypoxic damage and increased sympathetic activation due to OSAS. For this reason, we aimed to compare the anterior segment findings of sleep apnea patients with those of healthy individuals and to see if there is any difference between the groups with mild, moderate and severe sleep apnea syndrome.

METHODS

Forty-three eyes of 43 patients with sleep apnea (38 males, five females) who presented to the ophthalmology clinic between 2012 and 2016 were randomly included in the study. Forty-three eyes of 43 healthy individuals matched according to age and

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sex were included in the study. The study was approved by the Pamukkale University Medical Ethics Committee and the standards in the Helsinki Declaration were adhered to (Ethics Committee approval: 10.01.2017 dated and numbered 01).

Autorefractometric values, visual acuity, intraocular pressure measurements, fundus examinations, and topographic measurements of a randomly selected eye of the patients were recorded. Patients who had undergone intraocular surgery, had pterygium or a disease other than sleep apnea, or had a refractive error of more than-1.50 and +1.50 diopters, were not included in the study. The keratometric (K1, K2, Kmax) and pachymetric (CCT) measurements of the patients with a Pentacam HR (Oculus, Wetzlar, Germany), their corneal volumes (CV), anterior chamber depths (ACD), anterior chamber volumes (ACV), and anterior chamber angles (ACA) were recorded. The keratometric values of the patients and the control group were examined in three different categories; namely K1 (horizontal keratometry measurement), K2 (vertical keratometry measurement), and Kmax (maximum keratometry measurement). The corneal volume was determined by measuring the area with a radius of 5mm from the apex. The Pentacam HR is a device that evaluates the anterior segment making elevation-based measurements with a rotating Scheimpflug camera. To measure the curvature of the cornea and its diopter equivalent, the device evaluates two large meridians perpendicular to each other in the 3.0 mm corneal circle. K1 and K2 with Pentacam represent the keratometric readings simulated on the horizontal and vertical meridians (13).

The participants were firstly divided into sleep apnea patients and the control group. After comparing the data from these two groups of patients, the patients were divided into three groups, namely mild, moderate and severe, according to the severity of the disease. Apnea-hypopnea index (AHI) scores were determined on the basis of the polysomnography of the patients. The mild group consisted of patients with an AHI score of between 5-15, the moderate group between 16-30, and those with scores over 30 were also classified as having severe illness.

Statistical Analysis

IBM Statistical Package for the Social Sciences version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for the statistical analysis. Continuous variables were expressed as mean±standard deviation, median (minimum and maximum values), and categorical variables in numbers and percentages. When the parametric test assumptions were met, the Significance of the Difference Between Two Means Test and One Way Analysis of Variance were used to compare the independent group differences, and when the parametric test assumptions were not met, the Mann-Whitney U Test and Kruskal Wallis Variance Analysis were used to compare independent group differences. In addition, the relations between numerical variables were examined with Pearson Correlation Analysis. P values below 0.05 were considered statistically significant.

RESULTS

There was no statistically significant difference in the mean age, K1, K2, Kmax, anterior ACV, ACD, ACA findings between the sleep apnea group and the control group (p>0.05). The mean CCT of the control group was 567.23±31.17 and the same value was 544.4±36.44 in sleep apnea patients. This difference was statistically significant (p=0.002). The mean CV was found to be 60.51±8.44 in the control group and 59.78±3.47 in the sleep apnea group (p=0.04). The difference was statistically significant (p=0.04). The measured values of the two groups are shown in Table 1.

The average apnea/hypopnea index (AHI) score of sleep apnea patients was 21.82±12.79. There was no negative or positive cor-

Table 1. Measurement values of the control and OSAS groups

	Control (n=43)		OSAS (n=43)		p
Age	44.02±10.94	42 (25–67)	44.02±10.94	42 (25–67)	1
AHI	–	–	21.82±12.79	16 (5–56)	–
CCT	567.23±31.17	560 (503–631)	544.4±36.44	542 (451–645)	0.002*
K1	42.67±1.68	42.2 (39.9–46.9)	42.97±1.54	42.9 (40.1–46.2)	0.384
K2	43.54±1.73	43.3 (40.1–47.6)	43.86±1.97	43.7 (40.3–51.4)	0.476
Kmax	43.1±1.68	42.8 (40–47.2)	43.4±1.71	43.2 (40,2–48.7)	0.411
ACV	170.3±36.41	174 (97–243)	162.63±39.04	161 (82–250)	0.349
ACD	2.95±0.36	2.95 (2.27–3.77)	2.87±0.32	2.85 (2.21–3.5)	0.313
ACA	34.23±8.92	34 (17.1–54.4)	33.64±6.6	35.1 (19.5–45.8)	0.728
CV	60.51±8.44	61 (11.7–71)	59.78±3.47	60.2 (51.8–66.8)	0.04*

*p<0.05 was considered statistically significant

OSAS: obstructive sleep apnea syndrome; AHI: apnea hypopnea index; CCT: central corneal thickness; K1: horizontal keratometric value; K2: vertical keratometric value; Kmax: maximum keratometric value; ACV: anterior chamber volüme; ACD: anterior chamber depth; ACA: anterior chamber angle; CV: corneal volume

Table 2. Correlation of apnea hypopnea index with other measurements

		Age	CCT	K1	K2	Kmax	ACV	ACD	ACA	CV
AHI	R	0.233	–0.041	0.113	0.142	0.129	–0.120	–0.139	–0.102	0.007
	p	0.133	0.796	0.470	0.365	0.411	0.444	0.374	0.517	0.965

R: correlation coefficient

AHI: apnea hypopnea index; CCT: central corneal thickness; K1: horizontal keratometric value; K2: vertical keratometric value; Kmax: maximum keratometric value; ACV: anterior chamber volüme; ACD: anterior chamber depth; ACA: anterior chamber angle; CV: corneal volume

Table 3. Comparison of mild, moderate and severe OSAS groups with the control

	Mild (n=15)	Moderate (n=16)	Severe (n=12)	Control (n=43)	p
Age	43±9.81	41.31±9.87	48.92±12.78	44.02±10.94	0.317
AHI	9.63±3.86	20.59±4.98	38.7±7.5	–	–
CCT	541.8±43.3	555.13±22.63	533.33±40.94	567.23±31.17	0.007*
K1	42.65±1.57	43.18±1.53	43.11±1.57	42.67±1.68	0.634
K2	43.33±1.58	44.08±1.72	44.23±2.64	43.54±1.73	0.606
Kmax	42.97±1.56	43.63±1.61	43.64±2.05	43.1±1.68	0.657
ACV	169.27±34.68	160.81±30.23	156.75±54.23	170.3±36.41	0.648
ACD	2.93±0.29	2.87±0.24	2.79±0.44	2.95±0.36	0.546
ACA	35.19±6.18	32.2±6.87	33.62±6.85	34.23±8.92	0.746
CV	58.91±3.79	61.76±2.17	58.22±3.46	60.51±8.44	0.003*

*p<0.05 was considered statistically significant

AHI: apnea hypopnea index; CCT: central corneal thickness; K1: horizontal keratometric value; K2: vertical keratometric value; Kmax: maximum keratometric value; ACV: anterior chamber volüme; ACD: anterior chamber depth; ACA: anterior chamber angle; CV: corneal volume

relation between the AHI score and age, CCT, K1, K2, Kmax, ACV, ACD, ACA, and CV. Table 2 also shows the correlation between the AHI score and other characteristics of the patients.

There was a statistically significant difference between the four groups in the measurement of CCT when sleep apnea patients were classified as mild (AHI 5-15), moderate (AHI 16-30), and severe (>30), and compared with the control group (p=0.007). The CV showed a statistically significant difference between the four groups (p=0.003). Table 3 shows the measurement and p values of the four groups.

DISCUSSION

Central corneal thickness and corneal volume were found to be statistically significantly lower in 43 patients with sleep apnea syndrome compared to the control group. The apnea/hypopnea score (AHI) of the sleep apnea patients does not correlate with the CCT and CV. There were no significant differences between the two groups in terms of other measurement results.

The mechanisms of ocular complications in obstructive sleep apnea syndrome are influenced by many factors. Hypercoagulability, the emergence of free oxygen radicals, increased oxidative stress, and endothelial dysfunction are some of these. Sympathetic activation and anoxic damage resulting in optic nerve involvement is one of the mechanisms emphasized in this syndrome (14, 15).

Obstructive sleep apnea syndrome is associated with various eye problems as mentioned earlier. For example, the relationship between keratoconus and sleep apnea has been shown in previous studies. In a study by Saidel et al. (5), the risk of sleep apnea in keratoconus patients was found to be higher. Woodward et al. (16) showed the relationship between keratoconus and sleep apnea and demonstrated it to be more frequent compared with the normal population. In addition, this relationship was found to be higher in severe keratoconus patients in the same study. In our study, although the measurements of corneal volume and central corneal thickness were low in patients with sleep apnea, no keratoconus was detected in any of the patients. The lack of a diagnosis of keratoconus may be due to the small number of patient groups involved in the study.

Central corneal thickness measurements did not show any statistically significant change in a study by Aslan Bayhan et al. (11) compared to normal subjects. On the other hand, in a study by Koseoglu et al. (17), the CCT values (542.14±31.21) of sleep apnea patients were found to be significantly lower than the healthy control group (569.92±13.46) and correlated with the severity of the

disease. Similarly, our study found that CCT was significantly lower when compared to the control group. However, according to our findings, this does not correlate with the severity of the disease.

