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

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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

As we have reached almost a half year in combatting COVID-19 pandemic, healthcare professionals and academics continue to face a heavy burden of admissions and hospitalizations.

There is also an enormous increase in the number of publications on COVID-19. The number of submissions to the GMJ also showed an increase so far in 2020.

In the current issue of the GMJ, we have interesting original articles, review articles and case reports. As the journal's publishing team, we tried to cover a wide range of articles from different disciplines.

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

Prof. Dr. Omer Azal
Editor-in-Chief

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Natural irrigation solutions in endodontics

Betül Tekin, Kadriye Demirkaya

University of Health Sciences Turkey, Gülhane Faculty of Dentistry, Department of Endodontics, Ankara, Turkey

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Corresponding Author:
Betül Tekin, MD, University of Health Sciences Turkey, Gülhane Faculty of Dentistry, Department of Endodontics, Ankara, Turkey
betulsuntarbetul@gmail.com

ORCID:
orcid.org/0000-0001-6365-9986

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ABSTRACT

It has been discovered that due to the complex structure of root canals, mechanical instrumentation alone was not sufficient to remove microorganisms settled in the pulp cavity and the infected or non-infected pulp residues that could be nutrients for those bacteria. Therefore, it has been highlighted that the irrigation process carried out with the irrigation solutions that enable root canal disinfection by removing those microorganisms and tissue residues without damaging the surrounding tissues is extremely important. Although various irrigation solutions used for this purpose allow for a significant reduction in the bacterial population in infected root canals, in many clinical cases, some bacteria remain and proliferate, thereby cause re-infection of the canal and failure of the root canal treatment. In order to increase the success of root canal treatments, research studies to find an ideal irrigation agent are still underway. In recent years, the interest in the use of natural products has increased significantly. Conventional irrigation solutions currently in use today, however, are defined as synthetic chemical agents. As synthetic agents have certain disadvantages such as lacking the characteristic properties of an ideal irrigation material alone, failing to create sufficient effect at high concentrations, having potential side effects, causing drug interactions in combined use and not responding safety concerns, naturally sourced alternatives for endodontic use have begun to be investigated. In this context, this review aims to present current literature information about the known and developing natural root canal irrigation agents besides the known root canal irrigation agents.

Introduction

One primary objective in the root canal treatments is to ensure chemomechanical removal of the microorganisms and organic/inorganic tissue residues from the infected root canals. Studies in the literature report that due to the structure of the root canals, mechanical instrumentation alone could not perform a satisfying cleaning in the canal. In *ex vivo* and clinical studies, some areas have remained unreached and infected, thus irrigation has played a key role in the achievement of root canal treatments (1,2).

Irrigation is a process performed to make the mechanical preparation easier through lubrication by wetting the root canals with liquids of different types and concentrations, and to ensure the disinfection of the root canals by removing the organic/inorganic debris, infected pulp tissue, microorganisms, soft and hard tissue residues from the root canals both physically and chemically. An irrigation solution of optimal quality that can completely clean the root canals alone is not still available, and although there are new developments in the relevant field of research, a solution much closer to the ideal quality has not been developed yet.

Having many of the properties expected from root canal irrigation solutions, sodium hypochlorite (NaOCl) is the most ideal and the most widely used agent among all washing irrigation agents developed in recent years. NaOCl can be used at different concentrations but is commonly used in root canal treatments at concentrations from 0.5% to 6%. Besides its excellent properties such as high antimicrobial activity, satisfying tissue dissolving, accessibility, and a relatively lower cost, NaOCl also has certain disadvantages like failing to remove the smear layer alone, causing a bad smell, emphysema, possible allergic reactions, and toxic effect on the surrounding tissues. Recently, it has been discovered that it has a detrimental impact on dentin elasticity and bending resistance, as well (3,4).

Another irrigation solution, chlorhexidine gluconate (CHX), is reported to show a bactericidal effect by causing coagulation of intracellular components at high concentrations, while it has shown a bacteriostatic effect at low concentrations (4,5). For

the bacteriostatic effect, 0.1 to 0.2% aqueous solutions are recommended in the oral cavity, while 2% is the concentration of root canal irrigation solutions usually found in the endodontic literature (3). Although CHX is widely used in root canal disinfection due to its high antimicrobial activity, its efficacy in dissolving tissues is lower than NaOCl (4,5).

Ethylenediaminetetraacetic acid (EDTA), a chelating agent, is another product which is commonly used as an irrigation solution because of its utilization in the instrumentation of narrow and calcified canals and its ability to facilitate the preparation, to remove the smear layer formed in the root canal, and to ensure a better adaptation of the duct filling by increasing the permeability of dentin (6).

Mixture of tetracycline, acid, and detergent (MTAD), which contains various proportions of doxycycline, citric acid, and surface-active detergent, is the first endodontic solution capable of removing the smear layer and ensuring root canal disinfection at the same time (7).

Tetraclean is also a common irrigation solution, the combination of which is similar to the MTAD (antibiotic, citric acid, detergent), but the proportions of the ingredients are different. QMIX solution consisting of EDTA, CHX and a detergent is among the recommended products for irrigation (8).

Hydrogen peroxide, which is known for its poor antibacterial effect, causes foaming during the evaporation of oxygen when used in combination with NaOCl and is not often recommended as a routine solution due to those limitations, iodine potassium iodide, which has possible allergic reaction risks and causes stainings in dentin, and the HEBP (etidronic acid), which is thought to be the only chelator that can be used together with NaOCl without affecting its antimicrobial activity, are included among the irrigation solutions currently in use (9,10).

Those irrigation solutions commonly used today are synthetic chemical products and do not have the ideal properties of an irrigation material alone. Considering the undesirable and insufficient properties of the existing solutions, the continuous increase in the number of strains resistant to solutions, and the side effects of synthetic drugs; researchers have been seeking for remedies with the herbal and natural products, and in the studies, it has been shown that the natural alternatives for endodontic practice are quite promising (11).

The purpose of this literature review is to present a compilation of the data on the use and efficacy of herbal irrigation solutions besides conventional routine irrigation solutions applied to the root canal.

Naturally Sourced Irrigation Solutions

1. Vinegar

Vinegar is commonly used in alternative cures for cancer, cardiovascular diseases, and body or joint aches, also to control diabetes, cholesterol, blood glucose, blood pressure levels, and weight loss (12-14). Functioning as an antiseptic agent due to its medicinal properties, it has been used in the treatment of infected wounds (15). While distilled white vinegar and grape vinegar are mainly composed of acetic acid, apple cider vinegar consists of malic acid with therapeutic properties (16). In recent studies, the use of apple cider vinegar as an auxiliary solution for chemomechanical cleaning of the root canals has also been investigated and has attracted attention with promising results in comparison to traditional endodontic irrigators such as NAOCl and EDTA (17). As vinegar is easily accessible and lower in cost and it shows an interaction mechanism similar to EDTA on mineralized tissue, pioneering studies have been conducted to evaluate its effect on endodontic microorganisms, its physicochemical properties, and its role in periapical tissue healing.

Apple cider vinegar is capable of removing the smear layer consisting of organic and inorganic components that obstruct the dentinal tubule entrances (18-21). It has also been proven to have a bactericidal effect against microorganisms that are frequently associated with endodontic infections such as *Staphylococcus aureus* and *Enterococcus faecalis* (20). In 2018, Yagnik et al. (22) investigated the antimicrobial effects of apple cider vinegar on *Candida albicans, S. aureus and Escherichia coli*. In order to reduce their growth, 1/50 dilution of apple cider vinegar solution is sufficient for *E. coli* (minimum inhibition concentration: 62 µg/mL), a 1/2 dilution needs to be made for *S. aureus* (MIC: 125 µg/mL at a %2.5 acidity), and undiluted apple vinegar [minimum inhibition concentration (MIC): 250 µg/mL at 5% acidity] has been found to be sufficient for *C. albicans*.

Apple cider vinegar is a highly biocompatible material. It is thought that the high rate of malic acid in its combination contributes to the repair process in the periapical region (15). Malic acid is a substance increasing the resistance of an organism. Because it is one of the acids involved in the Krebs cycle, a reaction is responsible for the production of energy in cells. In addition, apple cider vinegar has significant medical potential as it includes vital minerals (potassium, phosphorus, magnesium, sulfur, calcium, fluoride and silicon) and other substances such as pectin, beta-carotene, enzymes and amino acids that attack the free radicals weakening the immune system (18-20).

Prabhu et al. (23) reported that the combined EDTA and apple cider vinegar irrigation provided better results than the NaOCl group in removing the smear layer in the middle ternary of the root canal. In their study, the stain removal capacity of malic acid in apple cider vinegar was also examined; apple cider vinegar and 5.25% NaOCl concentration gave significantly better results than the combined EDTA and 5.25% NaOCl concentration. In the study of Estrela et al. (20), 2.5% NaOCl - 2% CHX gel and EDTA-apple cider vinegar combinations were compared and the

best result was obtained with EDTA-apple vinegar combination. Similar results were obtained by Zandim et al. (21). In 2011, contrary to the previous studies Dornelles-Morgental et al. (24) found that the combination of 2.5% NaOCI and apple cider vinegar was less effective than only 2.5% NaOCI or CHX alone.

2. Propolis

Propolis is a resinous adhesive mixture that Apis mellifera bees prepare by collecting materials from different plants in order to preserve the honeycomb structure. More than 160 constituents have been identified in different propolis samples. It usually consists of waxes, resins, water, inorganic compounds, phenolics and essential oils (25). The structure of propolis varies according to the geographic region, climate, vegetation and season of the region. In the studies, it has been discovered that propolis has antibacterial, antiviral, antifungal, anti-inflammatory, regenerative, antihepatotoxic, immunomodulatory, antioxidant, antimutagenic and carcinostatic properties (26-28). Thanks to its properties, propolis is a popular natural product in dentistry as it is in many other fields. It has also been proven in the studies that there is no toxic effect (25). Kujumgiev et al. (29) investigated the antibacterial and antiviral effects of propolis samples from different regions. All samples were reported to be effective against Gram-positive bacteria, fungi; most of the samples also had antiviral activity. Antimicrobial activity of ethanolic extract (PEE) of propolis collected from Kayseri and its environs was investigated and MIC value against *E. faecalis* was measured as 128 µg/mL (30). In the study by Hubbezoğlu et al. (28), the antibacterial activity of propolis samples from Trabzon environs was investigated and it was found that, at high concentrations, it could show antibacterial activity on *E. coli* in the root canals. In contrast to similar studies, Magro-Filho and Carvalho (31) reported that anti-inflammatory properties of propolis solution were more active at a lower concentration, and that was because the flavonoid titers were higher in low concentration samples.

3. Chitosan

Chitosan is a natural polysaccharide and composed of a long biopolymer chain of N-acetylglucosamine. Due to its biocompatibility, adhesion, no toxicological activity, and no genotoxic effect, it has been included in research studies of dentistry (32,33). Chitosan is obtained by the deacetylation of chitin in crab and shrimp shells. Chitosan is abundant in nature and possible to be obtained with low production cost; that's why, it has become attractive for various applications (34). The possible uses and advantages of chitosan have been discovered and identified in many fields like medicine and pharmacy (antibacterial and antitumor agent, drug carrier, wound healing accelerator), biotechnology (enzyme and cell carrier, chromatography resin), environmental engineering (water treatment), agriculture (seed preparation), cosmetics and food industry (iron and calcium absorption accelerator, fiber source), yet, studies investigating its further utilization in different areas are still underway (35).

In 2000, Senel et al. (36) examined the antifungal activity of the gel containing 2% chitosan and found that it was effective against *C. albicans*. In 2012, Silva et al. (37) evaluated the smear layer removal efficacy of the irrigation agents used in final irrigation after the root canal instrumentation through scanning electron microscopy (SEM) imaging and compared calcium ion concentrations with atomic absorption spectrophotometry. In the SEM analysis, it was observed that 15% EDTA, 0.2% chitosan and 10% citric acid removed the smear layer better than 1% acetic acid and control group. In other words, a 0.2% chitosan solution was able to remove the smear layer at low concentration alone, similar results were only obtained with high concentration solutions such as 15% EDTA and 10% acetic acid.

4. Morinda Citrifolia

Exotic Morinda Citrifolia (Rubiaceae), also known as *noni*, has been used by the Polynesians for over 2000 years in herbal medicine. *Morinda Citrifolia Juice (MCJ)* has a wide range of therapeutic effects, including antibacterial, antiviral, antifungal, antiemetic, analgesic, hypotensive, anti-inflammatory and immunostimulant. A number of major components have been identified in the Noni plant such as octoanoic acid, linoleic acid caproic acid, ursolic acid potassium, scopoletin terpenoids, vitamin C, vitamin A, alkaloids, anthraquinones (such as nordamnacanthal, morindone, rubiadin, and rubiadin1-methyl ether, anthraquinone glycoside), carotene, b-sitosterol, flavone glycosides, Alizarin, amino acids, acubin, L-asperuloside, caprylic acid, rutin, and a putative proxeronine. MCJ is demonstrated to be safe for human consumption through extensive chemical, microbiological, and toxicological analysis and evaluation (38). Murray et al. (39), in 2008, compared *Morinda citrifolia*, NaOCI, chlorhexidine, and other solutions according to their efficiency in removing the smear layer from the root canal walls. It was observed that the growth of *E. faecialis* was inhibited with *Morinda citrifolia juice* solution at a concentration of 6%. It was determined that the effective removal of the smear layer was achieved with 6% CMJ and NaOCI and with 17% EDTA for final irrigation. In a study by Kandaswamy et al. (40), in 2010, the antimicrobial activities of CHX, 2% POV-I, propolis, *Morinda citrifolia* and $Ca(OH)_2$ were compared. CHX showed better antimicrobial activity and was followed by 2% POV-I, propolis, *Morinda citrifolia* and $Ca(OH)_2$.

5. Aloe Vera

Aloe vera (*Aloe barbadensis* miller) is a cactus-like plant that belongs to the Liliaceal family. It is a perennial succulent plant with long and pointed leaves, without stem or with a very short stem, in which large amounts of water are stored in the tissue that is a xerophyte. There are more than 400 species of Aloe, but

the most popular and widely used species is *Aloe barbadensis* Miller (commonly referred to *Aloe vera*). Other species used in health and medicine are included, but are not limited to *Aloe arborescens* Miller (a member of the asphodelacea family), *Aloe andongensis*, *Aloe ferox*, *and Aloeperryi* Baker (41). *Aloe vera* has 75 active ingredients including vitamins, minerals, enzymes, sugars, amino acids, organic and inorganic compounds. It has anti-inflammatory, antibacterial, antifungal, antiviral, antioxidant and antiseptic properties. Several studies have shown that *Aloe vera* has antimicrobial activity against various species, such as *S. pyogenes, E. faecalis, C. albicans* and *S. aureus* (42). The study of Tonea et al. (43) showed that the experimental mixture extract of *Aloe vera* gel with *Arctium lappa* was able to inhibit highly resistant microorganisms such as *E. faecalis* (inhibition zone diameter: 5.69 mm) and *C. albicans* (inhibition zone diameter: 11.62 mm). However, in the study performed by Sahebi et al. (44), *Aloe vera* solution which cannot show a strong effect against *E. faecalis* is not recommended as a root canal irrigation agent. In another study, it was reported that the antimicrobial activity of *Aloe vera* progressed slowly and after a longer contact, it had the same level of antimicrobial activity with $Ca(OH)_2$ and *Zataria multiflora* against *E. faecalis* (45).

6. Triphala

Triphala (an Ayurvedic herbal medicine) is a combination of three different medicinal herbs, which are *Terminalia bellerica (Bibhitaki), Terminalia chebula (Haritaki)* and *Emblica officinalis (Amalaki),* and it is obtained by drying and powdering those three plants. Triphala contains major four phenolics chemical constituents such as syringic acid, gallic acid, tannic acid and epicatechin along with ascorbic acid (46) In the study of Prabhakar et al. (11), triphala, MTAD, 5% NaOCl and green tea polyphenols were evaluated according to their antimicrobial activities on the biofilm layer containing *E. faecalis*. The inhibition zone of Triphala against *E. faecalis* was 24 mm, the MIC was 3.125 mg/mL, and it was found to have antimicrobial activity.

7. Salvadora Persica (Miswak)

It is a chewing stick known by different names in different cultures. Its main components include a high ratio of alkaloids, such as salvadorine, trimethylamine, chlorides and fluorides; mid concentrations of silica, sulfur, and vitamin C; and small amount of flavonoids, sterols tannins and saponins. Chemical analysis of *S. persica* has demonstrated the organic compounds, such as pyrrolidine, pyrrole, and piperidine derivatives; glycosides, such as salvadoside and salvadoraside; b-sitosterol and m-anisic acid chlorides, salvadourea, and gypsum; and flavonoids, including kaempferol, quercetin, quercetin rutin, and quercetin glucoside (47). As stated in the 2000 World Health Organization (WHO) consensus report on oral hygiene, miswak (chewing sticks) can be used in oral hygiene motivation (WHO 2000). In the study of Al-Salman et al. (48), it was suggested that 10% water extract of miswak showed antibacterial effect against both aerobic and anaerobic bacteria in necrotic pulp teeth and thereby could be used as a root canal irrigation solution. Also, in the study by Shingare and Chaugule (49), it was reported that Miswak had antimicrobial properties that could make it an alternative to NaOCl.

Conclusion

Until now, various synthetic irrigation agents have been investigated and they are still being studied. However, as in medicine, there is an endeavor to return to natural solutions in dentistry and endodontics. In this sense, herbal irrigation solutions also seem to be promising. However, in order to develop ideal herbal irrigation solutions, there is a need for a review of the current literature and more extensive research both *in vitro* and *in vivo* types.

Ethics

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Authorship Contributions

Concept: B.T., K.D., Design: B.T., K.D., Data Collection or Processing: B.T., K.D., Analysis or Interpretation: B.T., K.D., Literature Search: B.T., K.D., Writing: B.T., K.D.

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Different nutritional approaches in the treatment of irritable bowel syndrome

E. Nüket Ünsal[1], Gamze Akbulut[2], Harun Erdal[3]

[1]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Nutrition and Dietetics, Ankara, Turkey*

[2]*Gazi University Faculty of Medicine, Department of Nutrition and Dietetics, Ankara, Turkey*

[3]*University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey*

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Corresponding Author:
E. Nüket Ünsal, MD, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Nutrition and Dietetics, Ankara, Turkey
nuketbuyukgenc@hotmail.com

ORCID:
orcid.org/0000-0002-1491-7093

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ABSTRACT

Irritable bowel syndrome (IBS) is defined as a combination of pain associated with abdominal discomfort and changes in bowel habits. IBS has an important economic effect on healthcare system and it decreases the life quality of patients. Nutrition treatment is really important to reduce IBS symptoms. In this review, nutritional recommendations are based on scientific literature. The topics which are discussed in this review are low Fermented Oligosaccharide, Disaccharide, Monosaccharide and Polyol Diet, increasing dietary soluble fiber, and probiotic use. Different nutritional approaches are used in the treatment of IBS patients but there is still no clear evidence about them. Therefore, further well-designed, randomized controlled trials are needed.

Introduction

Irritable bowel syndrome (IBS) is defined as a combination of pain associated with abdominal discomfort and changes in bowel habits. IBS is one of the most common functional gastrointestinal diseases that affect about 14% of the global population (1). Global IBS prevalence varies between 10% and 20% depending on the diagnostic criteria and the geographic region (2). Although the etiology is clearly known, changeable bowel motility, visceral hypersensitivity, abnormal brain bowel interaction, nutrient intolerance and altered microflora have been shown to play a role in the IBS (3).

It is known that IBS has negative effects on patients' quality of life. This situation highlights the dietary interventions for treatment (4). Healthy eating and lifestyle suggestions are very important in IBS. Providing hydration and regular physical activity are among the suggestions (5). Besides the regular meal consumption, alcohol, caffeine and spicy food intake should be limited (6). Other nutritional interventions include increasing dietary fiber, regular probiotic use, and a low Fermented Oligosaccharide, Disaccharide, Monosaccharide and Polyol Diet (FODMAP) diet approach (7).

Increasing dietary fiber intake is recommended to alleviate the symptoms of patients with IBS (8). There is no evidence of the optimal fiber dose to be used in IBS, but the target (20-30 g/day) should be reached in the total dietary fiber (5). Dietary recommendations for patients with IBS include soluble fiber such as psyllium rather than insoluble fiber (9). In the study, it

has been shown that the consumption of insoluble fiber does not improve IBS symptoms while consumption of soluble fiber improves general IBS symptoms (8).

Probiotics play a major role in the IBS management (4). Probiotics alter colonic fermentation, stabilize the colon microbiota and keep it in balance. They also increase mucosal integrity and improve the intestinal barrier (10,11). As a result of systemic review and metaanalysis in which the effects of probiotics are examined in patients with IBS, it is seen that the use of probiotics results in a reduction in general IBS symptoms (12). However, it is not yet clear which strain and dose are useful in IBS (4).

There are clinical studies supporting that a low FODMAP diet is beneficial for patients with IBS. In these studies, it is observed that there is a reduction in the symptoms such as abdominal pain, gas, bloating and consequently, an increase in their quality of life (13,14).

This article aims to address nutritional approaches that play an important role in the correction of IBS symptoms.

Irritable Bowel Syndrome and Medical Nutrition Therapy

IBS can be affected by various cultural, social, environmental and behavioral factors as with many functional disorders. Nutrition style, physical activity level, hormonal and psychological effects may increase IBS symptoms. Nutrition is one of the most important factors leading to the exacerbation of symptoms in IBS patients (15). Approximately two out of three patients with IBS think that the symptoms of the gastrointestinal tract are food-dependent (2). 60-70% of patients with IBS state that the symptoms worsen after meals, 50-70% of them are unable to tolerate some foods, and more than 70% of them state that the foods cause some symptoms. For this reason, it is recommended to take a careful nutritional history and conduct dietary interventions when it is necessary in order to determine possible causes of symptoms (16). At the same time, despite its common use, there are limited data supporting the use of special diets in the treatment of IBS symptoms (17).

Standard recommendations for IBS patients include regular meal consumption, regular physical activity, good hydration, and reduction of insoluble fiber, alcohol, caffeine, spicy foods and fat intake (5).

Cozma-Petruţ et al. (5) created a specific nutritional pyramid for IBS. While physical activity and hydration form the basis of the pyramid, the second level emphasizes the correct nutritional habits that can improve health status in IBS and states which food group to consume in what amount per day. The top of the pyramid contains fried and processed foods that should be removed from the diet of IBS patients. Many studies suggest that IBS patients have much more irregular eating habits than the control group, which can affect colonic motility and contribute to IBS symptoms (18).

Some studies emphasize that the focus should be on the elimination diet in order to determine the role of nutrient intolerance in IBS patients. In a study, it was found that approximately half of the women with IBS had symptomatic improvement after a strict 3-week elimination diet that excluded dairy products, cereals, citrus fruits, potatoes, tea, coffee, alcohol, additives and preservatives (2).

a) Fiber

Dietary fiber is the complex lignin polymers found in undigested carbohydrates and plants that have physiological effects in humans (8). Dietary fiber is divided into two groups as soluble fiber (water-soluble) and insoluble fiber (water-insoluble). As soluble fiber, pectin in foods such as apple, quince, etc., gums in resin, β-glucan in foods such as oats etc., and the mucilages are found in plants. From insoluble fiber group, cellulose in wheat, hemicellulose in grains and lignin is abundant in wheat (19).

Dietary fiber has been used in the treatment of various gastrointestinal diseases for many years. Its deficiency can reduce the diversity in the intestinal microbiota, causing disruption of microbiota balance and increase in chronic diseases (20). IBS is thought to be caused by insufficient dietary fiber intake, and it is recommended to increase dietary fiber intake to alleviate the symptoms of patients (8).

Fiber has been considered as the basis of treatment for IBS symptoms for many years and is considered a bulking agent to improve bowel transit and reduce constipation (9). The beneficial effect of fiber is the production of short-chain fatty acid which provides the colon fermentation in order to indicate a prebiotic effect (4). Fermentation of acetate, propionate and butyrate, short-chain fatty acids, which are by-products of dietary fiber, provide the growth of beneficial bacteria such as lactobacilli and bifidobacteria. The effect of fiber is variable in IBS, not all types of pulp are useful (8). Dietary recommendations usually include soluble fiber supplements (9). Supplements which are long chain, medium viscosity, soluble, and moderately fermentable dietary fiber such as psyllium improve the general symptoms of IBS (21).

It is recommended to increase dietary fiber intake to 20-35 g daily in order to regulate stool and reduce abdominal pain, gas and bloating (8).

The role of fiber in IBS continues to be subject to controversy with high quality evidence and conflicting data. In a systemic review, 12 randomized controlled trials involving 621 patients were evaluated, and the beneficial effect of the soluble and insoluble fiber cannot be found in improving abdominal pain or symptom scores in patients with IBS (5). Twelve systematic meta-analysis showed that patients with IBS who increased dietary fiber intake did not improve IBS symptoms compared to a placebo or low-fiber diet (8). In contrast, in the study

which examined 14 RCTs that 906 patients participated, it was concluded that the use of psyllium soluble fiber could have beneficial effects on IBS, but the positive effects of insoluble fiber such as bran were not detected or even it could worsen the symptoms (22).

Nowadays, the fiber intake of many people is below the recommended levels. Therefore, changes to dietary habits in order to increase dietary fiber are important for maintaining good health (23).

b) Low FODMAP

The low FODMAP diet has been developed by Monash University in Australia and is used to treat IBS symptoms based on evidence from prospective studies showing an approximately 75% improvement in symptoms (1). Increasing evidence supports the effectiveness of the low FODMAP diet in the treatment of IBS (24). The low FODMAP diet reduces gastrointestinal symptoms, improves the quality of life of patients, and positively affects the intestinal microbiota (25).

FODMAPs are fermentable oligosaccharides (wheat, rye, onion and legumes and chicory with garlic and galactans in kernels) and disaccharides (lactose in milk and dairy products), monosaccharides (fructose in artificial sweeteners) and polyols (sugar) (15). FODMAPs are short-chain carbohydrates (1). Foods are classified into two groups as those with high and low FODMAP contents and they are given in Table 1 (26).

Low FODMAP diet should never be followed in the long term. A 3 or 4-week restriction phase is usually sufficient to get clinical response. If any symptoms improve within 4 weeks of following a low FODMAP diet, intervention should be stopped and other treatment options should be emphasized (5).

Dietary FODMAPs induce hydrogen and methane production in the intestines of IBS patients. Possible changes in intestinal pH and flora can cause local inflammation. These changes can significantly increase symptoms such as excessive gas and bloating in patients with IBS (1).

In a randomized, controlled, single-blind study by Halmos et al. (27,28), 30 patients with IBS and 9 healthy individuals were given 21 days of FODMAP diet or typical Australian diet; 70% of patients with IBS (all four subtypes of IBS) reported they felt better on the low FODMAP diet. In another randomized controlled study comparing the low FODMAP diet with the high FODMAP diet, it was found that a low FODMAP diet reduced the severity and frequency of abdominal pain in individuals with IBS (29).

If the symptoms improve within 4-6 weeks after applying the low FODMAP diet, the process of adding food back into

Table 1. Food Sources of Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (26)

	High FODMAP Food Source	Low FODMAP Food Source
Excess fructose	Fruits (mango, apples, pears, nashi pears, sugar snap peas, clingstone peaches, tinned fruit in natural juice, watermelon) Honey Sweeteners (fructose)	Fruit (durian, banana, blueberry, grape, carambola, grapefruit, lime, honeydew melon, kiwifruit, tangelo lemon, mandarin, paw paw, orange, strawberry passionfruit, raspberry, rockmelon) Honey substitutes (maple syrup, golden syrup) Sweeteners (any except polyols)
Lactose oligosaccharides	Milk (sheep, goat and cow) Ice cream Yoghurt Soft cheeses	Milk (rice milk, lactose-free) Cheese (camembert, hard cheeses) Yoghurt (lactose-free) Ice cream substitutes (sorbet, gelati) Butter
Polyols (27)	Vegetables (brussels sprout, artichokes, asparagus, beetroot, peas, broccoli, cabbage, shallots, fennel, garlic, onions, leeks, okra) Cereals (wheat and rye when eaten in large amounts) Legumes (chickpeas, baked beans, lentils, red kidney beans) Fruits (persimmon, watermelon, custard apple, rambutan, white peaches)	Vegetables (tomato, bamboo shoots, choy sum, bokchoy, carrot, silverbeet, celery, capsicum, parsnip, choko, corn, eggplant, pumpkin, green beans, spring onion, lettuce, chives) Onion/garlic substitutes (garlic-infused oil) Cereals (spelt bread/cereal products and gluten-free)
Fructans and/or galactans	Fruits (apples, longon, apricots, cherries, lychee, nashi pears, pears, nectarine, peaches, watermelon, plums, prunes) Vegetables (avocado, snow peas cauliflower, mushrooms) Sweeteners (sorbitol, maltitol, mannitol, xylitol, isomalt)	Fruits (durian, banana, blueberry, raspberry, carambola, grapefruit, grape, honeydew melon, lime, mandarin, orange, rockmelon, kiwifruit, lemon, passionfruit, paw paw) Sweeteners (sucrose, glucose)

Adapted from the reference 26.

the diet should be started. The goal at this stage is to be able to create an individually modified FODMAP layout. One of the most important reasons for the inclusion of foods in the diet is that the restricted foods are also prebiotic. Studies have shown that after 3-4 weeks of restricted FODMAP diet administration, there is a negative change in microbiota because of reduced prebiotic intake (29). More detailed studies are needed regarding insufficiencies that a low FODMAP diet can cause (30).

c) Probiotic/Prebiotic Supplementation

Probiotics are living and non-pathogenic microorganisms that are taken with or separately from food, regulate the intestinal flora and stimulate the immune system and positively affect host health (31). Fermented yoghurt, cheese, pickle, sausage, bread, beer, wine, chicken and kefir are the nutritional sources of probiotics (32). Prebiotics are called undigested carbohydrates (33). Prebiotics are necessary for feeding of microorganisms which are beneficial for our body (31).

Probiotics can modulate the gastrointestinal luminal immunity by changing the cellular environment from the proinflammatory to the anti-inflammatory state (12). They can also convert undigested carbohydrates into short-chain fatty acids. It is claimed that probiotics can lead to symptomatic improvements in IBS patients and that each strain of bacteria can affect selected symptoms (3).

Numerous studies investigating the effectiveness of probiotics in patients with IBS have been conducted. Although most of these studies are double-blind randomized controlled, the different diagnostic criteria of IBS, the difference in the probiotic type used, its dose, delivery intervals, duration of study, and patient groups prevent the studies from being compared (34,35).

Didari et al. (36) investigated the efficiency of probiotics in IBS patients in 2015 and demonstrated that probiotics reduced the pain and symptom severity scores and had beneficial effects compared to placebo. In the study of Šmid et al. (37) in 2016, IBS patients were given probiotic yoghurt and dietary fiber for eight weeks, and as a result of the study, it was reported that there was averagely 18% improvement in the patients' quality of life scores (decrease in bloating severity, bowel movements, etc.).

Nowadays, it is recommended to use prebiotics with other treatment options because of the lack of effective treatment in IBS patients and the probiotics' being safe. IBS patients using probiotics should be advised to choose one product at the same time and monitor its effects. As a result of a metaanalysis, probiotics should be used at the dosage of the manufacturer's recommendations, and it has been proposed to be used for at least four weeks so that the efficacy can occur (38).

There are few randomized controlled trials that examine the effects of prebiotic use in patients with IBS. In the study of Olesen and Gudmand-Hoyer (39), IBS patients were given 22 g/day fructooligosaccharide for 12 weeks, and it was found that these high doses increased the complaints of patients in 4-6 weeks. Silk et al. (40) gave a dose of 3.5 and 7 g/day galactooligosaccharide to 60 IBS patients for four weeks, and at the end of the treatment, they found significant improvement in both general IBS symptoms and symptoms of bloating in patients receiving low-dose prebiotic therapy.

Conclusion

In recent years, healthy nutrition and lifestyle changes have gained great importance in the treatment of IBS. There are studies suggesting that especially soluble fiber reduces symptoms and improves quality of life in patients with IBS. Nowadays, there is increasing evidence to support the use of a low FODMAP diet in most patients with IBS. Another approach which is important in IBS management is the use of probiotics. However, it is not yet clear which strain and dose are beneficial. Therefore, in order to verify and assess the approach of increasing fiber in diet, having low FODMAP diet and using probiotic in the long term, further well-designed and randomized controlled trials are needed.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.E., E.N.Ü., G.A., Design: H.E., E.N.Ü., G.A., Data Collection or Processing: E.N.Ü., Analysis or Interpretation: H.E., Literature Search: E.N.Ü., Writing: H.E., E.N.Ü.

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Association of complete blood count parameters with IgE levels and disease severity, atopy type in allergic rhinitis patients

Ali Selçuk[1], Gürhan Taşkın[2]

[1]*University of Health Sciences Turkey, Regional Training and Research Hospital, Clinic of Immunology and Allergic Diseases, Erzurum, Turkey*

[2]*University of Health Sciences Turkey, Kanuni Training and Research Hospital, Clinic of Intensive Care, Trabzon, Turkey*

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Corresponding Author:
Ali Selçuk, MD, University of Health Sciences Turkey, Regional Training and Research Hospital, Clinic of Immunology and Allergic Diseases, Erzurum, Turkey
draliselcuk@gmail.com

ORCID:
orcid.org/0000-0003-4089-7564

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ABSTRACT

Aims: The aim of this study was to investigate the relationship between complete blood count (CBC) parameters and atopy type, disease severity, presence of concomitant conjunctivitis in patients with allergic rhinitis (AR).

Methods: In this retrospective study, patients who presented to the immunology and allergic diseases outpatient clinic with rhinitis symptoms and who were found to have proven AR by allergy tests were included. CBC parameters and specific/total immunoglobulin E (IgE) analyses which were measured in the period of active disease were recorded.

Results: Totally 242 patients met the enrollment criteria and were included in the study. AR patients with concomitant conjunctivitis had a significantly higher eosinophil count than patients without conjunctivitis (280.13±228.58/mm^3 vs. 231.50±199.92/mm^3, respectively, p=0.047). The presence of both concomitant pollen and mite atopy was significantly more frequent in the moderate/severe persistent group than in the other groups (p<0.001). Serum total IgE levels were significantly higher in group with patients who had both mite and pollen atopy than in the other groups (168.11±189.27, 149.69±178.21 and 368.53±430.31 IU/mL, respectively, p=0.005). The presence of conjunctivitis was significantly more frequent in patients with pollen atopy than in patients who did not have (46.9% vs. 30.3%, p=0.021).

Conclusions: Although serum eosinophil count and total IgE levels are not sensitive enough in predicting the severity of AR patients, we believe that they can be helpful in diagnosis of patients with concomitant conjunctivitis and in presence of multiple aeroallergen sensitivity.

Introduction

Allergic rhinitis (AR) is an inflammatory nasal mucosa disease characterized with symptoms such as itchy nose, sneezing, rhinorrhea and nasal congestion (1). AR is the most common form of chronic rhinitis which affects almost 10-20% of the general population. It may cause sleep disorder, fatigue, nervousness, decreased school/work performance and quality of life (2).

Other than rhinitis, adult AR patients may have concurrent conjunctivitis, sinusitis and asthma. Bilateral eye itching, redness, burning, photophobia, watering and conjunctival edema may occur in allergic conjunctivitis patients (3).

In addition to the history and physical examination findings of the patients, skin prick and allergen specific immunoglobulin E (IgE) tests including aeroallergens are used in AR diagnosis. AR is classified as intermittent or persistent based on the duration of the symptoms and as mild or moderate/severe based on the severity of the disease (4).

AR occurs as the result of IgE mediated type 1 hypersensitivity reaction against inhaled allergen (mostly pollen and mite). Typical symptoms and findings occur with the effect of mediators (such as histamine, leukotrienes) released from IgE-related mast cells in this inflammation accompanied by eosinophils (2,5,6).

The objective of this study was to investigate whether there was a relation between allergen sensitivity, disease severity

and complete blood count (CBC) parameters, serum total IgE levels.

Methods

Two hundred and forty-two AR patients with at least one positive inhalant skin prick and/or allergen specific IgE test, aged ≥18 years, who were admitted to University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Immunology and Allergic Diseases outpatient clinic between February 2017 and March 2019, were included in the study. Electronic records of included patients were examined, retrospectively.The study was approved by the Local Ethical Committee (Ethical Committee of Erzurum Ataturk University Faculty of Medicine, approval number: 13.03.2019/03). The procedures were in line with the Helsinki Declaration. The procedures were in line with Helsinki Declaration. Age, gender, concurrent conjunctivitis, atopy sensitivity, CBC parameters and serum total IgE results of the patients were recorded. Patients were classified according to the classification system reported by ARIA (Allergic Rhinitis and its Impact on Asthma) study group (4). Patients were accordingly separated into three groups as intermittent, mild persistent and moderate/severe persistent. Patients with systemic/chronic diseases (including asthma), pregnancy, anemia/polycythemia, leukopenia/leukocytosis, thrombocytopenia/thrombocytosis and patients receiving systemic corticosteroid, anti-inflammatory or anticoagulant drugs were excluded from the study. CBC and allergy tests (inhalant skin prick, serum total and specific IgE) were performed simultaneously during the active period when the disease was symptomatic.

CBC parameters were studied on Sysmex XN-10 (Sysmex Comp., Kobe, Japan) device for each patient. Serum total IgE and allergen specific IgE tests were analyzed with chemiluminescence immunometric (Immulite 2000, Siemens) system for each patient. The allergen-specific IgE panel contained grasses-mix, trees-mix, mite-mix and mold-mix. Histamine was used as positive control and serum physiological solutions were used as negative control for skin prick test. 15-20 minutes after the application of inhalant prick panel on the forearm, aeroallergens with a wheal ≥3 mm diameter were defined as a positive result. Inhalant skin prick test panel consisted of Dermatophagoides pteronyssinus, Dermatophagoides farinae, grasses mix, cereals mix, trees mix, weed-mix, Alternaria alternata, cockroaches, cat dander and dog dander (Lofarma Allergeni, Milan, Italy).

Statistical Analysis

All predetermined parameters were saved in a software database, then statistically analyzed (SPSS© v20.0 software, IBM, Ili, USA. Lic.no. 10240642). Distribution of normality for quantitative data were tested by the Kolmogorov-Smirnov test. Student's t-test was used for the comparison of the normally distributed continuous numerical variables between two independent groups and the one-way ANOVA test was used for the comparison of normally distributed variables between three independent groups. The Mann-Whitney U test and Kruskal-Wallis test were used when the data did not fit a normal distribution. The Pearson chi-square test or Fisher's exact test were used to assess differences of rates between the groups. The receiver operating characteristic (ROC) analysis was performed to distinguish the patients with allergic rhinitis according to atopy group and to determine the cut-off points for IgE levels. The area under the curve (AUC), cut-off point, sensitivity, specificity values were presented for IgE level. Data and results were presented as mean±standard deviation (SD), minimum-maximum values, numbers (%), and also p values <0.05 were considered as statistically significant and accordingly, confidence interval of 95% was considered.

Results

Totally 242 patients met the enrollment criteria and were included in the study. Of these, 158 (65.3%) were female and 84 (34.7%) were male. The mean (±SD) age of patients was 26.43±9.18 (18-59) years.

Comparison of AR Patient Groups According to the Presence of Concomitant Conjunctivitis

Patients were divided into 2 groups according to the presence of concomitant conjunctivitis. One hundred three (42.6%) patients were in AR patients with conjunctivitis group, while 139 (57.4%) were in AR patients without conjunctivitis group. The mean age of patients with and without conjunctivitis groups were similar (25.87±9.05 and 27.18±9.35 years, respectively, p=0.241). Gender was also similar between these groups. AR patients with concomitant conjunctivitis had a significantly higher eosinophil count than patients without conjunctivitis (280.13±228.58/mm^3 vs. 231.50±199.92/mm^3, respectively, p=0.047). The other CBC parameters and total IgE levels did not differ between the groups (Table 1).

Comparison of the AR Patients According to Disease Severity Groups

When AR patients were grouped in terms of disease severity, there were 60 (24.8%) patients in the intermittent group (group 1), 94 (38.8%) patients in the mild persistent group (group 2) and 88 (36.4%) patients in the moderate/severe persistent group (group 3). The presence of both concomitant pollen and mite atopy was significantly more frequent in group 3 than in the other groups (p=0.0001). There was no significant difference among the 3 groups in terms of demographic data, the presence of concomitant conjunctivitis and laboratory findings (Table 2).