Cornea volume has been shown to be significantly reduced in cases of keratoconus, which has been associated with the disease stage (18). Cornea volume was significantly lower in patients with sleep apnea than in the control group according to our study. As far as we have investigated in the literature, our study is the first to show this result. This parameter was not taken into account in the study by Koseoglu et al. (17) On the other hand, Aslan Bayhan et al. (11) did not find any change in the cornea volume or the measurements of the central corneal thickness compared to the healthy control group in their studies. We think that the most important cause of low CCT and cornea volume in OSAS patients is hypoxia. Increased matrix metalloproteinases in sleep apnea syndrome have been shown to be due to increased levels of IL-6 and TNF-alpha levels due to hypoxia (19). Matrix metalloproteinases have extracellular matrix regulatory properties. Therefore, the thinning of the cornea and decrease in cornea volume may be due to this. Defects in these biomechanical properties may also affect the CCT and cornea volume. We also think that hypoxia may affect the epithelium, stroma, and endothelium layers of the cornea, thereby altering the shape of the cornea through mechanisms such as edema or neovascularization in the stromal layer. The fact that central corneal thickness and the cornea volume are significantly lower in the patient group suggests that these two parameters are directly related to each other.

In this study, sleep apnea patients were compared with the control group both as a single group and by being divided into three groups according to the severity of the disease. Our goal here is to show how the severity of the disease affects the measurements. The values of CCT and cornea volume were significantly different in these four groups. However, there was no correlation between the AHI score indicating disease severity and these variables.

The biggest limitations of our study are the low number of patients and its retrospective nature. Another limitation is that the number of endothelial cells, one of the factors affecting corneal thickness, was not calculated. We think that there is a need for prospective studies where more patients are evaluated and endothelial factors are assessed.

CONCLUSION

According to the results of the study, the values of CCT and CV were lower in the OSAS patients. It should be taken into account that CCT may be subtle in patients with sleep apnea, especially when it comes to intraocular pressure measurements. We think that it would be highly beneficial in terms of ocular health if physicians who manage patients with sleep apnea sent their patients to an ophthalmologist for ocular findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Pamukkale University (Approval: 10.01.2017).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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Original Research

Evaluation of P-Wave Dispersion, Ventricular Functions, and Atrial Electromechanical Coupling in Children with Type 1 Diabetes Mellitus

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ABSTRACT

Objective: The present study aimed to evaluate ventricular diastolic function, inter- and intra-atrial conduction delay, and P wave dispersion in pediatric patients with type 1 diabetes mellitus (DM).

Methods: This study comprised 30 pediatric patients with type 1 DM and 30 healthy children served as the control group. P wave dispersion (Pd)was measured on a 12-channel ECG. Both systolic and diastolic functions of both ventricles were evaluated using conventional and tissue doppler imaging (TDI) echocardiography (ECHO). Atrial electromechanical delay was measured using TDI accompanied with electrocardiography (ECG).

Results: On conventional transthoracic echocardiography (ECHO), the mitral E/A ratio and isovolumetric relaxation times (IVRT) were different between the patients with type 1 DM and the control group (1.67±0.46 vs. 1.95±0.43, p=0.017 and 74.5±7.0 vs. 63.3±5.2, p<0.001, respectively). On TDI, LV septal peak systolic (S_m) and early diastolic (E_m) velocities and E_m/A_m ratio were found to be significantly lower in the patients with type 1 DM than in the control group (p=0.047, p=0.003, and p=0.001, respectively). Regarding atrial electromechanical conduction, prolongation was detected in PA lateral, PA septal, PA tricuspid, and inter-atrial (PA lateral–PA tricuspid) and intra-atrial (PA septal–PA tricuspid) conduction delay (p<0.001, p<0.001, p<0.001, p<0.001, and p<0.05, respectively).

Conclusion: Our findings suggest that intra- and inter-atrial conduction delay, p wave dispersion, and ventricular diastolic functions are abnormal in patients with type 1 DM.

Keywords: Atrial electromechanical delay, children, diastolic function, left atrial mechanical function, type 1 diabetes mellitus

INTRODUCTION

Type 1 DM is one of the most common chronic diseases in adolescents and children. Poorly controlled type 1 DM is associated with many complications such as nephropathy, neuropathy, retinopathy and cardiovascular diseases. There is an increased risk of cardiovascular diseases such as ischemic heart diseases, systolic and diastolic heart failure, conduction system abnormalities and arrhythmias in patients with type 1 DM (1, 2). Atrial fibrillation, which is associated with high mortality and morbidity, is frequently encountered in daily practice (3). It is known that prolonged intra- and inter-atrial conduction delay and non-homogenous distribution of sinus impulses increase predisposition to Atrial fibrillation (AF). Risk of this predisposition can be determined by noninvasive methods such as P wave dispersion (Pd) and tissue doppler imaging (TDI) (4, 5).

There are a few studies conducted on pediatric cases in the literature. Similar to the methodology and design of the previous study conducted by Irdem et al. (6) on pediatric patients with hypothyroidism, we aimed to evaluate ventricular diastolic function, inter- and intra-atrial conduction delay and P wave dispersion in pediatric patients with type 1 DM.

METHODS

Thirty pediatric patients (18 females, 12 males, mean age 9.6±2.4 years) who have been diagnosed with type 1 DM in accordance with the criteria of the American Diabetes Association (7), who have received insulin therapy for at least one year and have been followed for a mean time period of 3.0±1.2 years in our clinic, as well as 30 healthy children (16 females, 14 males, mean age 8.4±3.6 years), as the control group, were enrolled in this study. Pediatric cases with hypertension, cardiomyopathy, valvular heart disease, branch block in ECG, atrioventricular conduction disorders, thyroid function disorder, kidney disease, lung disease, hypercholesterolemia and a bad presentation in ECG and Transthoracic echocardiography (TTE) in both type 1 DM and control groups were excluded from the study. In addition, individuals in both groups were not using any drugs that could affect heart

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rhythm and they had sinusoidal heart rhythm. P wave dispersion was measured as described by Dilaveris et al. (8) in resting ECG. Individuals in both groups provided written informed consent was obtained before the study. Ethics committee approval was not received. The current research was performed in accordance with the principles of the Helsinki Declaration as revised in 2008. We used the method from our previous study on pediatric patients with subclinical hypothyroidism while planning this study (6).

Transthoracic echocardiography (TTE) (Vivid S5 Pro device, GE, Horten, Norway, 2-4MHz phased-array transducer) was performed with 2-dimensional, M-mode, pulse and color flow Doppler imaging on all cases. A recording was made with one lead ECG throughout the TTE. Using conventional TTE, the mean values of the mitral and tricuspid early diastolic E wave, late diastolic A wave, isovolumetric relaxation times (IVRT), deceleration time (DT) and E/A ratio were calculated from three cycles obtained with Doppler and evaluated according to the American Echocardiography Association guidelines (9). Left atrial (LA) diameter was measured from the parasternal long axis, whereas left ventricular end diastolic diameter (LVEDd) and left ventricular end systolic diameter (LVEDs) as well as ejection fraction (EF) were measured using M-mode.

Atrial Electromechanical Coupling and tissue Doppler imaging assessments were performed using minimal optimal gain and adjusting spectral pulse Doppler signal filters until reaching Nyquist limit 0.15-0.20 m/s with transducer frequencies between 3.5-4 MHz in Tissue Doppler echocardiography. LV lateral mitral annulus, septal mitral annulus and RV tricuspid annulus TDI measurements were obtained using pulse Doppler in the Apical 4 chamber. Atrial electromechanical delay (PA), the time interval from the onset of P wave to the beginning of the late diastolic (A_m) wave on surface ECG was measured in milliseconds from the LV lateral mitral annulus (PA lateral), septal mitral annulus (PA septal) and RV tricuspid annulus (PA tricuspid) (10). Values were calculated by averaging the measurements from 3 sequential beats. The difference between lateral and tricuspid PA (lateral PA-tricuspid PA) was defined as inter-atrial electromechanical delay, and the difference between septal PA and tricuspid PA (septal PA - tricuspid PA) was defined as intra-atrial electromechanical delay.

In calculating the P wave in 12-lead resting ECG, the beginning of the first positive wave deflecting upwards from the isoelectric line or the beginning of the first negative wave deflecting downwards from the isoelectric line was determined as the beginning of the P wave. The point where the wave returned to the isoelectric line was determined as the end of the P wave. The longest (P_{max}) and shortest (P_{min}) P wave in any derivation of the twelve-derivation ECG were measured in milliseconds in order to calculate P wave dispersion (P_d) (P_d=P_{max}-P_{min}). All measurements were performed by two experienced investigators who did not have any information about the clinical condition of the patients. Among the variables measured by two investigators, only those with less than 5% difference were included in the study.

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences 11.0 (SPSS Inc.; Chicago, IL, USA) software. All continuous variables were described as mean±standard deviation, and categorical variables as percentage. Categorical variables were compared with the Chi-square test. The relationship between the two variables was analyzed using the Pearson Correlation analysis. Student t test was used in comparing continuous variables between the two groups. P<0.05 was accepted as statistically significant.

RESULTS

Age, gender, body weight, height, body mass index, systolic and diastolic pressures, LA diameter, LVEDd, LVEDs and LV EF were similar in both groups (p>0.05) (Table 1). Maximum P wave duration and P_d values were found to be significantly higher in patients with type 1 DM (p<0.001) (Table 1). The mean HbA_{1c} level was 8.1±0.7% and the mean duration of the disease was 3.0±1.2 years in patients with type 1 DM.

Isovolumetric relaxation times was higher in the type 1 DM group as compared to the control group (p<0.001) (Table 2). Mitral and tricuspid E, A wave velocities and DT were similar in both groups (p>0.05) (Table 2). Mitral E/A ratio was significantly lower in the type 1 DM group as compared to the control group (p=0.017) (Table 2).

LV septal S_m, E_m velocities and E_m/A_m ratio were significantly lower in the type 1 DM group as compared to the control group (p=0.047, p=0.003, p=0.001, respectively) (Table 2). A_m velocity and E/E_m ratio, on the other hand, were significantly higher in patients with type 1 DM in comparison to the control group (p=0.010, p=0.038, respectively) (Table 2). LV lateral E_m velocity and E_m/A_m ratio were significantly lower in the type 1 DM group as compared to the control group (p=0.009, p=0.012, respectively) (Table 2). A_m velocity

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

	Patients (n=30)	Control (n=30)	p
Age (Years)	9.6±2.4	8.40±3.6	0.120
Female (n, %)	18 (60)	16 (53.3)	0.602
Body mass index (kg/m^2)	16.3±2.2	15.9±3.7	0.615
Height (cm)	130.9±12.0	124.5±19.9	0.136
Systolic pressure (mmHg)	100.2±7.9	97.9±9.8	0.320
Diastolic pressure (mmHg)	61.5±4.7	63.3±5.6	0.200
Heart rate (beats/min)	90.75±13.0	87.1±16.7	0.352
P_{max} (ms)	106.2±12.0	91.3±8.0	<0.001
P_{min} (ms)	77.5±9.9	74.3±7.9	0.173
P_d (ms)	28.6±8.2	16.9±7.3	<0.001
HbA_{1c} (%)	8.1±0.7	–	–
Duration of disease (years)	3.0±1.2	–	–

LVEDd: left ventricular end diastolic diameter; LVESd: left ventricular end systolic diameter; P_{max}: maximum P–wave; P_{min}: minimum P–wave; P_d: P–wave dispersion

Table 2. Comparison of the variables measured using conventional and tissue Doppler imaging between patients and control groups

	Patients (n=30)	Control (n=30)	p
Conventional Doppler parameters			
Ejection fraction (%)	70.9±3.7	70.2±4.8	0.528
LVEDd (cm)	3.9±0.3	3.7±0.5	0.067
LVESd (cm)	2.4±0	2.3±0.3	0.087
Left atrial diameter (cm)	2.3±0.2	2.2±0.3	0.143
Mitral E velocity (m/s)	0.92±0.16	0.99±0.17	0.128
Mitral A velocity (m/s)	0.57±0.09	0.54±0.15	0.406
Mitral E/A	1.67±0.46	1.95±0.43	0.017
DT (ms)	160.4±14.5	154.7±14.2	0.132
IVRT (ms)	74.5±7.0	63.3±5.2	<0.001
Tricuspid E velocity (m/s)	0.70±0.12	0.65±0.10	0.128
Tricuspid A velocity (m/s)	0.46±0.09	0.44±0.10	0.512
Tricuspid E/A	1.45±0.18	1.46±0.29	0.816
Tissue Doppler parameters			
Septal LV			
S_m (m/s)	0.09±0.02	0.11±0.01	0.047
A_m (m/s)	0.07±0.01	0.06±0.01	0.010
E_m (m/s)	0.12±0.0	0.14±0.0	0.003
E_m/A_m	1.7±0.6	2.2±0.5	0.001
E/E_m	7.8±1.6	7.0±1.2	0.038
Lateral LV			
S_m (m/s)	0.10±0.02	0.08±0.02	0.001
A_m (m/s)	0.07±0.02	0.07±0.02	0.906
E_m (m/s)	0.13±0.04	0.15±0.03	0.009
E_m/A_m	1.8±0.6	2.1±0.4	0.012
E/E_m	7.3±1.7	6.5±1.6	0.068
RV lateral annulus			
S_m (m/s)	0.12±0.02	0.12±0.0	0.813
A_m (m/s)	0.10±0	0.11±0.0	0.125
E_m (m/s)	0.13±0.0	0.16±0.02	0.001
E_m/A_m	1.4±0.4	1.5±0.4	0.243

DT: deceleration time; IVRT: isovolumetric relaxation time; LV: left ventricle; S_m: septal systolic velocity; E_m: early diastolic velocity; A_m: late diastolic velocity; RV: right ventricle

Table 3. Atrial electromechanical interval measurement results obtained from tissue Doppler

	Patient (n=30)	Control (n=30)	p
PA lateral (ms)	69.8±4.8	53.2±4.7	<0.001
PA septum (ms)	46.3±2.3	41.1±2.9	<0.001
PA tricuspid (ms)	40.6±3.5	37.8±3.1	0.001
PA lateral-PA tricuspid (ms)[a]	29.1±6.1	15.4±5.5	<0.001
PA septum-PA tricuspid (ms)[b]	5.6±4.4	3.3±3.9	<0.001

Data was provided in mean ± standard deviation. PA; the time interval from the onset of P wave to the beginning of the late diastolic wave (A_m) on ECG measured by tissue Doppler. [a]inter-atrial electromechanical delay. [b]intra-atrial electromechanical delay

and E/E_m ratio were similar in both groups (p=0.906, p=0.068, respectively) (Table 2). In addition, RV lateral E_m velocity was significantly lower in the type 1 DM group as compared to the control group (p=0.001) (Table 2). S_m, A_m velocities and E_m/A_m ratio were similar in both groups (p>0.05) (Table 2).

Patients with type 1 DM were found to exhibit a significantly prolonged PA lateral, PA septum, PA tricuspid, inter-atrial (PA lateral-PA tricuspid) and intra-atrial conduction delay (PA septum-PA tricuspid) in comparison to the control group (p<0.001, p<0.001, p=0.001, p<0.001, p<0.001, respectively) (Table 3).

No correlation was found between the duration of disease and HbA1c, atrial conduction delay (r=0.003, p=0.493; r=-0.092, p=0.315, respectively).

DISCUSSION

It is known that type 1 DM constitutes a risk of heart disease. In addition, DM increases the risk of heart failure by directly affecting the heart without the presence of coronary heart disease and also causes functional and structural changes in individuals with impaired glucose tolerance without the presence of microvascular disease (11-13). Cardiac dynamic changes (increased heart rate, arrhythmia etc.) due to autonomic nervous system dysfunction, systolic and diastolic dysfunction in the heart, and cardiomyopathy can manifest in patients with DM (14, 15). Patients with DM can frequently have heart rhythm disorders with advancing age. The most common of such disorders is atrial fibrillation (AF) (16). Previous studies showed that conditions which cause left atrial enlargement lead to inter-atrial conduction delay (4, 5). Filtered P wave analysis is useful in detecting atrial electrophysiological abnormalities in paroxysmal AF. Atrial electromechanical delay can be measured by various methods (17, 18). Today, it is frequently measured by calculating the time interval between the onset of P wave on ECG and the onset of A_m wave in both ventricles on TDI in milliseconds while performing TTE. Studies have shown that patients with paroxysmal AF and mitral stenosis also had intra- and inter-atrial conduction delay (4, 5). There was intra- and inter-atrial conduction delay in our study despite the normal size of the left atrium.

The decrease in mitral or tricuspid early systolic A velocity correlated with reduced atrial contraction. Both parameters are affected by many cardiac conditions such as heart rate, preload and afterload (19). Previous studies have reported different results regarding left ventricular systolic and diastolic function in patients with DM; i.e. some of these studies reported systolic dysfunction whereas others reported diastolic dysfunction (20-23). However, impaired glucose tolerance leads to systolic and diastolic dysfunction in the heart also in the early phase of DM (13, 21, 24). Left ventricular systolic dysfunction may improve by itself if serum glucose concentrations return to normal levels (11). In our study, although ventricular systolic functions were normal in patients with type 1 DM, some parameters of the ventricular diastolic function were moderately impaired. The reason why our patients exhibited diastolic dysfunction in both ventricles and especially in the right ventricle, although mean duration of the disease was short, can be attributed to high HbA_{1c} levels.

Intra- and inter-atrial conduction time can be determined by calculating P wave dispersion and maximum P wave duration in twelve-lead ECG. It is known that non-homogenous sinus impulses constitute a risk factor for AF. It was reported that inter-atrial electromechanical delay measured using TDI has a correlation with P wave dispersion (10, 22). Increased atrial heterogenous electrical activity facilitates developing atrial fibrillation/atrial flutter by causing atrial reentry. Pd and Pmax have been used to predict the risk of AF development in many studies (3-5, 25). It is known that an increase in the left atrial diameter is significant for AF development. However, studies demonstrated that Pd increased in patients with AF, although the atrial diameter was normal. Our study also revealed that maximum P wave duration and P_d were significantly higher in patients with Type 1 DM, although LA diameter was normal. Consequently, patients with type 1 DM have higher atrial conduction delay in comparison to healthy individuals and this may indicate an increased risk of developing atrial rhythm disturbance in patients with type 1 DM.