Comparison of the AR Patients According to Atopy Groups

Of 242 AR patients, 63 (26%) were in group 1 (patients with mite atopy), 137 (57%) were in group 2 (patients with pollen

atopy) and 42 (17%) were in group 3 (patients with mite and pollen atopy). Patients with mite and pollen atopy were found to be significantly younger than the other two groups (28.19±9.92, 26.21±9.24 and 24.50±7.39 years, respectively, p=0.045). Additionally, total IgE levels were significantly higher in group 3 than in the other groups (168.11±189.27, 149.69±178.21 and 368.53±430.31 IU/mL, respectively, p=0.005) (Table 3). In the ROC curve analysis for IgE levels to distinguish patients with both mite and pollen atopy from other atopy groups, it was observed that, for patients with total IgE levels ≥145.5, the

Table 1. Comparison of allergic rhinitis patient groups according to the presence of concomitant conjunctivitis

	AR patients without conjunctivitis n=139 (57.4%)	AR patients with conjunctivitis n=103 (42.6%)	p value
Demographics			
Age	25.87±9.05	27.18±9.35	0.241[a]
Female, n (%)	89 (64)	69 (67)	0.632[b]
Eosinophil count, /mm^3	231.50±199.92	280.13±228.58	**0.047[a,*]**
Platelet, 10^3/µL	285.50±62.37	287.77±59.89	0.844[a]
WBC, /µL	7605±1706	7422±1808	0.424[c]
Hemoglobin, g/dL	14.84±1.50	14.81±1.61	0.695[a]
Hematocrit, %	44.74±3.90	44.45±4.34	0.474[a]
MPV, fL	10.24±2.89	10.07±1.15	0.558[a]
Total IgE level, IU/mL	172.79±206.02	233.90±323.11	0.269[a,#]

WBC: White blood cell, MPV: Mean platelet volume, IgE: Immunoglobulin E, SD: Standard deviation, AR: Allergic rhinitis
Data are given as mean±SD unless otherwise indicated.
[a]Mann-Whitney U test
[b]Chi-square test
[c]Independent sample t-test
*p<0.05
#Data of 112 patients with IgE results available were included

Table 2. Comparison of allergic rhinitis patients according to disease severity groups

	Group 1 (Intermittent) n=60 (24.8%)	Group 2 (Mild persistent) n=94 (38.8%)	Group 3 (Moderate/severe persistent) n=88 (36.4%)	p value
Demografics				
Age, year±SD	25.93±9.01	26.82±10.00	26.35±8.43	0.762[b]
Female, n (%)	36 (60)	62 (66)	60 (68.2)	0.582[a]
Conjunctivitis, n (%)	26 (43.3)	32 (34)	45 (51.1)	0.065[a]
Atopy groups, n (%) Mite atopy Pollen atopy Mite+pollen atopy	 6 (10) 54 (90) 0 (0)	 27 (28.7) 56 (59.6) 11 (11.7)	 30 (34.1) 27 (30.7) 31 (35.2)	**<0.0001[a,*]**
Eosinophil count, /mm^3	299.57±302.24	227.18±174.21	246.61±172.08	0.278[b]
Platelets, 10^3/µL	289.71±64.71	289.43±58.63	281.07±61.80	0.531[b]
WBC, /µL	7611±1715	7437±1601	7566±1930	0.807[c]
Hemoglobin, g/dL	15.02±1.55	14.75±1.64	14.78±1.44	0.497[b]
Hematocrit, %	44.82±4.21	44.54±4.11	44.57±4.01	0.851[b]
MPV, fL	10.38±4.11	9.99±1.39	10.21±1.11	0.262[b]
Total IgE level, IU/mL	228.37±251.89#	202.58±329.42#	186.58±182.44#	0.767[b]

WBC: White blood cell, MPV: Mean platelet volume, IgE: Immunoglobulin E, SD: Standard deviation
Data are given as mean±SD unless otherwise indicated.
[a]Chi-square test
[b]Kruskal-Wallis test
[c]One-way ANOVA test
*p<0.05
#Data of 112 patients with IgE results available were included

sensitivity was 72.7%, the specificity was 70.0% and the AUC was 0.722 (p=0.005) (Figure 1).

Another important finding of our study was revealed in the comparison between AR patients according to pollen atopy. The presence of conjunctivitis was significantly more frequent in patients with pollen atopy than patients who did not have (46.9% vs. 30.3%, p=0.021).

Discussion

To our knowledge, this has been the first study performed on a quite high number of adult AR patients in Erzurum.

It is well-known that allergic conjunctivitis is caused by airborne allergens contacting the eye, which leads to IgE-mediated allergic inflammation. In the literature, it was reported that nearly 60% of AR patients had concurrent ocular allergy. In our study, ocular allergy was seen in 42.6% of AR patients (3). In the studies published before, it has been shown that, the presence of concurrent conjunctivitis in AR patients is significantly associated with pollen atopy (1,3). Similar to these data, the prevalence of conjunctivitis in AR patients with pollen atopy was higher than in those without pollen atopy in our study (p=0.021) (1,3).

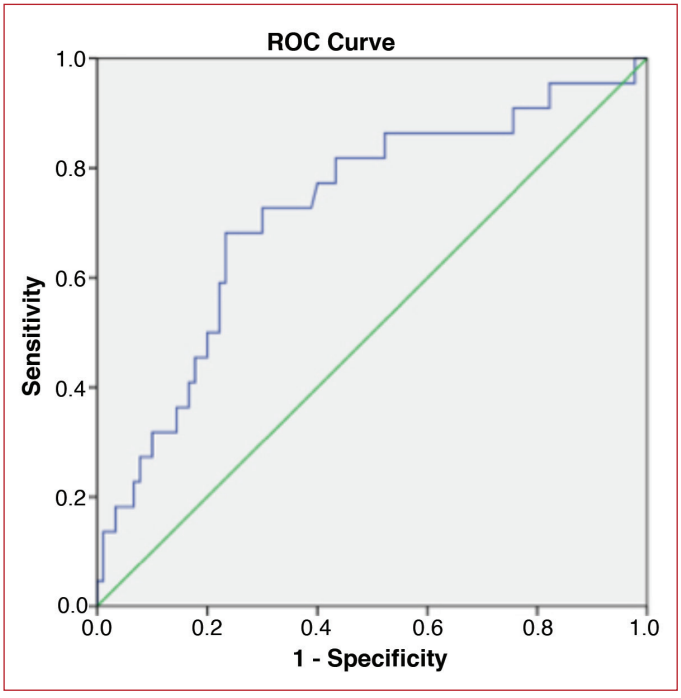

Figure 1. Receiver operating characteristic curve analysis of immunoglobulin E (IgE) levels for mite and pollen atopy group in allergic rhinitis patients. IgE; IgE levels were significantly higher in the mite+pollen atopy group (p=0.005). It was observed that for patient with IgE levels ≥145.5 the sensitivity was 72.7%, the specificity was 70.0% and the AUC was 0.722 (p=0.005)

IgE: Immunoglobulin E, AUC: Area under the curve, ROC: Receiver operating characteristic

Similar to the pathophysiology of atopic diseases like AR, eosinophils also play a significant role in ocular allergies (7). High serum ECP (eosinophil cationic protein), which is a demonstrator of the activation of systemic eosinophils, and eosinophils in tear drop and conjunctival scrapings were detected in ocular allergy patients (8,9). In our study, serum eosinophil count was detected to be higher in AR patients with concurrent ocular allergy (p=0.047). Based on this result, we evaluated that patients who had concurrent rhinitis and conjunctivitis with a similar pathophysiology had higher activation of systemic eosinophils. In previous studies, it was revealed that allergic conjunctivitis or allergic rhinitis patients had a higher serum eosinophil count when compared to healthy controls (10-12).

To date, the studies evaluating serum total IgE levels at the diagnosis of AR patients have reported controversial results. Burrows et al. (13) reported that the diagnosis of AR was primarily associated with skin prick test, independently of the serum total IgE levels. Also, it was reported that the measurement of serum total IgE level had low sensitivity for the diagnosis of patients with current AR (14). It is below 100 IU/mL in healthy adult individuals. According to the recommendations in several previous studies, the cut-off value for an elevated IgE level was set at 100 IU/mL (15-17). In the evaluation of 112 AR patients with serum total IgE levels, while 52.7% of patients had levels above 100 IU/mL, 47.3% of them had normal levels. Based on these results and similar findings in literature, we believe that normal serum total IgE levels do not exclude AR diagnosis (18,19). In the present study, there was not found a significant difference between AR patients with allergic conjunctivitis than those without conjunctivitis for the mean IgE levels (p=0.269). In some of the previous studies, it was observed that its levels might increase in ocular allergy compared to the healthy controls (9,11,20). In addition, when patients with high IgE levels were evaluated, no significant difference was found in terms of the frequency of concomitant conjunctivitis in this study (55.3% vs. 50.8%, respectively, p=0.634).

In the present study, the incidence of mite allergy was 10% in the intermittent group, while it was 40.4% and 69.3% in the mild and moderate/severe groups, respectively. In a study by Dogru et al. (21) on pediatric AR patients, there was no significant difference between mild and moderate/severe disease severity groups for serum total IgE levels and eosinophil counts. Similar to this study, no significant difference was found in serum total IgE levels and eosinophil counts among the disease severity groups of adult AR patients in our study. Based on these results, it can be concluded that serum total IgE and eosinophil count were not sensitive enough in demonstrating the severity of AR patients.

In Erzurum, where this study was conducted, the humidity is low and the altitude is high and in parallel with these geographic

Table 3. Comparison of the allergic rhinitis patients according to atopy groups

	Group 1 (Patients with mite atopy) n=63 (26%)	Group 2 (Patients with pollen atopy) n=137 (57%)	Group 3 (Patients with mite+pollen atopy) n=42 (17%)	p value
Demographics				
Age	28.19±9.92	26.21±9.24	24.50±7.39	**0.045[b,*]**
Female, n (%)	46 (73)	87 (63.5)	25 (59.5)	0.291[a]
Conjunctivitis, n (%)	19 (30.2)	64 (46.7)	20 (47.6)	0.068[a]
Eosinophil count, /mm^3	237.06±146.21	257.94±252.31	256.14±154.75	0.369[b]
Platelets, x10^3/µL	291.52±65.59	285.83±59.35	280.95±61.34	0.937[b]
WBC, /µL	7582±1834	7490±1636	7566±2003	0.930[c]
Hemoglobin, g/dL	14.62±1.58	14.86±1.58	15.04±1.37	0.269[b]
Hematocrit, %	43.96±4.07	44.67±4.14	45.44±3.85	0.117[b]
MPV, fL	10.11±1.31	10.24±2.82	10.01±1.55	0.837[b]
Total IgE level, IU/mL	168.11±189.27[#]	149.69±178.21[#]	368.53±430.31[#]	**0.005[b,*]**

AR: Allergic rhinitis, WBC: White blood cell, MPV: Mean platelet volume, IgE: Immunoglobulin E, SD: Standard deviation
Data are given as mean±SD unless otherwise indicated.
[a]Chi-square test
[b]Kruskal-Wallis test
[c]One-way ANOVA test
*p<0.05
[#]Data of 112 patients with IgE results available were included

data, pollen was the most common aeroallergen sensitivity in our study (74% of all patients). Serum eosinophil count was detected as 252.19±213.49/mm^3 in the whole study group. When serum eosinophil counts were compared between atopy groups, no significant difference was found among patients with only pollen atopy and those with only mite atopy (p=0.359). Also, serum total IgE level was significantly higher in patients with both mite and pollen atopy and those with only mite atopy (p=0.005). Based on these results, we evaluated that high serum total IgE values may increase more in multiple atopies occurring with the addition of mite which is a perennial allergen in patients with pollen atopy. In parallel with our results, a study by Min et al. (22) revealed that serum total IgE levels increased in line with the increasing number of allergens.

Studies published recently, which have focused on the mean platelet volume (MPV) levels as a biomarker of systemic inflammation in chronic urticaria, have shown controversial results (23-26). Additionally, there are similar studies on adult asthma patients, but studies evaluating MPV levels in AR patients are scarce (27). In the present study, there was not any relationship between serum platelet count, MPV levels and atopy type, disease severity or conjunctivitis.

This study has the inherent limitation as a retrospective study because there may be other undocumented factors that may contribute to results. Another potential limitation of this study is that its single-centered design does not allow the results to be generalized to the Turkish population.

Conclusion

Although serum eosinophil count and total IgE levels are not sensitive enough in predicting the severity of AR patients, we believe that they can be helpful in the diagnosis of patients with concomitant conjunctivitis and in the presence of multiple aeroallergen sensitivity. In addition, we think that our study may lead new methods that can help the diagnosis and predict the prognosis of AR.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee (Ethical Committee of Erzurum Ataturk University Faculty of Medicine, approval number: 13.03.2019/03). The procedures were in line with the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Can increased or decreased COX2 and P21 expression be used in illness monitoring of gastric cancer and its potential precursor lesions?

Sait Yeşillik[1], Melih Alömeroğlu[2], Birol Yıldız[3], Bilgin Bahadır Başgöz[4], Mustafa Gülşen[5]

[1]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Internal Medicine, Division of Immunology and Allergy, Ankara, Turkey

[2]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Pathology, Ankara, Turkey

[3]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Internal Medicine, Division of Medical Oncology, Ankara, Turkey

[4]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey

[5]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Internal Medicine, Division of Gastroenterology, Ankara, Turkey

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Corresponding Author:
Sait Yeşillik, MD, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Internal Medicine, Division of Immunology and Allergy, Ankara, Turkey
syesillik@yahoo.com

ORCID:
orcid.org/0000-0003-1160-1381

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ABSTRACT

Aims: Early diagnosis and treatment can improve the prognosis of patients with gastric cancer. Therefore, identification and follow-up of patients who are under the risk of gastric cancer can improve the success of treatment and quality of life.

Methods: In our study, cyclooxygenase-2 (COX2) and P21 expressions of the patients with gastric adenocarcinoma and its precursor lesions atrophic gastritis and intestinal metaplasia were examined retrospectively with the immunohistochemical method.

Results: Forty patients were enrolled in each group. Grade and intensity of COX2 expressions were high in all three groups in accordance with the literature. In contrast with COX2 expressions, the grade and intensity of P21 expressions were very low in all three groups. Expressions of P21 were not observed in the vast majority of the gastric cancer group. Due to slight expressions, we detected statistically significant differences in both grading and intensity of P21 expressions between precancerous lesions and gastric cancer.

Conclusions: High COX2 expressions were consistent with literature. Decreased P21 expressions can reveal the relationship between loss of P21 expression and poor prognosis. Increased COX2, expression, especially in atrophic gastritis patients, and decreased P21 expression may be used in the follow-up of patients with gastric cancer and its precursor lesions.

Introduction

Although the incidence of gastric cancer decreases, it is still one of the most common causes of cancer mortality due to late diagnosis. Early diagnosis and treatment may be beneficial for preventing diseases, survival, and cost-effectiveness. Therefore, identification and follow-up of patients who are under the risk of gastric cancer increase the success of treatment.

Homeostasis of gastric mucosa is sustained by prostaglandins (1). Cyclooxygenase-2 (COX2) is expressed at gastric mucosa which is low in healthy tissue and high in the granulation tissue

of gastric ulcus and gastric cancer (2,3). Also, COX2 expression is increased in Barret's metaplasia, dysplasia, and esophagus adenocarcinoma (4-6).

P21 gene is the primer mediator of P53 which induced cell apoptosis. Protein P21, encoded by this gene, inhibits G1 cyclin-dependent kinase and helps drive cells into S phase (7). Czerniak et al. (8) reported P21 expression to be negative in almost all benign gastric and colonic lesions and positive in all malignant gastric and colonic lesions.

This study aims to determine the differences of COX2 and P21 expressions between patients with gastric cancer and its precursor lesions, atrophic gastritis and intestinal metaplasia.

Methods

In our study, pathology specimens of gastrectomy surgery and upper gastrointestinal endoscopy biopsies were assessed retrospectively. This study was conducted from June 2003 to December 2004. Anti-COX2 and anti-P21 were purchased from BD Biosciences (San Jose, CA, USA). Expressions of COX2 and P21 were evaluated in the pathology slides of patients with atrophic gastritis, intestinal metaplasia and gastric cancer (intestinal and diffuse type adenocarcinoma). 40 patients were enrolled for each group, and each pathology slide was labeled with COX2 and P21 antibodies separately, using immunohistochemical method. A total of 240 preparations were stained and evaluated.

Exclusion criteria included being under the age of 18 years, having another inflammatory, autoimmune *rheumatic*, infectious diseases and other types of cancers.

Immunohistochemical Method

Two independent pathologists made the evaluation. KS 400 software was used for grading and intensity. Each slide was evaluated with 100 X magnification and visualized by KS 400 software on Microsoft R Windows NT 4.OR Service Pock 6.0 operating system. P21 and COX2 were marked for measurement on available sides. Positive and negative cells were marked by using KS 400 software and results were reported by software as percentages. P21 and COX2 positive cells stained brown (Figure 1).

COX2 and P21 expressions were evaluated in terms of grading, intensity, and immunoreactivity. Grade: Classified as 0, 1 (1-29%), 2 (30-59%), 3 (60-100%), according to involvement of COX2 and P21 antibodies percentage in the pathology slides.

Intensity: Classified as 0 (no involvement), 1 (mild involvement, diffuse cytoplasmic staining is less than 10% of cells), 2 (moderate involvement, strong granular cytoplasmic staining in 10-90% of cells), 3 (severe involvement, strong granular cytoplasmic staining in more than 90% of cells) according to power of involvement of COX2 and P21 antibodies in the pathology slides (9).

Immunoreactivity score: Calculated by the multiplication of grade and intensity (2).

Statistical Analysis

Commercially available software SPSS (version 21.0, SPSS Inc, Chicago, IL) was used for the statistical analyses. The chi-square test and one-way ANOVA test were used for the comparison. $P<0.05$ was considered significant.

Results

A total of 120 patients (40% women) were enrolled with an average age of 64 years (25-87) in this study. There was no significant difference between the expression levels of men and women (p=0.054). In this study, 19 of 40 gastric cancer patients were intestinal type, and 21 were diffuse type adenocarcinoma. Only 1 of the patients was early stage-gastric cancer.

COX2 Expressions

COX2 expression grades were observed to be high and similar in the three groups. Third-grade expression was detected in most of the lesions. There was no significant difference between COX2 expression grades (p=0.06), (Figure 1). No expression was detected in 3 (2.5%) of 120 patients, 2 (1.7%) of which were in atrophic gastritis group, and 1 (0.8%) was in the gastric cancer group. Grade 3 expression was observed in thirty-two (26.7%) patients with atrophic gastritis, 35 (29.2%) with intestinal metaplasia and 25 (20.8%) with gastric cancer (Table 1).

The strongest intensity of expressions was observed in the intestinal metaplasia and gastric cancer group, weaker intensity of expression was observed in the group with atrophic gastritis. There was a significant difference in COX2 intensity of expression between atrophic gastritis and gastric cancer (p=0.026).

Table 1. Cyclooxygenase-2 expression grades and patient numbers

Diseases	Grade 0 (0%)	Grade 1 (1-29%)	Grade 2 (30-59%)	Grade 3 (60-100%)	Number of patients
Atrophic gastritis	2 (5)	2 (5)	4 (10)	32 (80)	40 (100)
Intestinal metaplasia	0 (0)	1 (2.5)	4 (10)	35 (87.5)	40 (100)
Gastric cancer	1 (2.5)	8 (20)	6 (15)	25 (62.5)	40 (100)

Grade: Classified as 0, 1 (1-29%), 2 (30-59%), 3 (60-100%)

While strong expressions were detected in 3 (2.5%) patients with atrophic gastritis, 9 (7.5%) with intestinal metaplasia and 12 (10%) with gastric cancer, there was no expression detected in 2 (1.7%) with atrophic gastritis and 1 (0.8%) with gastric cancer (Table 2).

The intensity of COX2 expression was detected similar between intestinal metaplasia and gastric cancer groups as 2nd and 3rd grade. COX2 expression was also detected in the atrophic gastritis group, but the intensity of expression was mostly 1st and 2nd grade. Same results were observed in the statistical analysis made with immunoreactivity scores.

When we evaluated immunoreactivity scores of COX2 expression between the groups, we found a significant difference between the groups with atrophic gastritis and intestinal metaplasia (p=0.02), and also in the groups with atrophic gastritis and gastric cancer (p=0.033). There was no significant difference between the groups with intestinal metaplasia and gastric cancer (p=0.345).

P21 Expressions

There was a significant difference in grading and intensity of P21 expression between the atrophic gastritis, intestinal metaplasia, and gastric cancer groups (p<0.001, p<0.001, respectively) (Figure 1).

There was no expression in 61 (50.8%) of 120 patients. Grade 1 expression was observed in the majority of atrophic gastritis, intestinal metaplasia, and gastric cancer patients. Grade 2 expression was observed in 3 (2.5%) patients with atrophic gastritis, 3 (2.5%) of the patients with intestinal metaplasia and 1 (0.8%) of the patients with gastric cancer. Grade 3 expression was not observed in any patient.

The intensity of P21 expression was not observed in the vast majority of the gastric cancer group (90%).

Grade 2 intensity of expression was observed in 1 (0.8%) of the patients with atrophic gastritis, 6 (5%) of the patients with intestinal metaplasia, and 2 (1.7%) of the patients with gastric cancer. Grade 3 intensity of expression was not detected in any patient (Table 3,4).

Results of grading and intensity of P21 expression were found to be similar. When we evaluated immunoreactivity scores of P21 expression, we found it low in all three groups. Expression was not observed in the vast majority of the gastric cancer group. Because of slight expression in the

Table 2. Cyclooxygenase-2 expression intensity and patient numbers

Diseases	Intensity 0 (%)	Intensity 1 (%)	Intensity 2 (%)	Intensity 3 (%)	Number of patients (%)
Atrophic gastritis	2 (5)	19 (42.5)	16 (40)	3 (7.5)	40 (100)
Intestinal metaplasia	0 (0)	8 (20)	23 (57.5)	9 (22.5)	40 (100)
Gastric cancer	1 (2.5)	10 (25)	17 (42.5)	12 (30)	40 (100)

Intensity: Classified as 0 (no involvement, no stained cell), 1 (mild involvement, cytoplasmic staining is less than 10% of cells), 2 (moderate involvement, cytoplasmic staining is in 10-90% of cells), 3 (severe involvement, cytoplasmic staining is more than 90% of cells)

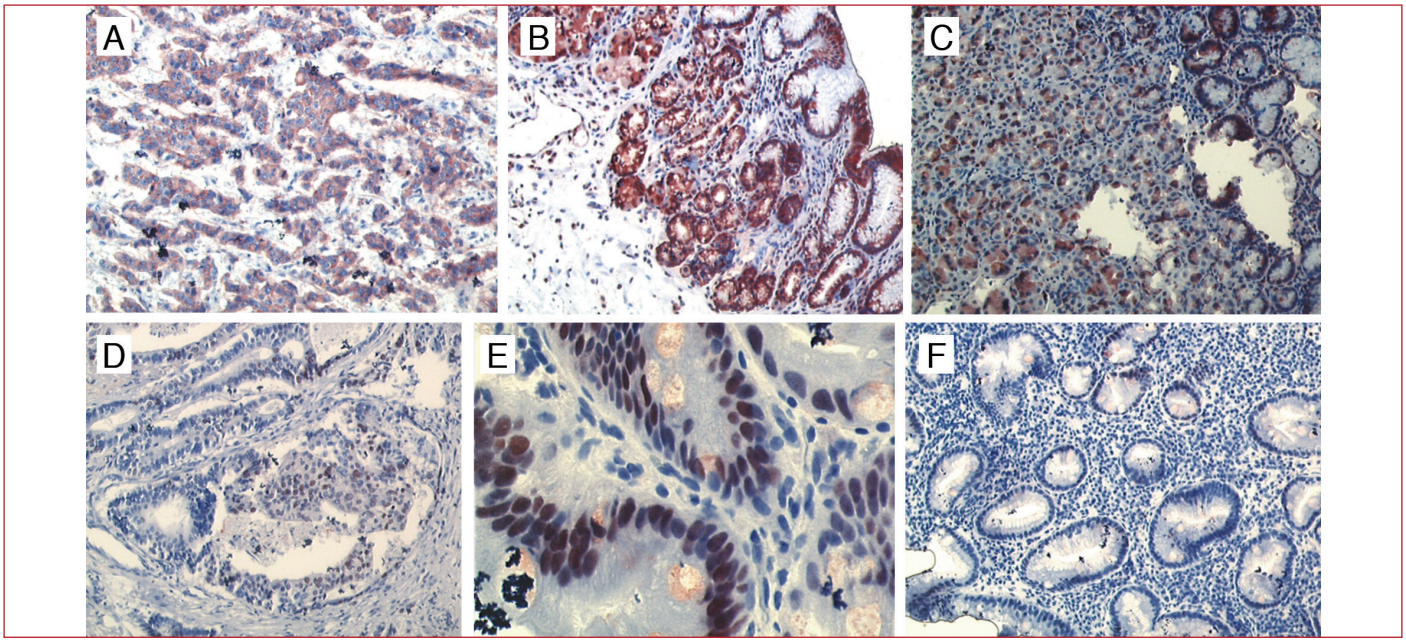

Figure 1. Cyclooxygenase-2 expression in (A) gastric cancer, (B) atrophic gastritis, (C) intestinal metaplasia, P21 expression in (D) gastric cancer, (E) atrophic gastritis, (F) intestinal metaplasia

Table 3. P21 expression grades and patient numbers

Diseases	Grade 0 (0%)	Grade 1 (1-29%)	Grade 2 (30-59%)	Grade 3 (60-100%)	Number of patients
Atrophic gastritis	13 (32.5)	24 (60)	3 (7.5)	0 (0)	40 (100)
Intestinal metaplasia	12 (30)	25 (62.5)	3 (7.5)	0 (0)	40 (100)
Gastric cancer	36 (90)	3 (7.5)	1 (2.5)	0 (0)	40 (100)

Grade: Classified as 0, 1 (1-29%), 2 (30-59%), 3 (60-100%)

Table 4. P21 expression intensity and patient numbers

Diseases	Intensity 0 (%)	Intensity 1 (%)	Intensity 2 (%)	Intensity 3 (%)	Number of patients
Atrophic gastritis	13 (32.5)	26 (65)	1 (2.5)	0 (0)	40 (100)
Intestinal metaplasia	12 (30)	22 (55)	6 (15)	0 (0)	40 (100)
Gastric cancer	36 (90)	2 (5)	2 (5)	0 (0)	40 (100)

Intensity: Classified as 0 (no involvement, no stained cell), 1 (mild involvement, cytoplasmic staining is less than 10% of cells), 2 (moderate involvement, cytoplasmic staining is in 10-90% of cells), 3 (severe involvement, cytoplasmic staining is more than 90% of cells)

atrophic gastritis and intestinal metaplasia groups, there was a statistically significant difference between gastric cancer and these two groups ($p<0.001$). There was no significant difference between the groups of intestinal metaplasia and atrophic gastritis ($p=0.339$).

Discussion

In this study, COX2 and P21 expressions of the patients with gastric adenocarcinoma and its precursor lesions (atrophic gastritis and intestinal metaplasia) were evaluated. There was no significant difference in COX2 expression grades among the three groups. Grade 3 expression was seen in the vast majority of pathology slides in all groups. There was a significant difference in terms of COX2 expression intensity among the groups. Although COX2 expression was observed in all three groups, intensity was lower in the atrophic gastritis group. COX2 expression was more intense in the gastric cancer and intestinal metaplasia group. Especially increased COX2 expressions in atrophic gastritis patients can help doctors to predict cancer progression. It can be related to progress to gastric cancer. In our study, the increase in COX2 expression was found to be significant in gastric cancer and its precursor lesions, in accordance with the literature (2-6). In our study, the intensity of COX2 expression in lesions and lesion free healthy gastric mucosa, as a control group, was evaluated in each pathology slides. There was no significant difference between healthy and atrophic areas of gastric mucosa in patients with atrophic gastritis. Expression levels were similar. We evaluated that COX2 expression in healthy gastric mucosa might be a result of atrophy at the molecular level even if pathological atrophy did not occur yet. *Helicobacter pylori* (HP) infection might be included in this situation (10).

COX2 expressions were high in both gastric cancer and its precursor lesions. Thus, COX2 expression may be used in the follow-up of patients with gastric cancer and its precursor lesions. Increased levels of COX2 can help the doctors to follow up such patients, especially in cancer progression and metastasis.

When healthy gastric mucosa and intestinal metaplasia areas were compared in the intestinal metaplasia group, COX2 expression was observed in both areas. We thought that this might be a result of intestinal metaplasia started at the molecular level or might be a result of HP infection which is known to increase COX2 expression and very common in our society (10).

Lim et al. (2) found that COX2 expression was increased in intestinal metaplasia and gastric cancer areas while COX2 expression could be detected in healthy mucosa.

In the gastric cancer group, COX2 expression in healthy areas was statistically significantly lower than in areas with cancer. Shirvani et al. (5) also reported COX2 expression in Barrett's metaplasia and dysplasia was higher than healthy mucosa, as in our study.

We believe that this is because of the advanced cancer stages of our patients. Saukkonen et al. (11) demonstrated COX2 expression as 58% and 6% in intestinal metaplasia and early-stage gastric cancer patients, respectively. We found similar expressions in groups and it was 97.5%. We thought that this was a result of 39 of 40 patients in our study who were in the advanced stage of cancer. In our study, COX2 expression in atrophic gastritis, intestinal metaplasia, and gastric cancer groups complies with literature.

We thought that increased COX2 expression was associated with inflammation, HP existence, growth factors, and cytokines besides cancer and could be beneficial in precursor lesions to follow up.

Rossolymos et al. (12) detected that increased COX2 expression scores were associated with the severity of gastritis, despite our positive findings, he found a weak correlation between COX2 expression scores and precancerous lesions like atrophic gastritis and intestinal metaplasia.

We also investigated the significant difference in P21 expression grade between healthy and atrophic areas of gastric mucosa in the atrophic gastric group. Probably due to the inability of P21 expression in atrophic cells, P21 expression was weakly increased as a result of atrophy at the molecular level in healthy tissue. Wang et al. (13) studied P21 expression in patients with chronic gastritis, atrophic gastritis, intestinal metaplasia, early-stage, and advanced gastric cancer. In this study, similar to our findings, P21 expression was found as 40% in HP (-) healthy mucosa areas, 10% in atrophic gastritis areas, 60% in intestinal metaplasia areas, 33% in nonneoplastic areas adjacent to early gastric cancer and 23% in nonneoplastic areas adjacent to advanced gastric cancer. P21 expressions in intestinal metaplasia and advanced gastric cancer areas of gastric mucosa were weak and similar. Despite the increase in COX2 expression, the loss in expression of P21 can be a predictor of cancer progression and metastasis.

Sun et al. (14) determined P21 expression in healthy areas of gastric mucosa. Noguchi et al. (15) showed P21 expression in intestinal metaplasia areas, and they failed to show P21 expression in healthy areas.

In our study, there was no P21 expression determined in almost all healthy and gastric cancer areas. While these findings in the normal tissue correlate with present literature, they are not in accordance with the gastric cancer tissue (8,16).

In our study, P21 expression was observed in 49.2% of 120 patients. In the majority of literature findings, lowest grade and intensity of expressions were demonstrated in our gastric cancer group (10%). We thought this was a result of that only one of the patients was early gastric cancer, 39 patients were advanced gastric cancer because many studies in literature showed that loss of P21 expression was a finding of advanced cancer and metastasis (17-20).

Grade and intensity of P21 expression were low and similar in atrophic gastritis and intestinal metaplasia groups. While Gamboa-Dominguez (21) and Kouraklis et al. (22) found a positive correlation between P21 expression and survival, other studies showed that the loss of P21 expression in cancer was associated with poor prognosis (18,23).

P21 expression was studied by Sun et al. (14) on 139 patients (42 incomplete metaplasia, 28 low-grade dysplasia, 21 high-grade dysplasia, 48 intestinal-type gastric cancer). They found P21 expression in some of the normal mucosa, similar to our findings. Although it was statistically insignificant, P21 expression demonstrated a reduction from incomplete metaplasia towards gastric cancer (incomplete metaplasia 47.6%, low-grade dysplasia 39.3%, high-grade dysplasia 33.3%, intestinal-type gastric cancer 29.5%). With these results, Sun stated that a gradual decrease observed in P21 expression might be significant in the progression of cancer.

In our study, the percentage and the intensity of P21 expression in gastric cancer were not in accordance with some of the literature (8,16). On the other hand, the studies that suggest the loss of P21 expression to be the cause of poor prognosis (14,17-23) support the low P21 expressions in our study.

Like in the expression of COX2 (the expression was significantly high), we thought this difference might be due to the fact that only one of our gastric cancer patient was early stage gastric cancer and the others were advanced gastric cancer. As it has been indicated before, multifactorial factors such as the organ, stage, immunohistochemistry and the molecular mechanism are all sufficient for the decision (24). It is possible to suggest that molecules such as COX2 expression and loss of P21 expression may be related to gastric cancer and poor outcome.

The limitation of our study is that if we could able to study consecutively P21 and COX2 expressions in the same patients with precursor lesions and gastric cancer, the results might be more significant. Our study was a retrospective study. Prospective researches with a larger number of patients attending and supported by genetic and experimental studies in the future will be able to demonstrate the importance of COX2 and P21 expressions in gastric cancer and precursor lesions more clearly. Also, in our study, most of the gastric patients were late diagnosed. We could have found different results if we had been able to study with early diagnosed gastric cancer patients.

Conclusion

To the best of our knowledge, this has been the first study evaluating both COX2 and P21 expressions in gastric cancer and its precursor lesions of atrophic gastritis and intestinal metaplasia.

In the future, COX2 expression may be used in the follow-up of patients with gastric cancer and atrophic gastritis. The loss of P21 expression may indicate poor prognosis and progression in gastric cancer.

Ethics

Ethics Committee Approval: This research was approved by Gülhane Training and Research Hospital Scientific Research Board, Ankara (AR-2004/54). During the time this study was conducted, retrospective studies were not subject to institutional review board approval.

Informed Consent: This research was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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The importance of R202Q polymorphism in clinical expression of Familial Mediterranean Fever

Emre Tekgöz[1], Fatma İlknur Çınar[2], Muhammet Çınar[1], Sedat Yılmaz[1]

[1]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey

[2]University of Health Sciences Turkey, Gülhane Faculty of Nursing, Department of Internal Medicine Nursing, Ankara, Turkey

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Corresponding Author:
Emre Tekgöz, MD, University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey
dr.emretekgoz@hotmail.com

ORCID:
orcid.org/0000-0002-0866-1503

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ABSTRACT

Aims: *R202Q* gene polymorphism is frequently encountered in Familial Mediterranean Fever (FMF) patients. We aimed to investigate the relationship between FMF clinical findings and *MEFV* gene mutations/polymorphisms with a particular attention to R202Q.

Methods: Total of 158 patients with FMF were included in the study that was conducted in a tertiary rheumatology outpatient clinic. The demographic and clinical features, as well as *MEFV* gene mutations, were recorded in a "Patient Assessment Form". The severity of the disease was evaluated with the FMF-severity score-2. The associations between clinical features and genetic alterations were calculated with the Pearson chi-square test.

Results: The mean age of patients was 24.3±5.1 years, the mean delay in diagnosis was 5.6±6.3 years, and 155 of the patients (98.1%) were male. The percentage of patients stating that they regularly used colchicine was 86.1%, and the mean dose was 1.4±0.3 mg/day. The most frequent mutation was M694V (76.6%), and R202Q, M680I and E148Q were found in a descending order (60.8%, 19.0% and 13.9%, respectively). M694V/R202Q was the most prevalent compound heterozygosis and found in 16 patients (10.1%). This mutation (M694V/R202Q) was associated with fewer frequencies of myalgia and peritonitis, and with good response to colchicine.

Conclusions: The presence of R202Q polymorphism is associated with FMF, and should be considered in the routine genetic analysis of the disease. In our patients, its co-existence with M694V seems to be associated with good response to colchicine, and to alleviate the severity of the disease expression of M694V, which is known to be associated with severe course.

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive genetic disorder in which recurrent inflammatory involvement of serous membranes such as pleura, peritoneum, and synovium comprises the main clinical feature. Although FMF can be seen in many ethnic groups, it is more frequent in Middle Eastern and Mediterranean descent. The highest prevalence in Turks ranged between 1 per 400 and 1 per 1000 (1). The *Mediterranean fever* (*MEFV*) gene is located on the short arm of chromosome 16. There are a total of 10 exons on this gene and FMF-related mutations are mostly in exons 10 and 2. This gene encodes a protein called Pyrin or Marenostrin. Clinical manifestations of FMF are considered to occur due to the inability to control the post-inflammatory process of the incorrectly synthesized 'Pyrin' protein associated with *MEFV* gene mutations (2,3). A lot of mutations have been identified in the *MEFV* gene. The appearance of these gene mutations will not always be associated with the disease. Among these, M694V, M694I, V726A, and M680I are the most common disease-related mutations. On the other hand, the clinical significance of some other mutations like R202Q is unclear and their relationship with any clinical feature of FMF has not been clarified yet. In this context, although there have been many efforts to determine genotype-phenotype associations in FMF, there are no consistent data on this subject. In this study, we investigated the relationship between FMF clinical findings

and *MEFV* gene mutations, and we tried to emphasize the importance of *R202Q* gene polymorphism in the FMF clinic.

Methods

Study Design, Selection of Sample, and Setting

This study was conducted between April 2016 and December 2016. The study was approved by the Gülhane Ethical Review Board (date: April 5, 2016-190, number: 50687469-1491-289-16/1648-934) and written informed consent was obtained from each participant. Patients with FMF were invited to participate in the study. The inclusion criteria for the study are (a) being fulfilling the Tel-Hashomer diagnostic criteria (b) having a *MEFV* gene analysis containing M694V, M680I, M694I, E148Q, V726A, R761H, P369S, A165A, G138G, R202Q, K695R, A744S, and L110P mutations, (c) being aged 18 years and older, (d) absence of mental confusion or any other psychiatric disorder obtained from medical records, (e) being able to speak, read, and write in Turkish, and (f) volunteering to participate in the research. The exclusion criteria are i) having a major psychiatric disease diagnosis, ii) having concurrent terminal illness or being clinically unstable, and iii) having cognitive impairment. Total of 158 patients with FMF were enrolled in the study and were subjected to data analyses.

Data Collection and Procedure

The demographic and clinical data were collected through face-to-face interviews after the participants had been informed about the purpose of the study. The demographic and clinical features were recorded in a “Patient Assessment Form”. The severity of the disease was evaluated with the FMF-severity score-2 (F-SS-2), which consisted of six criteria, including the age onset of clinical findings, the number of affected sites in a single attack, the number of affected sites in the course of the disease, the number of pleuritic attacks during the course of the disease, the number of erysipelas-like erythema attacks during the course of the disease and the colchicine dose used for remission in patients. According to the F-SS-2, the score of 3 or more was classified as severe, the score of 2 was medium, and the score of 1 or below was mild disease severity (4). Also, patients were classified according to clinical attack frequency under colchicine treatment. Those who had no attacks within the last 6 months were considered as ‘‘complete remission’’ and if they had at least 1 episode per month, they were considered as ‘‘resistant’’ or ‘‘non-responsive’’(5). *MEFV* gene mutation analysis was performed with a commercial kit (SNP FMF Real Time Polymerase Chain Reaction Kit, Ankara, Turkey) which works real time polymerase chain reaction method in our hospital.

Statistical Analysis

Statistical analyses were performed in the IBM SPSS for Windows version 21.0 package program. Numerical variables were summarized by mean±standard deviation and categorical variables by number and percentage. The Kolmogorov-Smirnov test was used to examine whether the numerical variables showed normal distribution. The difference in categorical variables between the groups was examined by the chi-square test. The relationship between numerical variables was examined with the Pearson correlation coefficient. Significance level was accepted as $p<0.05$.

Results

Total of the 158 patients participated in the study, 155 (98.1%) were male and 3 (1.9%) were female. The mean age of the patients was 24.3±5.1 years. The number of patients having family history of FMF was 100 (63.3%). The mean age at onset of clinical findings was 11.6±6.6 years, whereas the mean age at diagnosis was 17.3±7.2 years, and the mean delay in diagnosis was 5.6±6.3 years. The number of patients who regularly used colchicine was 136 (86.1%) and the average colchicine dose taken was 1.4±0.3 mg/day. There were 34 (21.5%) patients in complete remission, and 27 (17.1%) patients in colchicine-resistant or non-responsive group. Ninety four patients (59.5%) had severe, 38 (24%) moderate, and 26 (16.5%) had low disease severity levels (Table 1).

The most common *MEFV* gene mutation was M694V. Homozygous and heterozygous M694V mutations were observed in 66 (41.8%) and 55 (34.8%) patients, respectively, and 121 (76.6%) patients had this mutation in total. Mutations of R202Q, M680I, E148Q, and V726A (60.8%, 19%, 13.9% and 8.2%, respectively) were detected with decreasing frequency. Thirty (19%) patients had compound heterozygote mutation. The most common type of compound heterozygote mutation was M694V/R202Q and detected in 16 patients (10.1%). M694V/M680I was detected in 5 (3.2%) patients and M694V/R761V mutation was found in 2 (1.3%) patients (Table 2).

In terms of the relationship between genotype and phenotype, M694V mutation frequency was significantly higher in patients with family history of FMF, compared to those without family history (82.0% vs. 67.2%, p=0.035). Furthermore, the frequency of M694V mutation was found to be higher in patients with arthritis, compared to those without arthritis (80.5% vs. 65%, p=0.045). E148Q mutation frequency increased in patients with history of orchitis (25% to 10.7%, p=0.029). Another significant association between E148Q mutation and clinical findings was hemodialysis due to end-stage renal failure secondary to FMF in the family (40% to 11.2%, p=0.005). The prevalence of non-periodic myalgia was 34.2% and the patients with V726A mutation declared not to suffer from this symptom (p=0.005) (Table 3a).

M694V/R202Q compound mutation was associated with an increase in the response rate to colchicine treatment significantly and a decrease in the frequency of myalgia and peritonitis

attacks (p=0.012, p=0.016, p<0.001, respectively). Another rarely observed compound heterozygous mutation, M694V/M680I, was observed in five patients in total, and associated with acute arthritis (p=0.016) (Table 3b).

In comparison to other mutations, the patients with M694V mutation had higher F-SS-2 severity score (p=0.01). There was no correlation between other mutation types and F-SS-2 severity score (Table 4).

Table 1. Demographic features, treatment response and severity score of patients

Characteristics	**n (%)**
Age (years) (mean±SD)	24.3±5.1
Sex	
Male (M)	155 (98.1)
Female (F)	3 (1.9)
Family history of FMF	100 (63.3)
Disease onset (years) (mean±SD)	11.6±6.6
Age at diagnosis (years) (mean±SD)	17.3±7.2
Diagnostic delay (year) (mean±SD)	5.6±6.3
Colchicine usage and FMF severity score	**n (%)**
Regular colchicine use	136 (86.1)
Colchicine dose	1.4±0.3
Colchicine response	
No response to colchicine	27 (17.1)
Complete response	34 (21.5)
FMF-severity score (F-SS-2)	
Severe	94 (59.5)
Moderate	38 (24.1)
Mild	26 (16.5)

Data represented either as the mean±SD or as the frequency.
M: Male, F: Female, FMF: Familial Mediterranean Fever, SD: Standard deviation, F-SS-2: FMF-severity score-2

Discussion

In this study, we have shown that R202Q polymorphism in *MEFV* gene more or less has an effect on the clinical findings of the disease. Hence, the most common mutation after M694V and the most common compound heterozygosity with M694V support the clinical significance of this mutation.