Our study has more than one limitation. The limiting factors of this study include the low number of cases in the study, short duration of follow-up, lack of LV posterior wall thickness measurements and lack of LA mechanical measurements.

CONCLUSION

In our study, it was seen that there was atrial electromechanical delay, i.e. left atrium was affected in patients with type 1 DM. In addition, we found in tissue Doppler imaging that systolic and diastolic functions of the left ventricle were sub-clinically affected in patients with type 1 DM.

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: Written informed consent was obtained from patients and healthy children and their parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.S., A.İ., O.B., D.A.Ş., M.Ker.; Design – M.S., A.İ., D.A.Ş.; Supervision – M.Ker., O.B., M.S.; Materials – M.Kes., A.İ., D.A.Ş.; Data Collection and/or Processing – A.İ., D.A.Ş., O.B., M.Ker., M.Kı.; Analysis and/or Interpretation – M.Ker., A.İ., O.B., D.A.Ş.; Literature Search – D.A.Ş., A.İ.; Writing Manuscript – D.A.Ş., A.İ. Critical Review – O.B., M.Ker., M.Kı., M.Kes.

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

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Original Research

Relationship Between Renal Resistive Index and Increased Renal Cortical Stiffness in Patients with Preserved Renal Function

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ABSTRACT

Objective: We aimed to investigate the relationship between cortical stiffness (CS) determined by shear wave elastography (SWE) and conventional ultrasonography (USG) parameters, and identify the determining parameters that increased CS.

Methods: In this study, 229 patients who underwent renal USG were included. In addition to conventional renal USG, SWE was performed. Patients were divided into two groups: with increased CS and without increased CS.

Results: The median CS value of the patients included in the study was 4.92 kPa. The increased CS value was taken as the limit value of 5.0 kPa. The age, creatinine and estimated glomerular filtration rate levels, and presence of diabetes and hypertension were significantly higher in the increased CS group ($p<0.05$). It was found that the cortical echogenicity increase (stage I-II), renal resistance index (RRI), and acceleration time values were significantly higher in patients with increased CS ($p<0.05$). When logistic regression analysis was performed to identify patients with increased CS, we found that RRI, diabetes presence, and cortical echogenicity stages I and II independently predicted an increase in CS ($p<0.05$). According to this analysis, RRI (every-0.1), diabetes, and cortical echogenicity stages I and II increased the risk of increased CS by 2.3 times, 14%, 10.5% and 18.2%, respectively. In ROC analysis for RRI, the area under the curve was 0.719. When the cut-off value for RRI was taken as 0.70, it was found to be 71.1% sensitive and 64.3% specific for increased CS.

Conclusion: The increase in renal echogenicity and RRI obtained by conventional USG studies independently identifies patients with increased CS.

Keywords: Conventional ultrasonography, cortical stiffness, renal resistive index

INTRODUCTION

Conventional renal ultrasonography (USG) can be used to detect kidney size, cortical thickness, and parenchymal echogenicity. It also can reveal indicators of chronic morphologic changes that happen in many renal diseases. However, these changes are not quantitative and clear. Atrophic changes cannot be shown with conventional renal USG in patients with stage 3-4 chronic kidney disease (CKD) with diabetes mellitus (DM), which is the most common reason for CKD. For this reason, conventional renal USG is not informative in determining the progression and stages of CKD (1-3). Shear wave elastography (SWE) is a non-invasive, stable, and cost-effective USG study that has been used in recent years to evaluate tissue elasticity and cortical stiffness (CS) (4-6). The CS evaluation with SWE has been shown to be a simple and practical technique that can be used in the detection of chronic morphological changes in patients with renal transplant, in renal tumors, and in CKD due to DM and in CKD grading (7-10). The SWE is used to screen patients for many organ pathologies in addition to kidneys. These include patients with liver, breast, prostate, pancreas, testicle, thyroid diseases, and renal transplant. However, the SWE examination is not available on every USG device, nor can any radiology specialist do it. In subgroup analyses with patients with renal transplant, a correlation between some conventional USG parameters and CS was reported in literature (10-13). As much as we investigated, no study has evaluated the relationship between CS value determined by SWE and conventional renal USG parameters in patients with preserved renal function who planned to undergo a renal USG screening.

In this study, we aimed to investigate the relation between conventional USG parameters and CS obtained by SWE, and determine the parameters that show an increased CS.

METHODS

Study Protocol and Study Population

Patients who underwent renal USG between September 2017 and May 2018 in University of Health Sciences, Adana Health Practice and Research Center, Radiology Clinic were screened, and 229 patients (173 males, 56 females; and mean age 62.1±12.1

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years) were included in the study. In addition to conventional renal USG (B-mode and Doppler) examinations, SWE examination was performed. The patients who had undergone renal USG examination, those who had estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, or patients who had proteinuria >30 mg/L were excluded from this study. Patients with renal artery stenosis and post-renal renal failure, nephrectomy, malignancy, systemic, or urinary tract infections during renal USG, non-detectable CS, and non-volunteers were excluded. The study was conducted according to the recommendations of the Declaration of Helsinki about biomedical research involving human subjects, and the protocol was approved by the institutional ethics committee. All forms of voluntary consent for all patients were explained in detail, and patients were included in the study after obtaining written consent.

After detailed physical examination of all patients, risk factors were questioned. Age, gender, hypertension (HT), hyperlipidemia, smoking, and DM presence were studied as demographic data of the patients included in the study. Creatinine and blood urea nitrogen levels were measured in all patients. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Patients were measured for height and weight, and their body mass index (BMI) were calculated.

Renal USG

All patients underwent renal USG screening using high-resolution USG device with 1-5 MHz high-resolution convex probe (Philips EPIQ 7, Philips Healthcare, Bothell, Washington, USA). Ultrasound scanner setting was made useful for every patient for all B-mode USG examination (gain [55-75 dB]; penetration depth [6-16 cm]; dynamics range [50-60] and zoom range [0.8-2.0]). The USG examinations were performed after minimum 6 h of fasting, and after minimum 20 min of rest. B-mode USG evaluation was first performed on the gray scale, and then quantitative Doppler parameters were obtained. Kidney sizes, cortical thickness, and parenchyma echogenicity were assessed on gray scale. Kidney length was measured in the coronal plane from its upper pole to the lower pole. Renal width was measured from middle pole, and it was recorded as the distance between renal hilum and renal capsule. Cortical thickness was recorded as the distance from the medial section of the renal medullary pyramid base to the renal capsule. Doppler USG was measured with peak systolic velocity (PSV), end diastolic velocity (EDV), and acceleration time (AT) was measured with Doppler USG in Doppler angle 30°-60° in the right and left common renal and interlobular arteries (Figure 1). After the PSV and EDV values were taken, spectral waveform was manually drawn on the device, and the renal resistive index (RRI) value was automatically obtained according to the PSV-EDV/PSV formula. The renal pulsatility index (RPI) was calculated based on the PSV-EDV/average flow rate formula on the spectral waveform. The AT was calculated as the time from the point where the systolic wave began to increase to the first peak point. All measurements were performed three times from the right and left kidney main and interlobular arteries. The arithmetic mean values of RRI, RPI, and AT values obtained from the right and left kidneys were recorded.

The SWE evaluation was performed using 5-1 convex abdominal probe, elastography point quantification (ElastPQ) technique. All measurements were performed as previously described (7). Patients were examined in left and right lateral decubitus position for renal USG. During renal USG, the probe was compressed as lightly as possible, and was placed in a stable position. The patient was asked not to breathe for a few seconds to minimize the movement of the kidney with respiration. The measurement was calculated by placing the region of interest (ROI) on the target (Figures 2 and 3) on the conventional USG image of the renal USG, after the target region was determined. The ROI was placed perpendicular to a vascular-free or cyst-free zone in the renal cortex. The main axis of the ROI was adjusted parallel to the axis of the kidney pyramid (perpendicular to the surface of the kidney). In our study, the ROI target distance was maximum

Figure 1. Renal resistive index measurement by Doppler ultrasonography: Increased RRI in 0.77 is displayed in the lateral right corner

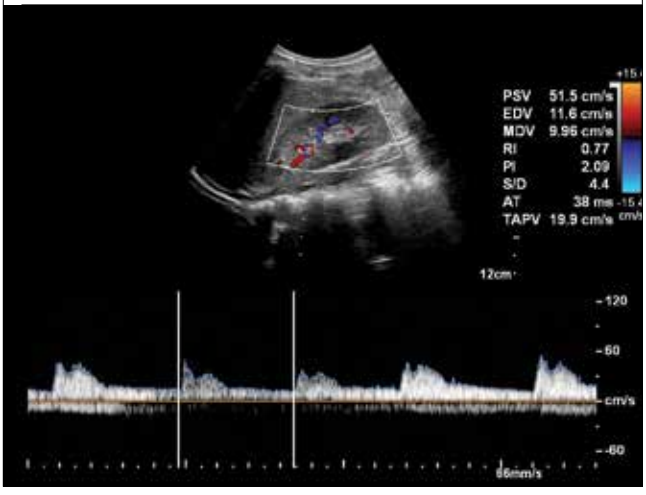


Figure 2. Cortical stiffness measurement by shear wave elastography: Normal shear wave velocity in 2.40±0.86 kPa is displayed in the lower left corner and grade 0 or normal renal parenchymal echogenicity