Although many of them are rare, hundreds of variants in *MEFV* gene mutations have been detected. However, no consistent association was found between these mutations and the clinical manifestations of the disease. While the genotype-phenotype relationship in FMF is not revealed inclusively yet, the association between the disease itself and some *MEFV* gene mutations such as M694V, M694I, V726A, M680I is quite clear (1). In our study, M694V mutation was the most common among MEFV mutations (76.6%) similarly to previous studies (6,7). The most frequently observed mutations in Turkish and Armenian studies are M694V, M680I, V726A, E148Q (8). Unlike these studies, the second most frequently observed mutation type after the M694V mutation was identified as R202Q in our study. R202Q polymorphism is the most frequently observed polymorphism in MEFV mutations (9). It has been alleged and accepted, at least in part, that this polymorphism in heterozygous patients has no disease-causing effect. On the other hand, there has been a discrepancy about the role of R202Q allele in the clinical expression of FMF. In literature, there have been studies indicating similar frequency rates of heterozygous R202Q allele in FMF patients and healthy controls (10,11). In the same studies, it was not the case for the frequency of the homozygous R202Q allele, since homozygous R202Q was higher in the patients with FMF. Heterozygous R202Q in 59 patients (37.3%) in our study is consistent with previous reports. Similar to the results of study completed by Yigit et al. (11), homozygous R202Q polymorphism was found in 37 patients (23.4%) in our study. Our findings give

Table 2. Frequency of MEFV mutations and compound heterozygosity

MEFV mutations	**Presence of any related mutation n, %**	**Heterozygote n, %**	**Homozygote n, %**
M694V	121 (76.6)	66 (41.8)	55 (34.8)
R202Q	96 (60.8)	59 (37.3)	37 (23.4)
M680I	30 (19.0)	25 (15.8)	5 (3.2)
E148Q	22 (13.9)	22 (13.9)	0 (0.0)
V726A	13 (8.2)	10 (6.3)	3 (1.9)
MEFV compound mutations	**Presence of any related mutation n, %**		
Any compound heterozygosity	30 (19.0)		
M694V/R202Q	16 (10.1)		
M694V/M680I	5 (3.2)		
M694V/R761V	2 (1.3)		

More than 1 agent might have been used in the same patient.
M694V/V726A, M694V/Q202Q, M694V/E148Q, E148Q/R202Q, R202Q/V726A, M680I/V726A and M680I/R761H were detected in 1 patient. MEFV: Mediterranean Fever

support to the consideration that R202Q is one of the causative genetic abnormalities in the pathogenesis of FMF. In addition to the contribution to the debate about whether the R202Q has a role in FMF or not, our study also gives evidence about the clinical significance of the R202Q alteration in patients with FMF. When we compared the compound heterozygous mutations M694V/R202Q with other mutations, we found that M694V/R202Q was associated with fewer frequencies of myalgia and peritonitis, and with good response to colchicine, in other words, with better course of the disease. This finding is somewhat consistent with the study of Çankaya et. al. (12), in which they detected that frequencies of symptoms were lower in the M694V/R202 subgroup. When taken together, these two studies suggest that R202Q alteration alleviates the disease course in patients with M694V mutation, which is known to be associated with more severe disease.

Colchicine has been used since the 1970s to prevent or at least to reduce frequency and severity of FMF attacks and more importantly to prevent the development of amyloidosis. The use of colchicine in sufficient doses prevents amyloidosis, the most important complication of FMF, and provides amelioration in patients who develop amyloidosis (3,13). However, its preventive effect is applicable only when it is used regularly. We concluded in our study that 136 (86.1%) of patients received

Table 3a. Relationship between MEFV mutation type and clinical findings

Clinical finding No/Yes		MEFV mutation No	MEFV mutation Yes	p value
M694V				
Family history of FMF	No	19 (32.8)	39 (67.2)	**0.035**
	Yes	18 (18.0)	82 (82.0)	
Arthritis	No	14 (35.0)	26 (65.0)	**0.045**
	Yes	23 (19.5)	95 (80.5)	
E148Q				
Orchitis	No	109 (89.3)	13 (10.7)	**0.029**
	Yes	27 (75.0)	9 (25.0)	
Family history of hemodialysis	No	127 (88.8)	16 (11.2)	**0.002**
	Yes	9 (60.0)	6 (40.0)	
V726A				
Non-periodic myalgia	No	91 (87.5)	13 (12.5)	**0.005**
	Yes	54 (100.0)	0 (0.0)	

FMF: Familial Mediterranean Fever, MEFV: Mediterranean Fever

Table 3b. Relationship between M694V compound heterozygosity mutation type and clinical findings

Clinical finding No/Yes		MEFV mutation No	MEFV mutation Yes	p value
M694V/R202Q				
Peritonitis	No	11 (64.7)	6 (35.3)	**<0.001**
	Yes	131 (92.9)	10 (7.1)	
Myalgia	No	68 (84.0)	13 (16.0)	**0.016**
	Yes	74 (96.1)	3 (3.9)	
Colchicine response	No	26 (96.3)	1 (3.7)	**0.012**
	Partial	90 (92.8)	7 (7.2)	
	Complete	26 (76.5)	8 (23.5)	
M694V/M680I				
Arthralgia	No	18 (85.7)	3 (14.3)	**0.017**
	Yes	135 (98.5)	2 (1.5)	
Acute arthritis	No	148 (98.0)	3 (2.0)	**0.016**
	Yes	5 (71.4)	2 (28.6)	

MEFV: Mediterranean Fever

Table 4. Relationship between MEFV mutation type and Familial Mediterranean Fever-severity score

MEFV mutation		FMF-severity score (F-SS-2)			p value
		Mild, n (%)	Moderate, n (%)	Severe, n (%)	
M694V	No	12 (32.4)	6 (16.2)	19 (51.4)	**0.010**
	Yes	14 (11.6)	32 (26.4)	75 (62.0)	
R202Q	No	13 (21.0)	13 (21.0)	36 (58.1)	0.427
	Yes	13 (13.5)	25 (26.0)	58 (60.4)	
E148Q	No	21 (15.4)	33 (24.3)	82 (60.3)	0.693
	Yes	5 (22.7)	5 (22.7)	12 (54.5)	
M680I	No	23 (18.0)	30 (23.4)	75 (58.6)	0.567
	Yes	3 (10.0)	8 (26.7)	19 (63.3)	
V726A	No	23 (15.9)	34 (23.4)	88 (60.7)	0.587
	Yes	3 (23.1)	4 (30.8)	6 (46.2)	
M694V/R202Q	No	23 (16.2)	34 (23.9)	85 (59.9)	0.954
	Yes	3 (18.8)	4 (25.0)	9 (56.2)	

FMF: Familial Mediterranean Fever, F-SS-2: FMF-severity score-2, MEFV: Mediterranean Fever

colchicine treatment regularly with a mean of 1.4±0.3 mg/day, consistent with our previous knowledge. Consequently, in this cohort with a high rate of regular colchicine usage, 27 patients (17.1%) did not respond to treatment despite the maximum dose of colchicine.

Although many scoring systems were established to determine the disease severity, F-SS-2 scoring system was used in our study. This scoring scale, developed by Mor et al. (4), distinguishes severity disease from non-severity disease by over 92% sensitivity and specificity. As discussed above, the severity of the disease is assessed in terms of response to colchicine treatment and clinical findings. In addition, the *MEFV* gene mutations that patients have may affect the clinical symptoms in some cases. In this regard, studies have been carried out to demonstrate the prognosis and predict the clinical severity of the disease, that is, the genotype- phenotype relationship. The most striking mutation type in FMF patients in terms of genotype-phenotype relationship is M694V. In our study, M694V mutation was associated with more severe disease (p=0.01). The previous studies on this subject supported our findings (14,15). Yilmaz et al. (16) used the Pras severity score differently, and the disease severity score was also high in those carrying the M694V mutation.

E148Q and V726A mutations in our cohort were observed less frequently than mutations M694V, R202Q and M680I. It has been suggested that the E148Q mutation may be a polymorphism with low penetration, but not a mutation that causes the disease (17). With respect to this mutation, another important relationship found in our study was that the E148Q mutation was associated with the orchitis and family history of hemodialysis due to end-stage renal failure secondary to FMF. A quite similar finding in the literature was reported by Gershoni-Baruch et al. (15), and they found an increased risk of renal amyloidosis as much as those carrying the M694V mutation in those carrying the V726A/E148Q mutation. However, they concluded that the risk of renal amyloidosis was increased by the V726A allele. One of the clinically important findings of our study is related to V726A mutation. Our results suggest a somewhat protective effect of this mutation since non-periodic myalgia was observed in 54 (34.2%) patients, but was not observed in patients carrying the V726A mutation. This finding needs further confirmation, but it should be kept in mind that non-periodic myalgia has not been widely examined in genotype-phenotype association studies.

One of the major limitations of our study was the inequality of female and male patient numbers. This may be due to the fact that consecutive patients that met the criteria of inclusion were included and that the majority of the patients followed up were men. Also, mutation studies were not performed in the parents for individuals with compound mutations.

Conclusion

R202Q polymorphism is frequently encountered in FMF patients both as heterozygous and homozygous. We think that R202Q polymorphism has a role in the expression of the disease. It is associated with milder clinical findings, reduced disease severity and increased rates of response to colchicine, when found in combination with M694V, which is known to be associated with severe disease course. In this respect, it can also provide opportunities for clinicians in the follow-up of patients with FMF, in terms of disease progression and treatment options. For this reason, R202Q polymorphism should be considered in the routine genetic analysis of the disease.

Ethics

Ethics Committee Approval: The study was approved by the Gülhane Ethical Review Board (date: April 5, 2016-190, number: 50687469-1491-289-16/1648-934).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Analysis of urinary stone types' distribution in Turkey according to the geographical regions where patients were born and live: A cross-sectional single-center experience

Selçuk Sarıkaya[1], Çiğdem Yücel[2], Nejdet Karşıyakalı[3], Erdim Sertoğlu[2], Engin Kaya[1], Turgay Ebiloğlu[1], Selahattin Bedir[1], Taner Özgürtaş[2]

[1]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Urology, Ankara, Turkey

[2]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Biochemistry, Ankara, Turkey

[3]Cukurca State Hospital, Clinic of Urology, Hakkari, Turkey

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Corresponding Author:
Nejdet Karşıyakalı, MD, FEBU, Cukurca State Hospital, Clinic of Urology, Hakkari, Turkey
nkarsiyakali@hotmail.com

ORCID:
orcid.org/0000-0002-0709-0331

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ABSTRACT

Aims: To evaluate the stone composition and the distribution of the stone types in the geographical regions of Turkey according to where patients were born and where patients live.

Methods: The patients who were treated for urinary system stone disease in our hospital between January 2011 and March 2019 were included in the study. Stone samples were collected by endoscopic stone surgery methods or shock wave lithotripsy. Stone analyses were made with manual chemical analysis methods. Stone types and distribution were recorded according to geographical regions of Turkey.

Results: A total of 706 patients who were treated for urolithiasis were included in the study. Calcium oxalate (CO) stones were at the highest rates for both genders [127 (68.6%) and 359 (68.9%), for females and males, respectively]. There were no statistically significant differences in terms of stone types between genders (p=0.323). There were statistically significant more CO (297), uric acid (17), mixed stones (78) in the Anatolian (central) region than the other regions according to the geographical region where patients were born (p<0.001, for each). Additionally, there were significantly more calcium phosphate stone formers (25) in the Anatolian region according to the geographical region where patients lived (p<0.001).

Conclusions: CO is the most common stone type in Turkey independently of where patients were born or where patients live. Higher prevalence rates of stone disease and CO stones were seen in Central Anatolia. Both geographic origin and dietary habits affect the incidence of urinary system stone disease.

Introduction

Urolithiasis is one of the most common urologic pathology that affects the urinary tract with a high prevalence rate between 2% and 20% (1,2). The prevalence and incidence are increasing in different parts of the world for both men and women (3). The higher incidence and prevalence rates were found to be related to dietary habits, socioeconomic conditions, water consumption, water quality and hot climate (4). Metabolic disorders like overweight/obesity, hyperlipidemia, hyperuricemia, and hyperglycemia have a role in the recurrence of urolithiasis (5). In Turkey, urolithiasis is an endemic disease and has a high incidence rate (15%) and it is more common in the south and southeast parts of the country (3). Stones can be seen in any location of the urinary tract and the mechanism of its formation is still unknown (6). Clinical conditions and the treatment choices mainly depend on the size, location of stones, degree of obstruction and the chemical composition of the stone (7,8). Many factors were found to be related to the stone composition as the body weight, metabolic syndrome, hypertension, body mass index and renal function (1,9,10). In addition, it has been shown that stone composition is one of the most important factors which is associated with the recurrence of stone disease (11).

Several *in vivo* and *ex vivo* methods were described in the literature in order to analyze the urinary stone types (12,13). Defining the stone type is very important for both the management and prevention of stone disease. Changing dietary habits and water intake are some of the key points for preventing stone disease (14). In the present study, we aimed to evaluate our single-center results in terms of stone composition and the distribution of the stone types in Turkey according to geographical regions of where patients were born and live. Secondly, we aimed to evaluate and compare if stone types were affected by changing the geographical regions of patients.

Methods

We retrospectively reviewed the medical records of the patients who were diagnosed with urinary system stone disease and treated with endoscopic (percutaneous nephrolithotomy, ureterorenoscopic laser lithotripsy, cystolithotripsy), laparoscopic nephrolithotomy or extracorporeal shock wave lithotripsy (SWL) at University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Urology between January 2011 and March 2019 in the study. Informed consent was not obtained from participants because of the retrospective nature of the study. Stone samples were collected during the stone surgery methods mentioned above and with SWL. Patients treated with SWL were requested to micturate into a bowl for collecting stone fragments after SWL sessions. Patients whose stone analysis data were missing, who could not collect stone fragments after SWL or who were unwilling to participate in the study were excluded. The study protocol was approved by the University of Health Sciences Turkey, Gülhane Training and Research Hospital, Ethics Committee for Non-Interventional Research (protocol no: 2020/169). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographics of the patients, stone locations, stone analysis results and distribution of stone analysis results according to the regions of Turkey [Anatolia (central), Marmara (north-west), Aegean (west), Black Sea (north), Mediterranean (south), Eastern Anatolia, Southeastern Anatolia] were recorded. The regions where patients lived and where they were born were both noted.

Stone locations were divided into three groups as kidney, ureter, and bladder. Manual chemical analysis was used to identify stone compositions. Stone analyses were made with wet chemical analysis method, firstly described by Uldall, (15), in the University of Health Sciences Turkey, Gülhane Training and Research Hospital, Biochemistry Clinic's metabolism laboratory. All analyses were carried out in the same laboratory by two experienced biochemistry specialists. Stone types were classified as calcium oxalate (CO), calcium phosphate (CP), uric acid (U), cystine (C), magnesium ammonium phosphate (MAP) and the mixed types. The calcium components and the infectious components were also analyzed because of the importance of prophylaxis. The seven regions of Turkey were analyzed statistically in detail according to the distribution of stone analysis results, calcium components and infectious components of stones. In addition, CO stones were compared according to the patient's geographical origin and location to evaluate if the changing the geographical region affected the incidence.

Statistical Analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median, minimum and maximum, number and frequency. The normal distribution of the quantitative data was analyzed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare two groups of quantitative variables showing abnormal distribution. The Pearson chi-square and Fisher's exact tests were used to compare qualitative data. A p value of <0.05 was considered statistically significant.

Results

A total of 706 patients were included in the study. Of the patients, 521 (73.8%) were male and 185 (26.2%) were female. The median age of the female patients was 44 (19-78) years and it was 41 (3-85) years for male patients. There was no statistically significant difference in terms of age and gender ($p>0.05$, for each). There were no statistically significant differences in terms of stone localization and stone types between the genders ($p=0.053$ and $p=0.323$, respectively). Only 16 (3.1%) male patients had stones in the bladder (Table 1). CO stones were at the highest rates for both genders [127 (68.6%) and 359 (68.9%), for females and males, respectively] (Table 1). The calcium component was observed in 166 (89.7%) female patients and 484 (92.9%) male patients, there was no statistically significant difference ($p=0.171$). In addition, there was no statistical difference in terms of the infectious component between the genders ($p=0.127$). The infectious component was observed in 16 (8.6%) female patients and 67 (12.9%) male patients (Table 1).

While evaluating the regions where people were born, CO, U, and mixed stone forms displayed statistically significantly higher prevalence in the Anatolian (central) region than in other regions ($p<0.001$) (Table 2). CO stones were the most observed stone type in the Anatolian (central) region (Table 2, 3). The calcium component was positive and the infectious component was negative in most of the patients in all regions. There was no statistical difference in infectious components according to geographical regions where patients were born ($p=0.313$) (Table 2).

While evaluating the region where patients lived, most of our patients were from Anatolia (central) region as it was

expected because our hospital is located in that region. There was an approximately similar number of patients from other geographical regions. When we compared the stone types according to regions where patients lived, there were statistically significantly more CO, CP, U and mixed stones in Anatolian (central) (p<0.001, for each) (Table 3).

When we compared the CO stone formers according to the patient's geographical origin and location, there was a statistically significant difference between the regions and we realized that migration had an impact on urinary system stone disease (Table 4).

Discussion

The overall incidence of urolithiasis is rising worldwide, including the United States and Northern Europe in the latest years (16,17). Turkey is among the countries with a high incidence of urolithiasis. Evaluating the regions of Turkey, it has a higher prevalence rate in the south and southeastern parts (3,18). The common features of these two regions are that they have similar hot climates and the nearest side of the country to the equator. In addition, people who live in these regions have similar dietary habits (oxalate-rich foods, high animal protein, high salt intake, etc.). The amounts of oxalate and calcium consumed in the diet are significant factors in the development of CO stone disease (19). Positive relation has been demonstrated between kidney stones and the consumption of oxalate-rich foods (20). Oxalate does not have a functional role in humans and is derived from the diet as an unnecessary product of metabolism (19). Therefore, the oxalate intake directly affects urinary oxalate concentration. As we have mentioned in the introduction section, a high fluid intake seems to be the most evidence-based measure for the prevention of idiopathic oxalate stone formation. A high fluid intake which guarantees a diuresis of 2 L/day seems together with some dietary oxalate and Na^+ restriction to be an appropriate measure to prevent idiopathic Ca nephrolithiasis. However, a consensus has not been reached yet for this to be an acceptable strategy for CO stone formation (21).

In the present study, we found that CO is the most common stone type in Turkey, independently of where patients were born or live. In Turkey, the central and western parts of the country are usually taking emigrants from the other regions of the country. Local food varieties and dietary habits of each region are so different in reality. For example, Mediterranean cuisine is dominated in the western regions while the consumption of red meat and animal proteins are common feeding habits in the south and east regions. In our cohort, CO stone formers' number and frequency were higher according to patients' location than patients' origin (450, 92.6% vs. 297, 61.1%, p<0.001). This difference can help to explain that migration has an impact on

Table 1. Demographics and stone characteristics of the patients

Variables		Gender		
		Female (185, 26.2%)	Male (521, 73.8%)	
		n (%)	n (%)	p value
Age (year) [median (minimum-maximum)]		44 (19-78)	41 (3-85)	0.437[a]
Stone localization	Kidney	117 (63.2)	314 (60.3)	0.053[b]
	Ureter	68 (36.8)	191 (36.7)	
	Bladder	0	16 (3.1)	
Stone type	Calcium oxalate	127 (68.6)	359 (68.9)	0.323[b]
	Calcium phosphate	9 (4.9)	20 (3.8)	
	Uric acid	12 (6.5)	16 (3.1)	
	Cystine	2 (1.1)	8 (1.5)	
	Magnesium ammonium phosphate	5 (2.7)	13 (2.5)	
	Calcium oxalate + calcium phosphate	12 (6.5)	27 (5.2)	
	Calcium oxalate + uric acid	7 (3.8)	24 (4.6)	
	Calcium oxalate + magnesium ammonium phosphate	11 (5.9)	54 (10.4)	
Calcium component	None	19 (10.3)	37 (7.1)	0.171[b]
	Exist	166 (89.7)	484 (92.9)	
Infectious component	None	169 (91.4)	454 (87.1)	0.127[b]
	Exist	16 (8.6)	67 (12.9)	

[a]Mann-Whitney U test
[b]Chi-square test

Table 2. Stone characteristics according to the geographical region where patients were born

Variables		Geographical Region								
		Anatolia (Central) (419, 59.3%)	Marmara (North-West) (43, 6.1%)	Aegean (West) (n, %=40, 5.7%)	Black Sea (North) (68, 9.6%)	Mediterranean (South) (49, 6.9%)	Eastern Anatolia (56, 7.9%)	Southeastern Anatolia (25, 3.5%)	Abroad (6, 0.8%)	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p value
Stone type	Calcium oxalate	297 (70.9)	33 (76.7)	29 (72.5)	43 (63.2)	28 (57.1)	36 (64.3)	16 (64.0)	4 (66.7)	<0.001[a]
	Calcium phosphate	14 (3.3)	6 (14.0)	1 (2.5)	1 (1.5)	5 (10.2)	2 (3.6)	0	0	
	Uric acid	17 (4.1)	0	3 (7.5)	5 (7.4)	0	2 (3.6)	0	1 (16.7)	<0.001[a]
	Cystine	4 (1.0)	0	0	3 (4.4)	1 (2.0)	2 (3.6)	0	0	
	Magnesium ammonium phosphate	9 (2.1)	1 (2.3)	1 (2.5)	2 (2.9)	2 (4.1)	1 (1.8)	2 (8.0)	0	
	Calcium oxalate + calcium phosphate	23 (5.5)	0	2 (5.0)	4 (5.9)	2 (4.1)	5 (8.9)	3 (12.0)	0	<0.001[a]
	Calcium oxalate + uric acid	18 (4.3)	1 (2.3)	0	7 (10.3)	5 (10.2)	0	0	0	<0.001[a]
	Calcium oxalate + magnesium ammonium phosphate	37 (8.8)	2 (4.7)	4 (10.0)	3 (4.4)	6 (12.2)	8 (14.3)	4 (16.0)	1 (16.7)	<0.001[a]
Calcium component	None	30 (7.2)	1 (2.3)	4 (10.0)	10 (14.7)	3 (6.1)	5 (8.9)	2 (8.0)	1 (16.7)	
	Exist	389 (92.8)	42 (97.7)	36 (90.0)	58 (85.3)	46 (93.9)	51 (91.1)	23 (92.0)	5 (83.3)	
Infectious component	None	373 (89.0)	40 (93.0)	35 (87.5)	63 (92.6)	41 (83.7)	47 (83.9)	19 (76.0)	5 (83.3)	0.313[a]
	Exist	46 (11.0)	3 (7.0)	5 (12.5)	5 (7.4)	8 (16.3)	9 (16.1)	6 (24.0)	1 (16.7)	

[a]Chi-square test

Table 3. Stone characteristics according to the geographical region where patients live

Variables		Geographical Region							
		Anatolia (Central) (648, 91.8%)	Marmara (North-West) (12, 1.7%)	Aegean (West) (11, 1.6%)	Black Sea (North) (12, 1.7%)	Mediterranean (South) (7, 1.0%)	Eastern Anatolia (11, 1.6%)	Southeastern Anatolia (5, 0.7%)	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p value
Stone type	Calcium oxalate	450 (69.4)	10 (83.3)	8 (72.7)	5 (41.7)	2 (28.6)	6 (54.5)	5 (100.0)	<0.001[a]
	Calcium phosphate	25 (3.9)	0	0	1 (8.3)	1 (14.3)	2 (18.2)	0	<0.001[a]
	Uric acid	26 (4.0)	1 (8.3)	0	1 (8.3)	0	0	0	<0.001[a]
	Cystine	8 (1.2)	0	0	0	1 (14.3)	1 (9.1)	0	
	Magnesium ammonium phosphate	15 (2.3)	0	1 (9.1)	1 (8.3)	0	1 (9.1)	0	
	Calcium oxalate + calcium phosphate	36 (5.6)	0	1 (9.1)	0	1 (14.3)	1 (9.1)	0	<0.001[a]
	Calcium oxalate + uric acid	28 (4.3)	0	0	3 (25.0)	0	0	0	<0.001[a]
	Calcium oxalate + magnesium ammonium phosphate	60 (9.3)	1 (8.3)	1 (9.1)	1 (8.3)	2 (28.6)	0	0	<0.001[a]
Calcium component	None	49 (7.6)	1 (8.3)	1 (9.1)	2 (16.7)	1 (14.3)	2 (18.2)	0	
	Exist	599 (92.4)	11 (91.7)	10 (90.9)	10 (83.3)	6 (85.7)	9 (81.8)	5 (100.0)	
Infectious component	None	573 (88.4)	11 (91.7)	9 (81.8)	10 (83.3)	5 (71.4)	10 (90.9)	5 (100.0)	
	Exist	75 (11.6)	1 (8.3)	2 (18.2)	2 (16.7)	2 (28.6)	1 (9.1)	0	

[a]Chi-square test

urinary system stone disease. In light of these data, we can say that people maintain their dietary habits when they migrate to another geographical region of the country and both geographical origin and dietary habits have a cumulative effect on the incidence of urinary system stone disease.

There are lots of epidemiological studies that have been conducted in order to analyze the stone types and prevalence. True prevalence would be underestimated because the patients with spontaneous stone passage do not need medical therapy (2). Several community-based studies revealed interesting results in the literature. Epidemiological studies can provide purposeful knowledge for the treatment and prevention of stone disease. Ogawa et al. (7) presented their results for Japan and the annual incidence for the stone disease was detected to be at higher rates as 114.3 (per 100,000) (7). Metabolic evaluation is an important point for stone prevention as some metabolic conditions as hypercalciuria, hypocitraturia, and hypomagnesuria were found to be strongly related to stone formation (22). In our study, we did not evaluate patients in terms of prevention for stone disease by metabolic evaluation. We aimed to show the distribution of stone types according to regions where patients were born and lived. In line with our study results, we have found that the most common stone type was CO in each region of Turkey. Wu et al. (23) reported similar results with our study as they reported the results of 12,846 patients and the most common stone type was CO in China (23). Although the overall incidence rate was lower in the general population, a recent 3-year retrospective study from Norway also showed that CO stones were the most commonly seen stones also in this country (17). Similarly, Jindal et al. (24) reported the results of 90 patients and the most common stone type was

Table 4. Comparisons of calcium oxalate stones according to patients' geographical origins and locations

Variables	Geographical region where patients born n (%)	Geographical region where patients live n (%)	p value
Anatolia (Central) (n=486)	297 (61.1)	450 (92.6)	<0.001[a]
Marmara (North-West) (n=486)	33 (6.8)	10 (2.1)	<0.001[b]
Aegean (West) (n=486)	29 (6.0)	8 (1.6)	<0.001[b]
Black Sea (North) (n=486)	43 (8.8)	5 (1.0)	0.006[b]
Mediterranean (South) (n=486)	28 (5.8)	2 (0.4)	1.000[b]
Eastern Anatolia (n=486)	36 (7.4)	6 (1.2)	<0.001[b]
Southeastern Anatolia (n=486)	16 (3.3)	5 (1.0)	<0.001[b]
Abroad (n=486)	4 (0.8)	-	-

[a]Chi-square test
[b]Fisher's exact test

CO in eastern India (24). Karabacak et al. (3) reported that the most common stone type was CO in Turkey when they evaluated the stone compositions according to gender and region (3). In concordance with our results, Karabacak et al. (3) reported that the prevalence of CO stones was higher in the Central Anatolia region (3). The explanation of this situation may be that both of our institutes are in the same region. In contrast, Akinci et al. (18) reported a higher prevalence of the stone disease in the southern and southeastern regions of Turkey (18). We think the reason for these similarities and differences is the different patient profiles of the institutes. When we consider the gender distribution of urinary stone patients in our study, we find that 73.8% of the patients were male and 26.2% of the patients were female. This is actually the expected ratio because higher levels of testosterone in males can be thought of as an independent risk factor for urolithiasis. This can be explained by the suppression of renal osteopontin expression by testosterone and causing increased urinary oxalate excretion. On the other hand, estrogen seems to inhibit stone formation by increasing osteopontin levels and decreasing oxalate formation (25). The stone compositions were found to be relevant to the kidney functions (9). U stones were found to be related to lower glomerular function rates (GFR) and CP stones were found to be associated with higher GFR levels (9). Several prevention strategies as changing dietary habits, higher water consumption and protection from hot climate could be taken according to the distribution of stone types in regions. In our study cohort, there were not many patients with U and CP stones, multicenter and prospective studies could provide more clear results for these stone types.

Nonetheless, this study has some limitations. First, it has a retrospective design and the inherent retrospective and non-randomized nature may have led to selection bias. Because of the limitations of stone types number in each region, we could not compare the regions in terms of C and MAP stones. Larger patient populations, multicentric and prospective studies are necessary for getting more information about the distribution of stone compositions in each region of Turkey. Finally, we did not evaluate patients in terms of recurrent disease or prevention methods. Nevertheless, our study is in concordance with several epidemiologic studies.

Conclusion

CO is the most common stone type in Turkey, independently of where patients were born or live. Higher prevalence rates of stone disease and CO stones were seen in Central Anatolia. The calcium composition was also detected at higher rates. Both geographic origin and dietary habits affect the incidence of urinary system stone disease. If the stone type distribution of each region is better understood, various prevention strategies such as patient-specific nutrition can be applied. Prospective and multicentric studies with larger patient populations are necessary for getting more information about the distribution of stone compositions in each geographical region of Turkey.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, Gülhane Training and Research Hospital, Ethics Committee for Non-Interventional Research (protocol no: 2020/169).

Informed Consent: Informed consent was not obtained from participants because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.B., T.Ö., Design: S.B., T.Ö., Data Collection or Processing: N.K., E.S., Analysis or Interpretation: S.S., Ç.Y., E.S., E.K., T.E., T.Ö., N.K., Literature Search: S.B., T.Ö., Writing: S.S., N.K., Ç.Y.

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Evaluation of post-Holmium laser enucleation of the prostate hospital readmissions

Eymen Gazel[1], Engin Kaya[2], Serdar Yalçın[2], Sercan Yılmaz[2], Selahattin Bedir[2], Mehmet Yılmaz[3], Lütfi Tunç[4]

[1]Acibadem Ankara Hospital, Clinic of Urology, Ankara, Turkey

[2]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Urology, Ankara, Turkey

[3]Zile State Hospital, Clinic of Urology, Tokat, Turkey

[4]Gazi University Faculty of Medicine, Department of Urology, Ankara, Turkey

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Corresponding Author:
Eymen Gazel, MD, Acibadem Ankara Hospital, Clinic of Urology, Ankara, Turkey
eymen_gazel@yahoo.com

ORCID:
orcid.org/0000-0003-3774-9982

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ABSTRACT

Aims: Re-admission to the hospital after operation and discharge has become a topic of increasing interest in recent decades and is being studied due to its impact on countries' medical costs. We tried to examine the rates and causes of re-admission to the hospital in 30 days in patients who performed Holmium Laser Enucleation of the Prostate (HoLEP), a popular minimally invasive surgery in recent years.

Methods: Patients who underwent HoLEP between July 2017 and April 2019 were retrospectively reviewed. Reasons and rates of re-admission to the hospital in the first 30 days of 300 patients meeting the inclusion criteria, and the way managing the situations were recorded.

Results: In our study, readmission after HoLEP was observed in 26 patients (26/300) as 8.67% rate with nonspecific and specific causes. Other than nonspecific reasons, hematuria requiring or not requiring transfusion was the most common cause of readmission (2.3%). The second most common reason for readmission was acute urinary retention requiring three-day anti-inflammatory therapy and recatheterization (1.67%). Urinary tract infection (1.33%) requiring oral or intravenous antibiotic therapy was the third most common specific cause.

Conclusions: In the literature, readmission rates after HoLEP change between 5.5% and 17.8%. Readmission rate in our study was 8.67%, which is compatible with the literature. Knowing the reasons and rates of readmission after HoLEP is important to predict early complications after surgery and to manage these complications.

Introduction

Lower urinary tract symptoms related to benign prostatic obstruction continues to be important as one of the most prevalent health problems observed among adult men (1). Although it is not included in the guidelines as the gold standard yet, use of laser in the treatment of benign prostate hyperplasia (BPH) is becoming more prevalent as a minimally invasive approach alternative to Transurethral Resection of the Prostate (TUR P) (2,3). It is revealed that Holmium Laser Enucleation of the Prostate (HoLEP), which is a minimally invasive and prostate-independent method, has surgical results comparable to traditional TUR P and has low perioperative and postoperative complications and good surgical results in BPH surgical treatment (2,4,5).

Readmission to the hospital after operation and discharge has become an increasing interest in the last decades and it is being analyzed due to its effect on medical expenses of countries (6). Moreover, hospital readmission rates are being evaluated as a criterion of the quality of healthcare services in the Western countries (6,7). In the present study, we aimed to present the hospital readmission incidences and causes within 30 days in patients we performed HoLEP, which is a recently popular minimally invasive surgery. We think that our study will contribute to the literature since the number of studies on

the reasons and rates of re-admission to hospital after HoLEP surgery is very low.

Methods

Patients who had HoLEP performed between July 2017 and April 2019 in Acibadem Ankara Hospital and Gülhane Training and Research Hospital were retrospectively analyzed. The study protocol was approved by Gazi University Ethical Committee, Turkey (approval number: 2020-150) and complied with the Helsinki Declaration. Diagnosis of obstruction was confirmed with urine flow rate, post-void residual (PVR) urine and preoperative International Prostate Symptom Score (IPSS). Inclusion criteria for HoLEP surgery were IPSS of >8, ≤15 mL/sec maximum urine flow rate, and PVR of ≥50 mL. Prior to the HoLEP surgery, all cases had cystoscopy performed in order to examine obstruction, bladder trabeculation, urethral and bladder pathologies and to exclude bladder tumor. A total of 9 patients were excluded from the study. These patients included three prostate cancer patients, two bladder cancer patients, one neurogenic bladder patient, and three urethral stricture patients. All patients signed an informed consent form prior to the surgery. The HoLEP procedure and technique performed were previously explained by the authors (8). Causes and rates of hospital readmissions in 300 patients, who underwent HoLEP and who, afterwards, had catheter removed and were discharged, were recorded along with the methods of managing the encountered situations.

Statistical Analysis

The Statistical Package for Social Sciences 23.0 software (SPSS 23.0, Chicago, IL, United States of America) was utilized. Descriptive statistics of scale samples and peroperative outcomes were expressed as mean±standard deviation or median±interquartile range.

Results

Causes and rates of hospital readmissions in 300 patients, who had HoLEP performed between July 2017 and April 2019, were evaluated along with the management of these situations. Patients' characteristics are presented in Table 1. The mean age was 62.6 years and the mean prostate size was 88.27 g. The difference between preoperative and postoperative PSA values was significant statistically (p<0.001). Causes and rates of readmissions and management methods are presented in Table 2. It was observed that highest rates of postoperative readmission were due to nonspecific symptoms such as postoperative emesis, fever, pain, etc. (2.3%). Other than these nonspecific symptoms; hematuria requiring or not requiring transfusion and requiring surgical intervention was observed as the most prevalent cause of readmission (2.3%), which was followed by re-catheterization and acute urinary retention requiring three-day anti-inflammatory treatment (1.67%). Urinary tract infection requiring oral or intravenous antibiotic treatment (1.33%), clot retention (0.67%), and hematuria requiring transfusion (0.67%) were observed. Temporary hematuria not causing low hemoglobin (1.67%), deep vein thrombosis (0.33%) were observed with less prevalence.

Discussion

Hospital readmission request and acceptance rates are being analyzed in the United States of America due to their effects on increasing medical costs (7). It has been shown that readmission request and acceptances to Centers for Medicare and Medicaid Services in United States of America cost 17.5 billion dollars in 2010 and moreover, 27% of the readmission requests and acceptances were preventable (7,9).

There are studies in the literature presenting the readmission causes, incidences, and predictive factors after open or endoscopic urologic surgeries (6,7,10-12). In a study, the most prevalent reasons for readmission within 30 days after TUR P were listed as hematuria (n=11; 6.8%), fever/urinary tract infections (UTI) (n=7; 4.3%) and acute urinary retention (n=5; 3.1%) (6). In a study, in which the readmission rates of the urologic surgeries performed as "outpatient" were analyzed, Rambachan et al. (9) observed the readmission rate in patients

Table 1. Preoperative measures and postoperative hemoglobin level, hemoglobin drop and prostate specific antigen levels

Value	Mean	Minimum	Maximum	p
Age (years)	62.6	46	86	
BMI (kg/cm^2)	23.89	17.10	33.20	
Prostate size (g)	88.27	21	400	
PSA-pre (ng/mL)	4.4	0.33	18.4	<0.001
PSA-post (ng/mL)	0.92	0.14	2.14	
Hgb-pre (g/dL)	14.29	10.14	17	
Hgb-post (g/dL)	13.48	9.31	16.79	>0.05
Hgb-drop (g/dL)	0.49	0.24	1.16	

Statistically analyzed with Mann-Whitney U test; another analyzed with Wilcoxon test.
BMI: Body mass index, Hgb: Hemoglobin, PSA: Prostate specific antigen

Table 2. Readmission causes within 30 days during the post-HoLEP period and management methods

Reasons for readmission within 30 days after discharge	n (%)	Management
Acute urinary retention	5 (1.67%)	3-day anti-inflammatory oral therapy and recatheterization
Urinary system infection	4 (1.33%)	Oral or Intravenous antibiotic treatment
Clot retention	2 (0.67%)	Clot drainage, by urethral catheter irrigation or by cystoscopic intervention
Hematuria (requiring transfusion)	2 (0.67%)	Transfusion
Temporary hematuria (no transfusion required)	5 (1.67%)	Follow-up-observation
Deep vein thrombosis	1 (0.33%)	Anticoagulant therapy, cardiovascular surgery consultation
Postoperative emesis, electrolyte imbalance, fever, pain, etc.	7 (2.3%)	Antiemetic, antipyretic, analgesic, diuretic, electrolyte treatments

HoLEP: Holmium Laser Enucleation of the Prostate

who underwent TUR P as 4.24% while the readmission rate after laser prostatectomy was 4.27%, which was at a similar rate with the most prevalent readmission cause, hematuria. In the study by Sood et al. (13), the rate of readmission within 30 days after prostatectomy performed with minimally invasive methods was observed as 3.8%.

There are very few studies on hospital readmission after HoLEP and these studies are those which usually include patients having same-day/outpatient surgery, as in who were discharged within the same day after the operation. In the previous HoLEP outpatient surgery series, readmission rates change between 5.5% and 17.8% (14-17). In our study, readmission rate after HoLEP was observed as 8.67% with nonspecific and specific causes. However, if the nonspecific admittance causes were to be excluded, the rate of readmission due to specific causes was observed to be 6.34%, which was in compliance with the literature. Lwin et al. (18) observed the readmission rate as 2.5% among the patients who had same-day HoLEP performed while the urinary tract infection within 30 days was reported as 4.8%. In another study analyzing the same-day HoLEP effectivity, Abdul-Muhsin et al. (14) reported that 17.8% of the discharged patients were readmitted with the most prevalent cause of hematuria. This elevation in this rate may be explained with the discharge on the same day as the surgery and thus hematuria follow-up not being performed as necessary. In our study, hematuria, which was a cause of readmission, was observed as 2.3%. If clot retentions were to be included in the hematuria group, hematuria could be accepted as the most prevalent readmission cause in our study. In the same study, Abdul-Muhsin et al. (14) observed that the urinary tract infection history among the patients who were readmitted to the hospital was more prevalent compared to the rest of the group (p=0.0304). In our study, urinary tract infection was observed at the rate of 1.33% and as the third most prevalent cause among specific causes. In the study carried out by Lee et al. (17), readmission rate after HoLEP was shown as 5.5%. Readmission causes were equally observed as hematuria (n=1), urinary tract infection (n=1), deep vein thrombosis (n=1), and inguinal pain of unknown origin (n=1). In the multivariable analysis, being in the morning operation list [odds ratio (OR): 6.124, 95% confidence interval (CI): 2.526-14.845, p<0.001] and low enucleated weight of ≤40 g (OR: 3.097, 95% CI: 1.619-5.924, p=0.001) were determined as the predictive factors for readmission to the hospital (17). When the studies are analyzed, it can be observed that readmission rates and causes after TUR P and HoLEP show similarities.

In our study, multivariate analysis was not performed to determine predictive factors for re-admissions after HoLEP surgery. This can be considered as a limiting factor for our article.

Conclusion

Most prevalent causes for post-HoLEP readmission are (besides nonspecific causes) hematuria, urinary retention, and urinary tract infection. The rates of these causes were acceptable and were comparable to TUR P. It is important to know the reasons and rates of readmission after HoLEP, to predict early complications after surgery, and to manage these complications.

Ethics

Ethics Committee Approval: The study protocol was approved by Gazi University Ethical Committee, Turkey (approval number: 2020-150) and complied with the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., S.Y., S.B., L.T., Concept: E.G., S.Ya., L.T., Design: E.G., S.Ya., S.Y., Data Collection or Processing: E.G., E.K., M.Y., Analysis or Interpretation: E.K., S.B., L.T., Literature Search: S.Ya., M.Y., Writing: E.G., M.Y.

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Relationship between vitamin D levels and platelet count: A retrospective study

Recep Alanlı, Murat Bülent Küçükay, Kadir Serkan Yalçın

Lokman Hekim University Faculty of Medicine, Ankara Hospital, Clinic of Internal Medicine, Ankara, Turkey

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Corresponding Author:
Recep Alanlı, MD, Lokman Hekim University Faculty of Medicine, Ankara Hospital, Clinic of Internal Medicine, Ankara, Turkey
recepalanli@gmail.com

ORCID:
orcid.org/0000-0003-4663-1898

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ABSTRACT

Aims: Vitamin D deficiency, increase in mean platelet volume (MPV) and high platelet counts are related to several diseases. The aim of this study is to analyze the relationship between vitamin D status and platelet count, MPV, age, gender, alkaline phosphatase (ALP), and uric acid on patients.

Methods: This study included 899 patients, who did not have any chronic diseases and conditions that affected platelet counts. Calcium, magnesium, ALP, uric acid, 25-hydroxyvitamin D3 levels and 22 parameter hemogram; including MPV and platelet counts were analyzed. Participants were separated into three groups according to their 25-hydroxyvitamin D3 levels: serious deficiency (24.96 nmol/L), deficiency (24.96-49.92 nmol/L), and insufficiency (49.92-74.88 nmol/L). The difference among the groups were analyzed by using the one-way ANOVA test. The Pearson's correlation analysis was used to evaluate associations between 25-hydroxyvitamin D3 levels and other variables.