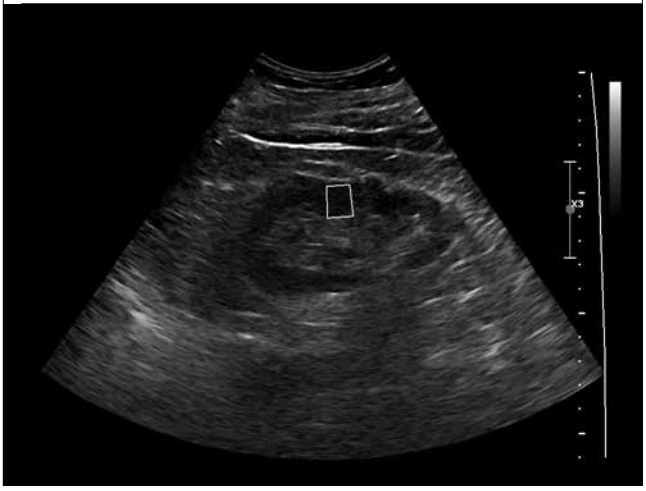


Figure 3. Cortical stiffness measurement by shear wave elastography: Increased shear wave velocity in 15.11±8.11 kPa is displayed in the lower left corner and grade II renal parenchymal echogenicity

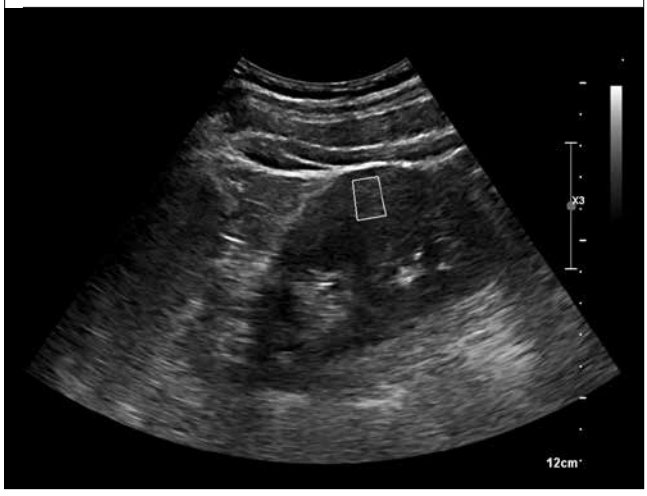
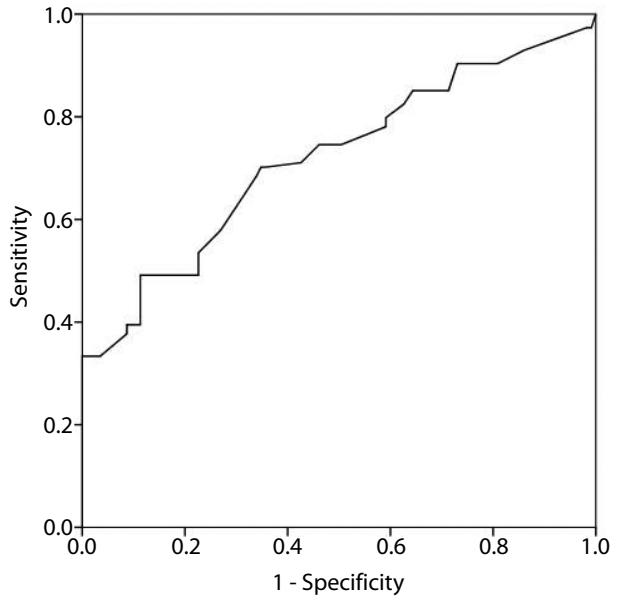


Figure 4. The ROC curve analysis of renal resistive index for predicting increased cortical stiffness



8 cm and the ROI fixed box size was 1 cm-0.5 cm. The compression applied was minimized as much as possible during imaging to avoid mechanical pressure to the kidney. Then, the same examination procedure was repeated for the contralateral kidney. In each case, six valid measurements were obtained for each kidney, and the mean value was calculated. If the measurement reliability is low, a result of 0.00 kPa will be displayed. The result is expressed in kPa value. Subjects were evaluated by a single well-experienced radiology specialist for conventional, Doppler, and SWE examinations. The specialist had more than five years of experience in the SWE studies and had performed at least 500 SWE procedures in a year.

Statistical Analysis

All analyses were performed using the IBM Statistical Package for the Social Sciences 22.0 (IBM SPSS Corp.; Armonk, NY, USA) statistical software package. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The continuous variables in the group were expressed as mean±standard deviation. Categorical variables are given in numbers and percentages. Student's t test was used to compare continuous variables between groups. Chi-square (χ^2) test was used to compare categorical variables. For univariate correlation analysis, Pearson correlation analysis was used. Logistic regression analysis was performed to determine the indices independent of the increased CS-related parameters detected in univariate analyses. An ROC curve analysis was performed to re-evaluate the countable parameters that independently determine the patients with elevated CS, and to determine the limit value of these markers. The value of the area under the curve was used as the measure of the accuracy of the test. $P<0.05$ was accepted as statistically significant.

RESULTS

The median and mean CS values of the patients included in the study were 4.92 kPa and 5.33±2.1 kPa, respectively. The increased CS value was taken as the limit value of 5.0 kPa. Patients were divided into two groups: patients with increased CS and without increased CS. All parameters were compared between the two groups, and parameters determining the patient group with increased CS were found.

Demographic Characteristics of Patients with and without Increased CS

When the demographic findings were compared between patients with and without increased CS, the age, creatinine, and eGFR levels as well as the frequency of DM and HT were significantly higher in patients with increased CS (Table 1).

Conventional Renal USG Findings of Patients with and Without Increased CS

When conventional renal USG findings were compared between patients with and without increased CS, among B-mod USG parameters, only cortical echogenity was found to be increased in patients with increased CS (Table 2). In the patient group with increased CS, the RRI and AT values determined with Doppler USG were found to be significantly higher (Table 2).

Identification of Patients with Increased CS

To identify patients with increased CS, when parameters found to be significant in univariate analysis were evaluated with logistic regression analysis, RRI, DM presence, and stage I and II cortical echogenicity independently defines an increased CS risk. According to this analysis, RRI (every 0.1), presence of DM, and stage I and II cortical echogenicity increased the risk of increased CS by 2.3 times, 14%, 10.5%, and 18.2%, respectively (Table 3).

ROC Curve Analysis for the Identification of Patients with Increased CS

When ROC analysis was performed to determine patients with

Table 1. Baseline characteristics and renal functions in patients with increased and normal cortical stiffness

	Increased CS n=119	Normal CS n=110	p
Age (years)	64.4±10.9	59.4±12.7	0.002
Gender (male)	92	81	0.005
Office systolic BP (mmHg)	126.9±9.2	126.9±12.2	0.969
Office diastolic BP (mmHg)	85.5±7.1	83.4±9.5	0.065
Heart rate (beat/min)	77.3±12.4	77.8±10.4	0.719
Weight (kg)	83.8±6.7	81.7±7.6	0.022
Height (cm)	169.1±5.2	167.1±7.6	0.021
Body mass index (kg/m^2)	29.4±2.3	29.3±2.4	0.782
Smoking, n (%)	38 (33.3%)	32 (27.8%)	0.223
Hypertension, n (%)	60 (52.6%)	36 (31.3%)	0.001
Diabetes mellitus, n (%)	49 (43.0%)	11 (9.6%)	<0.001
Hypercholesterolemia, n (%)	25 (21.9%)	16 (13.9%)	0.079
Blood urea nitrogen (mg/dL)	37.1±9.7	36.9±10.3	0.610
Creatinine (mg/dL)	0.91±0.21	0.81±0.16	0.020
eGFR (mL/min/1.73 m^2)	108±22	115±24	0.013

BP: blood pressure; CS: cortical stiffness

Table 2. Conventional renal ultrasound and shear wave elastography imaging parameters

	Increased CS n=114	Normal CS n=115	p
Renal resistive index	0.76±0.08	0.72±0.05	<0.001
Renal pulsatility index	1.94±0.70	1.83±0.49	0.178
Renal AT (m/s)	105.7±44.4	92.4±37.8	0.015
Kidney length (mm)	102.3±9.3	100.9±8.8	0.245
Kidney width (mm)	49.6±6.5	48.9±6.9	0.528
Cortical thickness (mm)	12.1±1.9	11.7±2.0	0.092
Cortical echogenicity Grade 0-I-II, n	70-36-8	90-24-1	0.003
Cortical stiffness (kPa)	7.42±2.11	3.95±1.01	<0.001

AT: acceleration time; CS: cortical stiffness

increased CS of RRI values, the area under the ROC curve was 0.719, which was statistically significant (p<0.001) (Table 4). The ROC curve for RRI is shown in Figure 4. When the cut-off value for RRI was taken as 0.70, it was found to be 71.1% sensitive and 64.3% specific for increased CS (Table 4).