Results: There was a significant negative correlation between 25-hydroxyvitamin D3 levels and platelet counts in groups (p=0.001, r=-0.108). The mean vitamin D level was 38.19±17.47 nmol/L in female participants and 42.68±12.48 nmol/L in males (p<0.001). A significant difference between platelet counts in serious vitamin D deficiency (286±68x10^9/L) and insufficiency groups (268±64x10^9/L) was also noted (p=0.008).

Conclusions: There was a negative correlation between 25-hydroxyvitamin D3 levels and platelet counts in all groups. Low levels of 25-hydroxyvitamin D3 were associated with an increased platelet count in participants.

Introduction

Platelets are basic components in primary hemostasis, immune system, and wound healing (1). Thrombopoiesis and platelet apoptosis determine actual platelet count. When there are no affecting conditions, platelet counts are usually stable at bloodstream. Platelet count may decrease in older ages. Gender, ethnicity, and environmental factors may affect platelet counts (2).

Mean platelet volume (MPV) reflects platelet size and is a marker of platelet function (3). Higher MPV levels may reflect the existence of large platelets which have higher aggregation tendency. Large platelets are found to be more active and thrombogenic compared to small platelets (4). MPV levels are increased in obesity, acute myocardial infarction, hyperlipidemia, hypertension, stroke, preeclampsia and renal artery stenosis (5). Platelet hyperactivity is a risk factor for coronary artery disease (CAD) and increased MPV was found to be associated with platelet hyperactivity (6). High MPV levels were associated with increased mortality in CAD (7). Also, MPV has been reported to be a risk factor for CAD and acute myocardial infarction in hemodialysis patients (8).

Vitamin D is synthesized from cholesterol and has hormonal activity. Vitamin D has some important metabolic effects such as regulation of calcium and phosphorus homeostasis, bone mineralization, enhancing immune system, regulating cell division and differentiation, regulating coagulation and decreasing inflammation. Vitamin D enhances calcium absorption in the duodenum and reduces calcium excretion by the kidney (9). Low vitamin D levels were associated with coronary heart disease, metabolic syndrome, insulin resistance, susceptibility to infections, allergic diseases, malignancies and autoimmune diseases (10).

The active form of vitamin D is 1,25 dihydroxyvitamin D. 25-hydroxyvitamin D is the major circulating form of vitamin D and is converted to 1.25 dihydroxyvitamin D mainly at the kidneys. 25-hydroxyvitamin D level in body is almost thousand fold compared to 1.25 dihydroxyvitamin D level. While 25-hydroxyvitamin D has a half-life of two to three weeks, 1.25 dihydroxyvitamin D has only four to six hours half-life. The best indicator of vitamin D status is the serum 25-hydroxyvitamin D concentration because it reflects both dietary intake from vitamin D and cutaneous synthesis of vitamin D (11).

Magnesium deficiency causes decreased production of vitamin D (12). Decreased calcium intake with diet may cause lower vitamin D levels and hypocalcemia decreases half-life of vitamin D (13).

Previous studies about the relationship between vitamin D and age, gender, platelet count, uric acid and alkaline phosphatase (ALP) demonstrated controversial results. The effect of calcium and magnesium serum levels on vitamin D metabolism was not considered. Taking this into account, this study was planned to inspect people who had normal serum calcium and magnesium levels.

The purpose of this study is to analyze the correlation between vitamin D deficiency and platelet count, MPV, age, gender, ALP, and uric acid on participants with normal calcium and magnesium levels.

Methods

This is a single-center, retrospective study conducted in an affiliated foundation hospital in Ankara. This study was approved by Lokman Hekim University Ethical Committee (2019/51). This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (link: https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/), and Uniform Requirements for manuscripts submitted to Biomedical journals (link: http://www.icmje.org/).

From the people admitted to internal medicine department between January 1, 2018 and December 31, 2018, a total of 899 were enrolled. Participants who had vitamin D level less than 74.88 nmol/L, normal levels of calcium and magnesium were included in the study. In order to prevent other factors affecting platelet count, some diseases and conditions were accepted as exclusion criteria. People under 15 years of age (since they were admitted to pediatrics clinics), people who had previous history of CAD, chronic obstructive pulmonary disease, stroke, chronic liver disease, chronic kidney disease (estimated GFR<60 mL/min), malignancy, calcium metabolism disorders and acute infectious conditions were not included in the study. People using drugs affecting platelet counts, such as angiotensin-converting enzyme inhibitors, anticoagulants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs were not included in the study.

Blood samples were obtained after 12 hours of fasting at admission and were analyzed in the laboratory without delay. Magnesium, calcium, ALP, and uric acid tests were analyzed by Roche Hitachi Cobas 501 (Switzerland). Platelet count and MPV were analyzed using XN-1000 analyzer (USA) with 22 parameters. 25-hydroxyvitamin D was measured by high-pressure liquid chromatography on the Roche Hitachi Cobas 601 (Switzerland) analyzer. According to Turkey Society of Endocrinology and Metabolism “Osteoporosis and Metabolic Bone Diseases Diagnosis Treatment Guidelines” patients were divided into three groups based on their vitamin D levels: serious deficiency 24.96 nmol/L), deficiency (24.96-49.92 nmol/L), and insufficiency (49.92-74.88 nmol/L) (14).

Statistical Analysis

All data were evaluated using the statistical software SPSS for Windows (version 25, SPSS, Chiago, IL, USA). All variables were checked with the Kolmogorov-Smirnov normality test. Variables in all groups showed a normal distribution. Using the one-way ANOVA test, these groups were analyzed. The Pearson’s correlation analysis was performed to evaluate the associations between vitamin D and other variables. P value smaller than 0.05 was considered to be statistically significant.

Results

There was a significant negative correlation between 25-hydroxyvitamin D3 levels and platelet counts in groups ($p=0.001$, $r=-0.108$). Increased platelet counts were found in people with low vitamin D levels. However, there was no significant correlation between vitamin D and age, gender, uric acid, MPV, and ALP in vitamin D groups. Significant difference between platelet counts in serious vitamin D deficiency ($286\pm68 \times 10^9$/L) and insufficiency groups ($268\pm64 \times 10^9$/L) was also noted ($p=0.008$). In the serious vitamin D deficient group, platelet counts were significantly higher than in other groups. Platelet counts according to vitamin D groups are shown in Figure 1.

The mean vitamin D level was 38.19±17.47 nmol/L in female participants and 42.68±12.48 nmol/L in males ($p<0.001$). Compared to male participants, vitamin D levels were lower in female participants in all groups.

Participants were between 15 and 70 years old, 585 (65.1%) were female and 314 (34.9%) were male. The mean age of participants was 40.3±14.3 years. Male participants’ mean age was 41.4±14 years. Female participants’ mean age was 40.3±14 years.

Characteristics of subjects and laboratory parameters according to vitamin D groups are shown in Table 1.

Discussion

Vitamin D deficiency is a problem all over the world and one billion people suffer from vitamin D deficiency (11). Vitamin D deficiency is also very common in Turkey. In Turkish Diabetes, Hypertension, Obesity and Endocrinological Diseases Prevalence Study-II, 9560 adults were examined and it was determined that 93% of participants' vitamin D levels were lower than 49.92 nmol/L (15). In another study with 35.667 participants, the mean serum vitamin D level was 36.19 nmol/L among females and 45.18 nmol/L among males. Also 94.4% of the participants' serum vitamin D levels were less than 74.88 nmol/L (16). In this reported study, the mean vitamin D level was 38.19±17.47 nmol/L in females and 42.68±12.48 nmol/L in males. All of our participants' vitamin D levels were less than 74.88 nmol/L.

Vitamin D levels of people may vary according to seasons because of the angle of the sunlight reaching the Earth changes. Santos et al. (17) reported that vitamin D levels were highest in August and lowest in March. In order to minimize seasonal changes that could affect the results, participants admitted in the whole year from beginning of January to the end of December were enrolled in this study.

In one study by Hovsepian et al. (18), it was demonstrated that vitamin D levels in female participants were significantly lower. In another study with 5531 participants who did not have any chronic disease, female participants had lower vitamin D levels than males (19). Compared to male population, female population have more sedentary lifestyle, spend more time indoors and use sunscreen creams more often; therefore, they do not get efficient benefit of sunlight. Consistent with other studies in the literature, the mean vitamin D level was lower in females in this reported study.

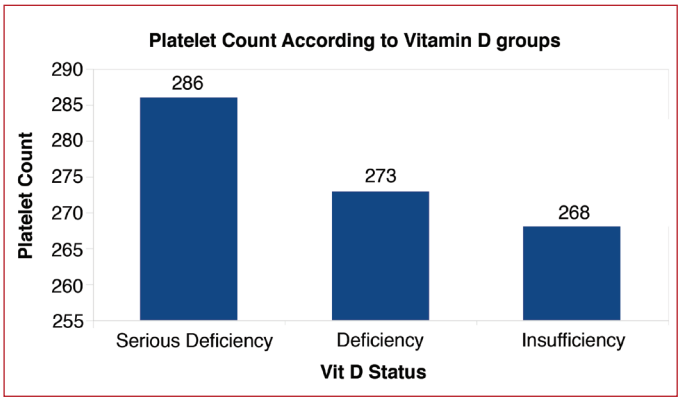

Figure 1. Platelet counts (x10^9/L) according to vitamin D groups

In one study with 78 participants, there was a significant negative relationship between vitamin D level and MPV in CAD patients (20). In another study, there was a negative relationship between vitamin D levels and MPV levels in gestational diabetes mellitus (21). Cumhur et al. (22) reported that there was no significant relationship between vitamin D deficiency and MPV levels on 434 healthy participants. These controversial results have been reported to be caused by the differences in measurement techniques, waiting time after obtaining blood samples, anticoagulants used in tubes that blood samples were stored. Also, there was no standardization in analysis method. All these factors may change MPV levels (23). In this reported study, there was no significant correlation between vitamin D levels and MPV levels.

There was a significant negative correlation between vitamin D levels and platelet counts in a study reported from Korea. This was explained by anti-thrombogenic, anti-inflammatory, antioxidant and anticoagulant activity of vitamin D (9). Aihara et al. (24) reported a study with vitamin D receptor (VDR) knock-out mice. In order to incite thrombosis, lipopolysaccharide injections were performed. Although calcium levels were divergent, thrombosis developed in many different tissues in these mice. They concluded that VDR system had an important role in anti-thrombogenicity *in vivo* (2). VDRs were found in mitochondria of thrombocytes and by these receptors vitamin D regulates protein synthesis and thrombocyte functions (25). Megakaryocytes are precursors for thrombocytes and they also have VDRs. The stimulation of these receptors regulates cell maturation and megakaryocyte

Table 1. Characteristics of subjects according to serious deficiency, deficiency, and insufficiency of vitamin D

	Serious deficiency	Deficiency	Insufficiency	p value
Age (y)	39.5±15.5	39.8±13.5	41.7±13.8	0.19
Gender (female/male) (%)	86.2/13.8	61.2/38.8	68.8/31.2	**<0.001**
ALP (μkat/L)	1.27±0.61	1.24±0.54	1.25±0.62	0.9
MPV (fL)	10±0.7	10±0.9	9.9±0.8	0.38
Platelet count (x10^9/L)	286.1±68	273.2±77.8	268.1±64.5	**0.04**
Uric acid (μmol/L)	279.58±83.28	291.48±89.23	297.43±77.33	0.36
Calcium (mmol/L)	2.35±0.07	2.35±0.10	2.38±0.05	0.06
Magnesium (mmol/L)	1.0±0.05	1.0±0.05	1.0±0.05	0.44
25(OH) vitamin D3 (nmol/L)	17.22±4.74	37.69±6.99	60.65±7.24	**<0.001**

ALP: Alkaline phosphatase, MPV: Mean platelet volume

proliferation. Besides, 1.25 dihydroxyvitamin D is reported to downregulate VDR (26). Vitamin D deficiency promotes megakaryocyte maturation and increases thrombocyte counts (25).

It was documented that vitamin D, itself, has antioxidant activity (27). A study reported an association between oxidative stress and platelet count (28). In another study, antioxidant consumption resulted in lower platelet counts (29). Oxidative stress is related with higher platelet counts (30). Interleukin-6 (IL-6) is an inflammatory cytokine and elevated IL-6 levels results in increased oxidative stress and promotes megakaryocyte production and maturation (31). There was an inverse correlation between vitamin D and IL-6 levels in a study on 1381 healthy participants (32). After all these findings, lower vitamin D levels were thought to be related with inflammation and elevated cytokine levels that would result in increased thrombocyte count.

Vitamin D suppresses vascular cell adhesion molecule-1 and membrane type 1 matrix-metalloproteinase expression and platelet activation, fibrinolysis and thrombosis will be decreased and endothelium will be preserved accordingly (33). Vitamin D insufficiency will cause lower nitric oxide levels (25). As a result, endothelial dysfunction develops in vitamin D insufficiency and this causes increased platelet activation and thrombosis (33). It has been thought that all these mechanisms caused increased thrombocyte production. In this reported study, there was a significant negative correlation between vitamin D levels and platelet counts.

Limitations of this study should be reported include that this was a single-center and retrospective study. The data were limited to the recorded information. Participants included in this study were people who were admitted to hospital and data from healthy population were not obtained, thus results of this reported study may not be generalized to the entire population.

Conclusion

In conclusion, there was no previous study which reported a relationship between platelet counts and vitamin D levels in patients whose serum calcium and magnesium levels were normal. According to the results of this study, lower vitamin D levels will cause higher platelet counts in people with normal calcium and magnesium levels. In literature, there is only one study that reported a significant correlation between vitamin D levels and platelet counts previously and this reported study will be the second. Elevated thrombocyte counts in vitamin D deficiency was thought to be caused by increased inflammatory cytokines and endothelial dysfunction. In patients who have thrombotic event risks, vitamin D supplementation may decrease thrombocytosis and development of thrombotic event. Hemogram is a basic test that can be analyzed everywhere. Increase in platelet count may reflect vitamin D deficiency in suspected people. This may be helpful in the diagnosis of vitamin D deficiency, where vitamin D levels cannot be studied.

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Ethics

Ethics Committee Approval: This study was approved by Lokman Hekim University Ethical Committee (2019/51).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: R.A., Design: R.A., M.B.K., K.S.Y., Data Collection or Processing: R.A., M.B.K., K.S.Y., Analysis or Interpretation: R.A., M.B.K., K.S.Y., Literature Search: R.A., M.B.K., Writing: R.A., M.B.K.

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Association between volume status as assessed by bioelectrical impedance analysis and echocardiographic parameters in peritoneal dialysis patients

Duygu Ersan Demirci[1], Deniz Demirci[1], Melahat Çoban[2]

[1]University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Cardiology, Antalya, Turkey

[2]Ankara City Hospital, Clinic of Nephrology, Ankara, Turkey

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Corresponding Author:
Duygu Ersan Demirci, MD, University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Cardiology, Antalya, Turkey
duygu_ersan@yahoo.com

ORCID:
orcid.org/0000-0003-2696-1531

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ABSTRACT

Aims: Fluid overload is one of the major problems causing severe complications in dialysis patients and the assessment of volume status is important for these patients. The aim of the study was to evaluate the relationship of fluid overload measured by bioimpedance analysis (BIA) with different echocardiographic parameters in peritoneal dialysis (PD) patients.

Methods: In this study, transthoracic echocardiography and BIA were performed on 35 PD patients. Patients were divided into two groups: overhydrated (OH) (OH ≥1.1) and non-OH <1.1. This study assessed the differences in echocardiographic parameters between two groups and the association between BIA parameters and echocardiographic parameters including right heart indices.

Results: A total of 35 dialysis patients (21 males) were enrolled in the study. Based on OH, 21 patients (60%) with OH ≥1.1 (lt) were considered OH and 14 patients (40%) were considered non-OH. There was no significant difference in respect to gender, age, hypertension, diabetes and dialysis vintage between two groups. Among the left heart echocardiographic parameters, left ventricular (LV) mass index (LVMI) was significantly higher in the OH group (119.0±40.3 vs. 239.4±37.4 g/m^2, p=0.046). There was no significant difference with regard to other left and right ventricular echocardiographic parameters. Among various BIA parameters, we investigated OH, OH/extracellular water (ECW), ECW/total body water ratios and their correlations with echocardiographic parameters. We did not find any significant correlation between BIA parameters and echocardiographic findings.

Conclusions: The present study demonstrated the association between the hydration status and LVMI. We conclude that avoiding hypervolemia should be an important clinical goal in the follow-up of PD patients to prevent the progression of LV hypertrophy.

Introduction

The leading cause of morbidity and mortality for end-stage renal disease patients is the cardiovascular diseases (1). Fluid overload is a common and serious problem leading to severe complications in hemodialysis (HD) and peritoneal dialysis (PD) patients. It is known that fluid overload is clearly associated with left ventricular (LV) hypertrophy, hypertension, and heart failure (2). The management of hypertension is difficult in dialysis patients and many patients have uncontrolled hypertension despite the use of antihypertensive drugs (3); hence, accurate control of the volume is one of the major targets of the therapy.

Hydration status can be measured by different methods. In routine evaluations, fluid management is largely based on subjective clinical assessment, such as blood pressure, edema and changes in body weight, but those may lead to misinterpretations. Therefore, more reliable, practical and objective methods are extremely needed. In this respect, bioelectrical impedance analysis (BIA) has been recommended for the assessment of hydration status parameters.

BIA is a safe, easy, rapid and noninvasive method that has been used to evaluate hydration status in patients on dialysis therapy (4-7). Its working principal is associated with the human body's resistance to alternating electrical currents. It assesses hydration status, intracellular water (ICW) and extracellular water (ECW), the extracellular and intracellular ratio, the total water volume and also some nutritional parameters (8). However, BIA is not available in many centers.

Transthoracic echocardiography is another method for the assessment of the volume status in dialysis patients. However, there are insufficient data on echocardiographic parameters indicating hydration status in patients undergoing dialysis. In the present study, we aimed to assess the relationship between hydration status measured with BIA technique and both left and right ventricular echocardiographic parameters in PD patients.

Methods

This cross-sectional study design included 35 (14 women, 21 men, mean age 52.2±14.1 years) stable chronic ambulatory PD patients treated and followed up in the same center between November 2015 and February 2016. They were over 18 years of age and had been on PD therapy for at least 6 months. The study was approved by the Institutional Ethics Committee (Health Sciences University Turkey, Antalya Training and Research Hospital Ethics Committee 2013-022, 15/7, date: 28/02/2013) and informed consent was obtained from all patients at the time of study enrollment.

Five patients with a previously known severe valvulopathy, six patients who had LV systolic dysfunction with ejection fraction lower than 50%, two patients with arrhythmia, two patients with contraindication for BIA (metallic prosthesis and pacemaker), one patient with previous renal transplantation and one patient with peritonitis were excluded from the study.

All patients were subjected to a thorough clinical evaluation. Blood samples were obtained in the morning after an overnight fasting, in the same day with BIA. Blood pressure, heart rate, clinical history, demographic characteristics, laboratory parameters and medication were recorded. Routine serum biochemical variables were analyzed. Body mass index (BMI) was calculated by dividing weight (kg) by height square (m^2).

Residual renal function (RRF) was determined by residual glomerular filtration rate, residual diuresis and renal creatinine clearance. Residual glomerular filtration rate was measured as the average of 24-hour urinary urea and creatinine clearance values (9). Urine and dialysate samples were collected for 24 hours in order to calculate weekly total Kt/Vurea. Total Kt/Vurea was determined as the total loss of urea nitrogen in the exchanged dialysate using the Watson equation (10). Peritoneal transport rates (PTR) were calculated by using standard peritoneal equilibration test as described by Twardowski et al. (11). According to the results, the patients were divided into four groups: high (H) (≥0.81), high-average (HA) (0.65-0.80), low-average (LA) (0.50-0.65) and low (L) (<0.50) PTR. H and HA transporters were accepted as H-PTR, whereas L-LA transporters as L-PTR.

Transthoracic Echocardiography

Echocardiographic examinations were performed with a 2-4 MHz transducer attached to a Vivid S5 echocardiography machine (GE Healthcare, Chicago, USA). Single lead ECG was recorded continuously during the examination in left lateral decubitus position. Analysis was performed according to the guidelines of the American Society of Echocardiography recommendations (12,13).

Three left atrium (LA) dimensions were used to calculate the LA volume as an ellipse using the following formula: LA volume = (π/6) (LAD1xLAD2xLAD3) where LAD1 is the anteroposterior LA dimension, and LAD2 and LAD3 are measurements of long- and short axis with the apical four-chamber view at ventricular end-systole, respectively (14). To find LA volume index (LAVI) LA volume was divided by body surface area (BSA). BSA was calculated using the formula: BSA = 0.007184 x $weight^{0.425}$ x $height^{0.725}$ (m^2). Interventricular septal thickness (IVST), posterior wall thickness (PWT), left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were used to calculate LV mass (LVM) using the following equation: LVM (g) = 1.04 x [$(LVEDD+IVST+PWT)^3$ - $(LVEDD)^3$] x 0.8+0.6. LVM was divided by BSA to find LVM index (LVMI). Based on the studies of Devereux et al. (15), the cut-off values to define left ventricular hypertrophy (LVH) using the LVMI was 125 g/m^2 for both genders. To evaluate the diastolic functions of the LV, early mitral inflow velocity (E wave), late mitral inflow velocity (A wave) and deceleration time were evaluated from the apical 4-chamber view. The early diastolic velocity of the lateral mitral annulus (Em) was recorded with tissue Doppler imaging (TDI). To calculate E/Em, E was divided by Em (16).