Table 3. According to multivariate regression analysis, independent risk factors for occurrence of increased cortical stiffness

	Odds ratio	95% Confidence interval	p
Renal resistive index (each 0.1)	2.323	1.442-3.758	<0.001
Diabetes mellitus (presence)	0.140	0.068-0.289	<0.001
Cortical echogenicity (Grade I)	0.105	0.012-0.920	0.042
Cortical echogenicity (Grade II)	0.182	0.020-1.658	0.037

Table 4. ROC curve analysis of renal resistive index for predicting increased cortical stiffness

Variable	AUROC Curve	p	Cut-off	Sensitivity	Specificity
Renal resistive index	0.719 (0.653-0.785)	<0.001	0.70	71.1%	64.3%

DISCUSSION

The most important finding of our study is that the CS values obtained by SWE examination in patients with preserved renal function is independently correlated with an increase in conventional USG parameters of RRI and cortical echogenity. It has been found that when the limit value for RRI is taken as 0.70, it independently determines the state of increased CS. Therefore, RRI can be used as an objective parameter in renal CS determination in patients with preserved renal function.

The SWE is a newly developed USG technique that can quantitatively measure tissue stiffness without an invasive procedure. It has been shown that renal fibrosis in patients with CKD increases renal CS, which can be measured by SWE (12-15). In addition to renal elasticity, SWE is used screen patients for many organ pathologies in addition to kidneys. These are patients with liver, breast, prostate, pancreas, testicle, and thyroid diseases, and patients with renal transplant. Studies in patients with renal transplant show the severity of renal histologic changes more clearly in the SWE examinations than B-mode USG (13, 16, 17). Similar findings have been shown in studies performed on native kidneys (18). According to the result of these renal elastography studies, the CS value determined by SWE can be used as a renal parenchymal disease and renal fibrosis indicator in clinical practice. In some studies comparing CS and demographic parameters, there was no significant relationship between CS and age and gender (7, 10, 19). However, another study by Goya et al. (6) found a positive relationship between CS and age in healthy controls (6). In the same study, no significant relationship was observed between CS and gender in patients with CKD and in healthy controls. Similar to the study conducted by Goya et al. (6), in our study, it was found that patients with increased CS were older, but gender is

not related with an increase in CS. In addition, it was found that DM-induced CKD was positively correlated with CS and proteinuria, and negatively correlated with eGFR (7). However, another study did not find a significant association between CS and eGFR in patients with renal transplant (10). In a study, it was reported that there is a close relationship between mean CS value and eGFR and creatinine value (6). In our study, we found that both creatinine level and eGFR were higher in patients with increased CS, but neither of these two parameters are associated with increased CS independently.

With conventional B-mode USG, non-invasive knowledge of renal size and position, renal mass and obstructive uropathy can be obtained, and is still the most reliable examination of screening renal diameter and morphology. The CS values were found to be unrelated to renal length and width in patients with diabetic CKD (7). Furthermore, in the same study, no relationship was observed between CS and renal cortical thickness in the healthy control group, whereas CS and renal cortical thickness were negatively correlated in patients with DM-related CKD (7). In another study conducted on a normal patient group, no relationship was reported between renal length, width, cortical and parenchymal thickness obtained by conventional renal USG, and CS obtained by SWE (19). In our study, kidney sizes were similar in patients with normal and increased CS.

Renal parenchymal changes secondary to systemic diseases, such as DM and HT, increase renal cortex echogenicity, and this finding may provide us with an idea of renal functional impairment (20). This finding, however, does not demonstrate specificity while detecting renal involvement with limited sensitivity (21). In addition, conventional B-mode USG does not provide sufficient information on the degree of renal function abnormality (22). Studies on conventional renal USG have shown that the increase in renal echogenicity is more closely related to renal histologic parameters such as glomerular sclerosis, tubular atrophy, interstitial fibrosis, and interstitial inflammation than renal length and width, cortical or parenchymal thickness (23). However, its power to detect these histopathologic changes of renal echogenicity is very weak. Moreover, the exact cause of increased echogenicity is not clearly predicted to be fibrosis or increased inflammation, and the pathogenesis of parenchymal disease has not been clearly elucidated with increased echogenicity (24). Recently, the SWE method has been developed to detect renal parenchymal diseases and CS non-invasively. In our study, we found that the increase in renal cortical echogenicity was greater in patients with increased CS. Both stage 1 and stage 2 echogenicity increase determines the likelihood of increased CS independently and increases that likelihood 10.5% and 18.2% respectively.

Doppler USG provides information about intra-renal hemodynamic changes resulting from structural and/or functional disorders. RRI detected with Doppler USG is an objective indicator of renal tissue changing that occurs from renal vascular resistance, compliance, arteriolosclerosis, and interstitial fibrosis in both native and transplanted kidneys (25-27). RRI is used as a prognostic and diagnostic parameter for many vascular and renal diseases. An increased RRI that >0.8 in CKD with or without DM is an indicator for worsening kidney functions (28). In patients with renal artery stenosis, RRI>0.73 in the other kidney is an indication that it is more difficult to revert renal function impairment (29). An increased RRI (>0.70) in patients with primary HT is related with worse renal and cardiovascular complications (30). In addition, increased RRI is an indicator for renal transplant success and rejection. Because RRI is a hemodynamic parameter, the relationship between RRI and renal parenchymal diseases is not clearly known. The increased RRI limit value of 0.70, which we use clinically in relation to our study results, is closely related to the increased CS obtained by SWE. Our study suggests that RRI>0.70 may be used as a measure of increased renal parenchymal stiffness as well as increased renal vascular resistance. As we researched, a few studies investigated the relation between CS and RRI in patients with renal transplant (10-13). In a study involving patients with transplanted kidney, it was shown that the renal CS detected by SWE was significantly and positively correlated with the RRI and RPI determined by Doppler USG (10). In another study of patients with renal transplant, both CS and RRI were found to be associated with renal fibrosis separately, but there was no significant association between CS and RRI (13). Another study of 40 patients with renal transplant in the near future found that the RRI from the main, segmental, and interlobar arteries was closely related to CS in the early post-transplant period (11). In this study conducted by Wang et al. (11) reported that the CS increase caused by fibrosis in early stages of kidney transplantation similarly increases RRI with hemodynamic changes. With SWE, CS and related parameters have been compared in end-stage renal patients, such as renal transplant or diabetic nephropathy, and no studies have been conducted on the clinical features of patients with renal USG in everyday practice. We have found a close and independent relationship between RRI and renal CS obtained in routine renal USG examination for patients with HT, DM, coronary artery disease, who do not have kidney function impairment. As we researched, we could not find another study that shows a relationship between CS and RRI in patients with native kidney and patients that not have CKD. Clinical and prognostic significance of RRI>0.70 has been shown in previous studies and in addition to previous studies it has been shown in our study that RRI>0.70 is also associated with increased renal CS.

Histological examination with renal biopsy reveals the ongoing fibrosis clearly, but it cannot be used because of being an invasive examination. For this reason, non-invasive examinations have been preferred. Detection of microalbuminuria is a strong predictor of DM-associated nephropathy, and the urine microalbuminuria is important for the earliest diagnosis of CKD development (31). However, in addition to nephropathy, microalbuminuria is affected by DM, HT, exercise, and blood glucose levels, and it may vary by 40%-50% during the day (32). Because of that, a more objective and stable parameter is needed for the early diagnosis of patients with CKD. The SWE is a promising and non-invasive study that shows the renal elasticity or tissue stiffness objectively, and can be used for this purpose. The CS increase in nephropathy patients compared to the control group in our study may be associated with excessive hyper filtration at the nephron levels or fibrosis that occurs at cellular and mild in-

terstitial level. For this reason, increased CS may be shown with a non-invasive examination, allowing closer follow-up and more aggressive treatment in this patient group.

Our study has several important limitations. Although the number of patients was relatively adequate, more patients could get a more meaningful result. Another limitation was that the study was not conducted in a specific group of patients, and therefore no control group was formed. Patients who came to the Radiology Clinic with routine USG examination were included in this study. In addition, our study did not include patients with known renal disease and patients with eGFR<60 mL/min/1.73m^2. We cannot use our data in this group of patients. In our study, increased RRI was indirectly associated with renal CS. Increased CS due to renal parenchymal diseases as well as renal vascular and intra-renal hemodynamic parameters may be causing an RRI increase. To be able to try something clear in this regard, it is necessary to carry out studies comparing the histological changes obtained with the renal biopsy result and the RRI measurement. Another important limitation of our study is this is not a follow-up study. Especially if patients with high renal CS value were followed up in terms of nephropathy development, they could give information about the relation of high CS value to development of nephropathy in the future.

CONCLUSION

The increase in renal echogenicity and RRI obtained by conventional B-mode and Doppler USG studies with the SWE method independently identifies patients with increased CS. The presence of stage 2 renal echogenicity and RRI>0.70 found with conventional USG was considered to be an increased parameter of renal CS in cases where SWE could not be performed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Adana City Health Practice and Research Center (Decision Date: 2018).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.S.K.; Design - A.S.K.; Supervision - H.E.S.; Writing Manuscript - A.S.K., H.E.S.; Critical Review - H.E.S.

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

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Case Report

Use of Eltrombopag in Patients with Platelet Engraftment Failure Following Second Allogeneic Peripheral Stem Cell Transplantation

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ABSTRACT

Thrombocytopenia after peripheral stem cell transplantation (PSCT) is associated with morbidity and mortality. Eltrombopag, a thrombopoietin receptor agonist, is successfully used primarily in the treatment of chronic idiopathic thrombocytopenic purpura and other thrombocytopenias associated with aplastic anemia and myelodysplastic syndrome. Recently, the use of eltrombopag in the treatment of thrombocytopenia after allogeneic PSCT has shown promising results. The use of eltrombopag in three patients with hematologic malignancy who experienced graft failure after the first PSCT and developed platelet engraftment failure following the second bone marrow (BM) transplantation was presented retrospectively. The patients included two males and one female, with the mean age of 52 (45–57) years. The diagnoses were acute myeloid leukemia, non-hodgkin lymphoma (NHL), acute lymphocytic leukemia. All patients underwent allogeneic PSCT with the myeloablative regimen. Platelet engraftment failure was detected during the follow-up of the patients. Acute grade 3 skin graft versus host disease developed in the patient with NHL. Mycophenolate-mofetil, cyclosporin-A, steroid-based immunosuppression therapy was given. Graft versus host disease completely responded to this treatment in the first week of treatment. However, thrombocytopenia persisted. None of the patients had any viral infection or relapse. BM biopsies of patients were hypocellular, and the number of megakaryocytes were found to be decreased. Eltrombopag was initiated in three patients after 110 (60–144) days of transplantation. Responses were obtained in all of the patients; the platelet value was ≥30 × 10^3/μL (30.000–247.000). The mean duration of response was 27 (20–35) days. Although engraftment failure is not a routine indication of the eltrombopag, it can be used safely and effectively in patients with platelet engraftment failure after PSCT.

Keywords: Allogeneic peripheral stem cell transplantation, eltrombopag, prolonged thrombocytopenia

INTRODUCTION

Thrombocytopenia after allogeneic peripheral stem cell transplantation is a very common complication (1). It may develop for several reasons. Some of these reasons include; reduced platelet production due to graft failure, viral infections, drug side effects and increased breakdown of platelets (1, 2). The treatment of thrombocytopenia is very important as thrombocytopenia may extend the duration of hospital stay, lead to transfusion dependence and fatal hemorrhage.

Rituximab, corticosteroids and intravenous immunoglobulin treatments have been used in immune-mediated thrombocytopenia (3). Donor leukocyte infusions and immunosuppressive agents can be used in the treatment of poor graft function (1). Yet, there is no standard treatment approach for the treatment of thrombocytopenia that develops after allogeneic peripheral stem cell transplantation (APSCT).

Eltrombopag and romiplostim are thrombopoietin receptor (TPO-R) agonists used for idiopathic thrombocytopenic purpura (4). There have been promising publications regarding their use in post-APSCT thrombocytopenia recently (5-7).

CASE PRESENTATIONS

Case 1: A 52-year old male patient presented to our clinic with weight loss and lethargy complaints and his examination showed: leukocyte: 43x10^3 /μL (3.39- 8.86), hemoglobin: 6.7 g/dL, platelet: 143x10^3/μL (158-374). Bone marrow aspiration, biopsy and flow cytometry were performed due to the pre-diagnosis of acute leukemia and the patient was then diagnosed with B-cell acute lymphoblastic leukemia (B-ALL). Conventional cytogenetics at the time of diagnosis was: 46; XY, normal karyotype. With the diagnosis of moderate risk B-ALL, Hoelzer Phase-I (Prednisolone, Daunorubicin, Vincristine, L-Asparaginase) was

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administered as remission induction treatment, Hoelzer Phase-II (Cyclophosphamide, Cytarabine, Methotrexate, 6-Mercaptopurine, central nervous system irradiation) was administered as consolidation treatment and Hoelzer Phase-III (Cytarabine, mitoxantrone) chemotherapy protocol was applied. After complete remission, transplantation was performed from 65-year old fully HLA compatible sister donor with 7.1x10/kg CD34+ peripheral stem cell infusion using Bu12,8Flu180ATGf10 (Busulfan, Fludarabin, Anti-Thymocyte globulin) preparation regimen. Neutrophil engraftment was achieved on day 19 and platelet engraftment on day 15. On post-transplant day 50, donor leukocyte infusion (DLI) was carried out. On post-transplant day 60: leukocyte was 870 (neutrophil: 20) /µL, hemoglobin: 8 g/dL, platelet: $8x10^3$/µL. The patient with hypocellular bone marrow was assessed as secondary engraftment failure. The second transplantation was performed with 6.3x10/kg CD34+ peripheral stem cell (PSC) infusion from the same donor using ATGf10 preparation regimen. Neutrophil engraftment (neutrophil: $2.1x10^3$/µL, hemoglobin: 11.3 g/dL) was achieved on day 21. On day 40 after the second transplantation, platelet level was around $9x10^3$/µL and the patient still had thrombocytopenia. The patient received nearly 2-3 units of platelet transfusion weekly. Patient did not respond despite the administration of methylprednisolone and intravenous immunoglobulin and developed mucosal bleeding. It was assumed that the patient, who didn't have any signs of GVHD, viral infections or relapse on day 60 and continued to exhibit thrombocytopenia, had isolated platelet engraftment failure. The patient was started on a weekly dose of 1x50 mg eltrombopag and the dose was increased to 2x50 mg after 14 days. Platelet level on day 7 during 100 mg/day eltrombopag treatment was $23x10^3$/µL. Platelet level was $>100x10^3$/µL on day 120 of eltrombopag treatment and increased up to the maximum level of $247x10^3$/µL. Chimerism results before and after eltrombopag treatment did not show any changes.

Case 2: A fifty seven-year old female patient presented to our clinic with malaise and dizziness complaints. Her examination showed leukocyte: $113x10^3$/µL (3.39- 8.86), hemoglobin: 6.8 g/dL, platelet: $21x10^3$/µL (158-374). Bone marrow aspiration, biopsy and flow cytometry were performed due to the pre-diagnosis of acute leukemia and the patient was then diagnosed with acute myeloid leukemia (AML). Conventional cytogenetics at the time of diagnosis was: 46; XY, normal karyotype, t(8;21) mutation was FLT-3/ITD negative. The patient was administered 3+7 (Idarubicin + Cytarabine) remission induction treatment and IDAC (Idarubicin + Cytarabine) chemotherapy as consolidation treatment due to moderate-risk AML. The patient had complete remission. Transplantation was performed from the 45-year old fully HLA compatible sister donor with 6.5x10/kg CD34+ PSC infusion using Bu12,8Flu180ATG10 (Busulfan, Fludarabin, Anti-Thymocyte globulin) preparation regimen. On post-transplant day 60, the patient had no neutrophil and platelet engraftment. The patient with primary engraftment failure received the second transplant from the same donor with 6.5x10/kg CD34+ PSC infusion using ATGf10 preparation regimen. Neutrophil engraftment after the transplantation (neutrophil: $1.9x10^3$/µL, hemoglobin: 10.8 g/dL) was achieved on day 16. On the other hand, platelet engraftment (platelet: $7x10^3$/µL) did not occur. The patient received 1-2 units of platelet transfusion weekly and bone marrow aspiration and biopsy performed on day 60 showed hypocellular bone marrow. The patient, who did not have any signs of GVHD, viral infections or relapse, was started on high-dose Eltrombopag (2x50 mg) treatment due to massive hematuria secondary to thrombocytopenia on post-transplant day 75. The dose was increased to 2x75 mg/day after receiving no response 2 weeks after the initialization of treatment. On day 71 of eltrombopag treatment and day 6 of 150 mg/day dose, platelet level increased to $26x10^3$/µL and to a maximum level of $43x10^3$/µL. The patient still receives 1x75 mg/day eltrombopag treatment.

Case 3: A 45 year-old male patient was administered 4 courses of CHOP (cyclophosphamide, adriamycin, vincristine, methyl prednisolone) treatment after being diagnosed with peripheral T cell lymphoma. The patient had primary refractory disease and was administered Hyper CVAD AB (Cyclophosphamide, Vincristine, dexamethasone, methotrexate, ARA-C) rescue therapy. Stem cell mobilization was performed using Hyper CVAD-2B. 8.5x10/kg CD34+ peripheral stem cells were collected. High-risk patient underwent autologous peripheral stem cell transplantation with 8.5x10/kg CD34+ PSC infusion using BEAM (carmustine, etoposide, cytarabine, melphalan) preparation regimen in the first complete remission. Engraftment was achieved with $1.1x10^3$/µL neutrophils on post-transplant day 12. On day 60 after the transplantation, the platelet level was still low at $11x10^3$/µL. Bone marrow biopsy revealed markedly hypocellular bone marrow and fewer megakaryocytes, therefore the patient was considered to have aplastic anemia. Transplantation was performed from the 50 year-old fully HLA compatible brother donor with 9x10/kg CD34+ PSC infusion using Bu6Fu180ATG10 preparation regimen. Neutrophil (neutrophil: $1.5x10^3$/µL, hemoglobin: 11.8 g/dL) engraftment was achieved on post-transplant day 18. However, the patient did not have platelet engraftment and developed acute grade-3 skin GVHD. Patient exhibited full response to immunosuppression therapy with mycophenolate-mofetil, cyclosporin-A and steroid in one week. Bone marrow biopsy of the patient with platelet engraftment failure revealed hypocellular bone marrow and few megakaryocytes on post-transplant day 100. The patient was started on 1x50 mg eltrombopag on post-transplant day 126. The dose was increased (2x50 mg) due to no response. Response was observed on day 35 of treatment. The patient's platelet level increased to $32x10^3$/µL.

DISCUSSION

Persistent thrombocytopenia after PSCT is a common problem and an important cause of morbidity and mortality (8-10). Prolonged isolated thrombocytopenia is defined as recovery of other cell counts with continuous dependence on platelet transfusions for greater than 3 months after PSCT. It develops in approximately 2.6-37% of the patients who undergo PSCT and is strongly associated with transplant-related mortality and total survival (1, 11-13). For instance, it is generally accepted as a sign of engraftment failure and disease recurrence in autologous transplants (1).

Thrombocytopenia formation is usually multifactorial. Despite the fact that the main causes of prolonged thrombocytopenia after allogeneic transplantation are reduced platelet production

and accelerated peripheral degradation, the exact mechanism is still unclear (1, 11, 13).

There are publications in literature that state donor type, existence and degree of GVHD, CMV infection, number of transfused CD34+ cells and such factors are the predictors of prolonged post-transplant thrombocytopenia (1). Yamazaki et al. (14) reported that TPO status in patients with prolonged thrombocytopenia after APSCT had a similar pattern with aplastic anemia and this played an important role in impaired platelet production. Bielski et al. (12) reported that the bone marrow biopsy performed on 12 patients with prolonged thrombocytopenia after PSCT revealed the absolute number of megakaryocytes to be lower than normal; Zhang et al. (15) reported that there were significant shifts towards low-ploidy cells and that the number of immature megakaryocytes was higher in patients with prolonged thrombocytopenia after PSCT as compared to non-thrombocytopenic patients.

There is no standard treatment approach in order to accelerate platelet healing or ensure platelet engraftment in the post-transplantation period. In this period, the use of thrombopoietin-mimetics with this purpose is a logical approach. Among the second generation TPO agonists, eltrombopag was approved by FDA for the treatment of Chronic ITP in 2008, it is widely accepted for the treatment of chronic viral hepatitis C-associated thrombocytopenia and studies for including eltrombopag in immunosuppressive therapy in the treatment of aplastic anemia are still ongoing, and recently eltrombopag has been mentioned in the literature with promising studies on post-transplant thrombocytopenia treatment (4).

Raut et al. (16) reported an increase in the number of platelets with no side effects within 29 days on average by administering 25-50 mg/day eltrombopag to 12 patients with post-transplant primary thrombocytopenia, 2 patients allogeneic (AML, aplastic anemia), 10 patients autologous (MM, lymphoma, AML). Reid et al. (8) reported that platelet levels were within the safe interval and patients no longer needed platelet infusion after administering 50 mg/day eltrombopag to two patients, one of which underwent allogeneic PSCT and the other autologous PSCT. Fujimi et al. (11) used eltrombopag in one case diagnosed with follicular lymphoma and underwent allogeneic transplantation in the third remission and reported that eltrombopag could be a suitable choice in cases with prolonged thrombocytopenia after APSCT.

In our case series, bone marrow biopsies of patients showed, similar to the results of Bielski et al. (12), fewer number of megakaryocytes and hypocellularity, which imply reduced platelet production. The common characteristics of the three patients were that they all developed graft failure after the first PSCT and platelet engraftment failure after the second bone marrow transplantation. Eltrombopag treatment was initiated in 3 patients 110 days (60-144) after transplantation on average. Responses were obtained in all of the patients; the platelet value was $\geq 30\times10^3/\mu L$ (30.000-247.000). The mean response time was 27 days (20-35). There were no side effects associated with Eltrombopag.

TPO affects multilineage progenitors and eltrombopag is expected to do the same. Eltrombopag binds to thrombopoietin receptors and stimulates megakaryopoiesis and therefore enables platelet release from mature megakaryocytes. Although the increase in the number of platelets is more remarkable, it also provides some increase in erythroid and myeloid cell lines. It also facilitates treatment compliance as it can be administered orally and leads to fewer and low-degree drug-related adverse events (nausea, headache, nasopharyngitis, lethargy) in patients with ITP. In the post-transplant thrombocytopenic period, it can be recommended for use in order to prevent bleeding rather than to normalize the number of platelets.

CONCLUSION

We determined that the use of Eltrombopag in the treatment of thrombocytopenia after PSCT was safe and effective in all three cases in accordance with the literature. Although there is need for further studies, Eltrombopag treatment is promising in that it can be used safely and effectively in patients with platelet engraftment failure after PSCT.

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

Peer-review: Externally peer-reviewed.

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Case Report

Diabetic Ketoacidosis Occurring in Patient on Newly Started Insulin Glargine U300

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ABSTRACT

Insulin glargine U300 is a 3-fold, concentrated, long-acting insulin analog providing a more stable effect compared with insulin glargine U100. However, stable plasma insulin concentration is reached on day 4 of the treatment. Patients with type 1 and type 2 diabetes mellitus with decreased insulin reserve are at an increased risk of diabetic ketoacidosis when there is insufficient exogenous plasma insulin concentration. Herein, we present a case of diabetic ketoacidosis occurring in a patient with insulin glargine U300 and emphasize the pharmacokinetic properties of insulin glargine U300.

Keywords: Glargine U300, diabetic ketoacidosis, pharmacokinetic

INTRODUCTION

Basal insulin secretion is essential for the maintenance of fasting glucose levels, especially through inhibition of excessive hepatic glucose output. Insulin glargine U300 is a novel long-acting basal insulin formulation that provides more stable effect than glargine U100. Because of the pharmacokinetic properties of glargine U300, the expected plasma insulin concentration is not achieved during the first 4 days of treatment. We report a case of diabetic ketoacidosis on the first day of glargine U300 administration due to low plasma insulin concentration.

CASE PRESENTATION

A 62-year-old female patient diagnosed with type 2 diabetes mellitus (DM) for 25 years, hypertension, hyperlipidemia, hypothyroidism, and previous history of cerebrovascular accident consulted our hospital for routine control. Her medications include insulin aspart 12 unit 3 times daily, insulin detemir 22 unit once daily, metformin 1000 mg twice daily, linagliptin 5 mg, levothyroxine 100 mcg, acetylsalicylic acid 300 mg, perindopril/indapamide 10 mg/2.5 mg, and atorvastatin 20 mg. According to the patient's anamnesis, it was noticed that in addition to the especially night hypoglycemia, the blood glucose levels of fasting and postprandial in the evening were high and she said that did not adhere to her diet. Physical examination revealed that her body mass indexwas 33 kg/m^2. Laboratory findings were as follows: HbA1c: 10.3%, c-peptide: 0.07 µg/L, Hb: 9.2 g/L, MCV: 89 fL, ferritin: 7.93 µg/L. The patient was hospitalized to regulate her blood glucose and to investigate anemia etiology. Insulin detemir, which was used by the patient, was replaced with glargine U300 U/mL, 30 units once daily because of the hypoglycemia at night and the high blood sugar levels in the evening. On the second day of treatment, abdominal ultrasound examination was required from the patient to research anemia etiology. Blood glucose was measured 450 mg/dL after returning from the ultrasound when she had not eaten breakfast. Ketones were detected in the urine along with pH: 7.29 and hCO3: 14 mmol/L in the blood gas of the patient with complaints of nausea and fatigue. There was no pathology except minimal abdominal tenderness on the physical examination. Tests performed for etiology showed 0.8 mg/dL C-reactive protein (normal: 0-0.8) and 0.02 ng/mL procalcitonin (normal: 0-0.5). Urine leukocyte esterase was negative and the electrocardiogram showed normal sinus rhythm. Insulin infusion was initiated by considering mild diabetic ketoacidosis (DKA) in the patient. Subcutaneous insulin therapy was switched on when the blood sample was taken at the 6th hour of the infusion with pH: 7.36 and hCO3: 19 mmol/L. The next morning, the patient underwent urea breath test and was examined using glucose-insulin-potassium (GIK) solution because the patient was still hungry. During this time, the blood glucose of the patient who followed the hourly basis was between 150 and 200 mg/dL. From the third day of the treatment onward, it was observed that the patient had steady blood glucose levels and night hypoglycemia was absent. Patient with erosive gastritis and H. pylori infection as anemia etiology was discharged.

DISCUSSION

Diabetic ketoacidosis is one of the acute metabolic complications of uncontrolled DM. A combination of hormonal disturbances causes DKA. In the setting of insulin deficiency, increased counter-regulatory hormones lead to increased extracellular glucose, decreased glucose use, and hyperglycemia (1). Inadequate dosing of insulin and infections are the most common causes of DKA (2). Other causes include pancreatitis, myocardial infarction, cerebrovascular accident, and drugs that interfere with carbohydrate metabolism such as corticosteroids (2). In this case, there

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were no other causes of DKA except inadequate dose of basal insulin, which is the most common cause of the DKA.

Basal insulin therapy is primarily important for regulating fasting glucose levels by inhibiting increased hepatic glucose output (3). It is known that patients who have received treatment with insulin detemir, in particular, should be given two doses daily to achieve fasting glycemic control (4). Considering the night hypoglycemia, evening fasting hyperglycemia and the high HbA1c level, our patient was treated using insulin glargine U300 U/mL because of the insufficient duration of single-dose insulin detemir treatment and hypoglycemia due to peak effect. However, for treatment of insulin glargine U300 U/mL to be stable, 4 days must pass (5).

CONCLUSION

For the first 4 days, it may be seen the diabetic ketoacidosis on the patients who have type 1 DM and, as in this case, long-term type 2 DM with decreased insulin reserve, who are newly administered insulin glargine U300 due to inadequate plasma basal insulin. When rapid-acting insulin is not applied in such patients, the GIK solution must be given especially for the first 4 days after insulin glargine U300 U/mL treatment is newly started.

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