Right ventricular diameters were measured in the parasternal long axis and apical 4-chamber views. The maximal tricuspid regurgitation velocity was measured by continuous wave Doppler echocardiography from the apical 4-chamber view. Systolic pulmonary pressure was calculated as follows: 4X $(tricuspid\ systolic\ jet)^2$ + right atrial pressure. Early (E) and late (A) right ventricular inflow velocities were measured with pulsed wave Doppler by placing the sample volume in between the tips of the tricuspid valve in the apical 4- chamber view. On the TDI images annular peak systolic velocity (Sa), early (Ea) and late (Aa) (peak annular diastolic velocities), tricuspid valve closure and opening time (TCO) and systolic velocity duration as ejection time (ET) were measured. The TDI-derived MPI, as a global estimate of both systolic and diastolic functions of the RV, was calculated with the formula 'TDI- MPI = (TCO-ET)/ET' (13). TAPSE was measured as placing an M-mode cursor through the tricuspid

annulus and determining the amount of longitudinal motion of the annulus at peak systole in the apical 4- chamber view. Right ventricular fractional area change (RV FAC) was calculated using the formula 'FAC = (end-diastolic area – end-systolic area) / end-diastolic area x 100' (17).

Bioimpedance Assessment

Bioimpedance was assessed using a Body Composition Monitor (BCM, Fresenius Medical Care, Deutschland GmbH). All measurements were obtained by the same operator. BIA was performed with empty abdomen in PD patients. The following parameters were obtained: overhydration (OH), ECW, ICW, total body water (TBW) in liters (L), ECW/TBW, ECW/ICW ratios. These volumes then were used to evaluate the amount of fluid overload. OH is the difference between 'normal' ECW (the patient's expected ECW under normal physiologic conditions) and measured ECW and indicates 'absolute' volume overload. Relative fluid overload is defined as the absolute fluid overload to ECW ratio (OH/ECW). It is considered as an independent predictor of mortality in patients on dialysis when it is greater than 15% (18). We used OH (lt) as an indicator of fluid status. Patients were classified by hydration status by means of OH normalized for healthy age and gender using the method described by Onofriescu et al. (19), that is -1.1 to +1.1 L, with volumes below and above this range, under- and over-hydration. Patients were divided into two groups: OH ≥1.1 and non-OH <1.1.

Statistical Analysis

Data were processed using the MedCalc version 18.11.3 and R version 3.4.4. Mean and standard deviation or median and interquartile range were used for the presentation of measurable continuous quantitative variables, depending on the distribution of variables. For categorical data, frequencies and percentages were used. Suitability of parametric test conditions was checked for the comparison of quantitative variables (number of subjects and deviation from normal distribution). The Shapiro-Wilk test was used for normal distribution assessment. Two group comparisons were performed with the Student's t-test for variables that met parametric test conditions, and the Mann-Whitney U test for others. The chi-square (χ^2) test and, if needed, the Fisher's exact test were used for the evaluation of categorical variables. Pearson's correlation coefficient was used to examine correlations between variables. Values of $p<0.05$ were considered statistically significant.

Results

Patients' Characteristics

A total of 35 dialysis patients (21 males) were enrolled in the study. Among the 35 patients included, the mean age was 52.2±14.1 years. 27 patients (77.1%) were hypertensive and nine patients (25.7%) were diabetic with a mean dialysis vintage of 44.4±34.3 months. Based on OH, 21 patients (60%)

Table 1. General characteristics of the studied population

	OH <1.1 (n=14)	OH ≥1.1 (n=21)	p
Gender (male) [n (%)]	10 (71)	10 (52)	0.409
Age (years) (mean±SD)	55.2±11.8	49.9±15.7	0.285
DM [n (%)]	3 (30.0)	6 (50.0)	0.405
HT [n (%)]	9 (64.3)	18 (94.7)	0.062
BMI (kg/m^2) (mean±SD)	27.47±5.3	28.48±5.92	0.611
Systolic BP (mmHg) (mean±SD)	128.0±16.56	131.05±19.11	0.628
Diastolic BP (mmHg) (mean±SD)	78.0±12.07	73.68±14.2	0.355
ECW (L) (mean±SD)	16.8±2.57	18.18±4.36	0.371
ICW (L) (mean±SD)	19.62±3.99	19.98±5.75	0.877
TBW (L) (mean±SD)	35.02±6.18	36.35±8.11	0.547
Dialysis vintage (months) (mean±SD)	43.6±34.1	45.4±35.74	0.768
Hgb (g/dL) (mean±SD)	10.3±3.3	10.9±1.4	0.402
Alb (g/dL) (mean±SD)	3.5±0.3	3.4±0.5	0.481
Cre (mg/dL) (mean±SD)	7.4±3.1	8.5±2.9	0.255
Ca (mg/dL) (mean±SD)	9.0±1.2	9.0±0.65	0.940
Ferritin (ng/mL) (mean±SD)	318.2±230.2	336.1±333.2	0.861
RRF (mL/day) (mean±SD)	654.2±728.4	906.7±654.2	0.272
Weekly total Kt/Vurea (mean±SD)	2.38±0.59	2.41±0.54	0.260
H-HA/L-LA PTRs [n (%)] (mean±SD)	13 (92.8)/1 (7.2)	17 (80.9)/4 (19.1)	0.858

SD: Standard deviation, Alb: Albumin, BMI: Body mass index, BP: Blood pressure, Ca: Calcium, Cre: Creatinine, DM: Diabetes mellitus, Hgb: Hemoglobin, HT: Hypertension, ECV: Extracellular volume, ICV: Intracellular volume, PTR: Peritoneal transport rate, RRF: Residual renal function, TBV: Total body volume, OH: Overhydration, HA: High-average, LA: Low-average, H: High, L: Low

with OH ≥1.1 (lt) were considered OH and 14 patients (40%) were considered non-OH. Table 1 summarizes the general characteristics according to the volume status. There was no significant difference with respect to gender [10 (71%) vs. 11 (52%) male, p=0.409], age (55.2±11.8 vs. 49.9±15.7, p=0.285), diabetes [6 (50%) vs. 3 (30%), p=0.405], systolic and diastolic blood pressure (131.05±19.1 vs. 128.0±16.56 mmHg, p=0.628; 73.68±14.2 vs. 78.0±12.07 mmHg, p=0.355, respectively), BMI (28.48±5.92 vs. 27.47±5.3 kg/m^2, p=0.611) and dialysis vintage (45.4±35.74 vs. 43.6±34.1 months, p=0.768) between the groups. The percentage of hypertension was higher in the OH group, but it was not statistically significant [18 (94.7%) vs. 9 (64.3%), p=0.062]. We found no significant difference with regard to biochemical parameters between two groups. We also demonstrated no significant difference in terms of RRF, Kt/V and PTR values between the groups.

Differences in Echocardiographic Parameters According to OH

Among the left heart echocardiographic parameters; IVST, PWT, thicknesses, LVEDD, LVESD, left ventricular outflow tract (LVOT) diameter, LA diameters and E/Em were higher in the OH group, but none of them was found to be significant. However, LVMI was significantly higher in the OH group (119.0±40.3

Table 2. Left ventricle 2-dimensional echocardiography findings

	OH <1.1	OH ≥1.1	p
LVMI (g/m^2) (mean±SD) Median/min/max	119.0±40.3 105/76/208	239.4±37.4 124/98/227	0.046*
IVST (mm) (mean±SD) Median/min/max	12.8±2.2 13/10/17	12.9±1.9 13/9/18	0.874
PWT (mm) (mean±SD) Median/min/max	11.7±1.4 12/10/14	12.6±1.6 12/11/16	0.153
LVEDD (mm) (mean±SD) Median/min/max	45.5±6.6 45/36/58	47.9±4.4 47/41/60	0.915
LVESD (mm) (mean±SD) Median/min/max	29.9±6.3 32/21/45	30.6±5.0 30/22/41	0.395
LVOT (mm) (mean±SD) Median/min/max	22.1±2.3 22/18/26	22.3±3.9 22/16/35	0.911
LAD D1 (mm) (mean±SD) Median/min/max	39.6±5.5 39.0/15.9/36.2	40.4±4.1 40.5/31.0/47.0	0.619
LAVI (mL/m^2) (mean±SD) Median/min/max	23.9±5.4 24.2/15.9/36.2	24.3±23.9 24.8/17.9/40.9	0.884
LV EF (%) (mean±SD) Median/min/max	63.3±5.2 65/55/65	63.4±5.8 65/55/65	0.521

IVST: Interventricular septum thickness, LAD D1: Left atrium anteroposterior diameter, LAVI: Left atrium volume index, LVMI: Left ventricular mass index, LVEDD: Left ventricular end-diastolic diameter, LV EF: Left ventricle ejection fraction, LVESD: Left ventricular end-systolic diameter, LVOT: Left ventricular outflow tract, OH: Overhydration, PWT: Posterior wall thickness, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 3. Left ventricular Doppler findings

	OH <1.1	OH ≥1.1	p
E (m/sn) (mean±SD) Median/min/max	0.68±0.2 0.7/0.50/1.30	0.71±0.16 0.70/0.40/1.0	0.631
A (m/sn) (mean±SD) Median/min/max	0.9±0.13 0.9/0.70/1.10	0.91±0.25 0.90/0.11/1.20	0.879
Em (cm/sn) (mean±SD) Median/min/max	6.82±2.16 7.00/3.00/12.00	6.95±2.77 7.00/3.00/12.00	0.886
Am (cm/sn) (mean±SD) Median/min/max	10.26±1.82 10.0/7.0/13.0	9.9±3.42 9.7/4.0/11.0	0.735
E/Em (mean±SD) Median/min/max	0.105±0.32 0.100/0.06/0.17	0.122±0.07 0.100/0.04/0.33	0.408
DT (mean±SD) Median/min/max	282.4±93.8 275.0/140.0/517.0	239.9±67.1 262.0/54/348	0.134

A: Peak late diastolic mitral inflow velocity, Am: Late diastolic myocardial velocity, E: Peak early diastolic mitral inflow velocity, Em: Early diastolic myocardial velocity, DT: Deceleration time, OH: Overhydration, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 4. Right ventricular 2-dimensional and M-mode echocardiography findings

	OH <1.1	OH ≥1.1	p
RA area (cm^2) (mean±SD) Median/min/max	20.9±24.4 15.4/7.0/105.0	13.2±3.3 13.0/7.70/105.0	0.192
RA long axis (mm) (mean±SD) Median/min/max	44.8±5.50 44.0/31.0/53.0	45.6±6.03 45.5/36.0/55.0	0.672
RA minor axis (mm) (mean±SD) Median/min/max	33.9±8.0 34.0/14.0/45	34.5±5.15 34.5/28/46	0.484
TAPSE (mm) (mean±SD) Median/min/max	23.3±5.2 24/14/33	22.03±3.9 24/2/30	0.535
RVFAC (%) (mean±SD) Median/min/max	42.72±17.86 40.0/20.0/93.0	39.6±9.32 40.39/21.32/56.82	0.520

RA: Right atrium, Lateral TDI MPI: Tissue doppler myocardial performance index at lateral tricuspit annulus, RVFAC: Right ventricular fractional area change, TAPSE: Tricuspid annular plane systolic excursion, OH: Overhydration, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 5. Right ventricle Doppler findings

	OH <1.1	OH ≥1.1	p
E (m/sn) (mean±SD) Median/min/max	0.60±0.11 0.60/0.40/0.90	0.62±0.17 0.60/0.31/0.90	0.766
A (m/sn) (mean±SD) Median/min/max	0.58±0.14 0.60/0.40/0.90	0.63±0.17 0.60/0.29/1.0	0.354
Ea (cm/sn) (mean±SD) Median/min/max	11.0±4.3 11.0/5.0/18.0	11.45±3.27 12.0/6.00/19.00	0.730
Aa (cm/sn) (mean±SD) Median/min/max	15.3±3.38 16.0/7.0/19.0	17.1±4.8 17.0/11.0/26.0	0.234
E/A (mean±SD) Median/min/max	1.08±0.32 1.16/0.63/1.75	1.03±0.83 0.66/0.09/1.10	0.661
Sa (cm/sn) (mean±SD) Median/min/max	17.75±3.38 16.0/7.0/19.0	14.0±4.43 14.0/5.0/22.0	0.140
Tr vel (cm/sn) (mean±SD) Median/min/max	2.27±0.61 2.50/1.30/3.10	2.12±0.58 2.3/1.0/2.90	0.521
Lateral TDI MPI (mean) (SD) Median/min/max	0.27±0.13 0.24/0.11/0.49	0.24±0.13 0.19/0.11/0.49	0.122
PVR (dyn*sn/cm^2) (mean) (SD) Median/min/max	1.28±0.56 1.33/0.16/2.16	0.99±0.47 1.12/0.61/1.66	0.540

E: Peak early diastolic tricuspid inflow velocity, A: Peak late diastolic tricuspid inflow velocity, Ea: Early diastolic velocity of tricuspid lateral annulus, Aa: Late diastolic velocity of tricuspid lateral annulus, DT: Deceleration time, Lateral TDI MPI: Tissue Doppler myocardial performance index at lateral tricuspid annulus, Sa: Systolic myocardial velocity of tricuspid annulus, TR vel: Tricuspid regurgitation flow velocity, OH: Overhydration, SD: Standard deviation, Min: Minimum, Max: Maximum, PVR: Pulmonary vascular resistance

vs. 239.4±37.4 g/m^2, p=0.046). Other LV echocardiographic parameters were similar in both groups (Table 2, 3). Among the right heart echocardiographic parameters, there was no significant difference between two groups (Table 4, 5).

Correlation Between Echocardiographic Parameters and Markers of Volume Status

Among various BIA parameters, we investigated OH, OH/ECW, ECW/TBW ratios and their correlations with echocardiographic parameters. No significant correlation between BIA parameters and echocardiographic findings was found. We also did not find any significant correlation between RRF and echocardiographic parameters.

Discussion

In the present study, the relationship between hydration status measured with BIA and echocardiographic parameters was assessed. In the patients from a single center, we found that LVMI was related to hydration status based on OH (L).

Fluid overload is frequently present in dialysis patients leading to adverse clinical outcomes such as hypertension (20), cardiovascular diseases (21,22) and higher mortality (23); thus, keeping dialysis patients euvolemic is essential (24). Managing fluid balance is still major challenge in both HD and PD patients. Based on many studies, BIA is recommended for determining the dry weight (25,26). In a study of Hur et al. (27) regarding

HD patients, assessment of fluid overload with BIA methods has been reported to be associated with better management of fluid status and regression of LVMI. However, access to BIA is limited in many centers leading determination of the volume status of patients only by clinical methods. Hur et al. (28), in a study including 81 PD and 89 HD patients, observed that OH/ECW ratio was positively correlated with LAVI. Di Gioia et al. (29), found that LAVI was related to hydration status based on bioimpedance measured time-averaged fluid overload. LAVI is a chronic marker of diastolic dysfunction that shows the average of increased filling pressures. In the present study, we did not find an association between hydration status and LAVI. In a study including 30 HD patients, Sabaghian et al. (30), found a significant correlation between inferior vena cava diameter index minimum (IVCDi min) measured by echocardiography and ECW, so they suggested this parameter as a good echocardiographic parameter associated with hydration in HD patients.

Another study by Yılmaz et al. (31) reported that increased OH/ECW ratio was independently associated with LVMI. Increased LVMI is associated with mortality and cardiovascular morbidity in this patient population (32). Despite the fact that several other factors play roles in the development of LV hypertrophy, the main causes are hypertension and fluid overload. Consistent with the previous reports, OH patients had significantly higher levels of LVMI compared to non-OH patients in our study. These findings emphasize the importance of volume control for cardiac protection in PD patients. Different from previous studies, we also investigated the association between right heart echocardiographic indices and BIA parameters, but we did not demonstrate any significant correlations. This can be due to the small sample size of our study and should be evaluated in larger scale studies.

Our study has several limitations. The most important limitation is that it included a small number of patients from a single center. We assessed right ventricular function with conventional echocardiography instead of strain echocardiography.

Conclusion

The present study demonstrated the association between the hydration status and LVMI. We conclude that avoiding hypervolemia should be an important clinical goal in the follow-up of PD patients in order to prevent the progression of LV hypertrophy. These results should be confirmed by further larger studies.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee (Health Sciences University Turkey, Antalya Training and Research Hospital Ethics Committee 2013-022, 15/7, date: 28/02/2013).

Informed Consent: Informed consent was obtained from all patients at the time of study enrollment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.E.D., D.D., M.Ç., Design: D.E.D., D.D., M.Ç., Data Collection or Processing: D.E.D., M.Ç., Analysis or Interpretation: D.E.D., D.D., Literature Search: D.E.D., D.D., Writing: D.E.D., D.D.

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The role of nutrition in patients with fibromyalgia: Is there an impact on disease parameters?

Özlem Köroğlu[1], Kübra Tel Adıgüzel[2]

[1]*University of Health Sciences Turkey, Gülhane Faculty of Medicine; Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Ankara, Turkey*

[2]*University of Health Sciences Turkey, Gülhane Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara, Turkey*

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Corresponding Author:
Kübra Tel Adıgüzel, PhD, Asist Prof, University of Health Sciences Turkey, Gülhane Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara, Turkey
dyt.kubra@gmail.com

ORCID:
orcid.org/0000-0003-1010-4316

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ABSTRACT

Aims: The aim of our study is to assess the associations between dietary intake and biochemical parameters, clinical assessments of pain, sleep quality and current health status of patients who were diagnosed with fibromyalgia.

Methods: This is a prospective study on patients with fibromyalgia. In patients' routine controls, data were recorded about their nutrition by using food consumption recording form. Also, the biochemical parameters were recorded. Clinical symptoms were evaluated by using Short form of MacGill Pain Questionnaire (SFMPQ), Fibromyalgia Impact Questionnaire (FIQ) and Pittsburg Sleep Quality Index (PSQI).

Results: Eighty-one patients with a disease duration of minimum 12 months were included. The mean age was 48.9 years and 90.1% of patients were female. The correlation analysis between serum vitamin B_{12} and clinical symptoms showed a weak negative correlation with FIQ (r=-0.257, p=0.021), sleep duration (r=-0.317, p=0.004), sleep disturbance (r=-0.279, p=0.012), sleep quality (r=-0.235, p=0.035), and PSQI total score (r=-0.316, p=0.004). Percentage of energy from dietary carbohydrate showed a moderate positive correlation with FIQ (r=0.383, p<0.001). Dietary fat showed a moderate negative correlation with FIQ (r=-0.29, p=0.007). While dietary saturated fat showed a moderate positive correlation with FIQ (r=0.361, p<0.001), dietary unsaturated fat displayed a weak negative correlation with FIQ (r=-0.228, p=0.041). Dietary fiber had a moderate negative correlation with FIQ (r=-0.357, p<0.001), SFMPQ-present pain intensity (r=-0.357, p<0.001), and SFMPQ-visual analogue scale (r=-0.419, p<0.001) subscores.

Conclusions: The current study results suggest that a healthy diet habit consisting of low saturated fat, carbohydrates and higher fiber, vitamins and minerals may provide improvement in fibromyalgia symptoms. Dietary assessment and intervention should be a part of the management of patients with fibromyalgia.

Introduction

Fibromyalgia is a chronic disease characterized by general pain in the body with particular tender points, fatigue, depression, anxiety, non-restorative sleep, morning stiffness, headaches, cognitive impairment, paresthesia, affective disorders, irritable bowel and bladder syndrome. Fibromyalgia symptoms can be associated with several factors such as dysfunction of hypothalamic axis and increase of cortisol, changes in the central nervous system, oxidative stress, mitochondrial dysfunction, and also changes in the intestinal microbiota (1,2). As the etiology is multifactorial, a multidimensional management which consists of a combination of pharmacological and non-pharmacological treatments is necessary for fibromyalgia'. Nutrients and nutritional supplements are also effective factors for fibromyalgia patients (3,4). There is a linkage between dietary patterns and fibromyalgia symptoms (5,6). However, according to the literature, the effects of different dietary approaches are not clear yet. A low fermentable oligo, di and monosaccharides, alcohols and polyols (FODMAPS) diet, a raw vegetarian diet and a hypocaloric diet may relieve pain and improve functional parameters in fibromyalgia patients. A

nutritionally balanced diet contributing to weight loss can reduce the severity of fibromyalgia symptoms (7).

Fibromyalgia is a chronic disease caused by some neurologic, genetic, psychological conditions or mineral-vitamin deficient status. However, to date, there are few studies linking biochemical parameters and fibromyalgia. A deficit of nutritive elements including necessary metal ions and vitamins might have an important effect in the occurrence of fibromyalgia. Patients with deficiencies of some fundamental nutrients may develop dysfunction of pain pathways together with fibromyalgia symptoms (8).

In the treatment of fibromyalgia, some minerals and vitamins have beneficial effects. Sufficient intake of vitamin D, vitamin B_{12} and magnesium is important. Deficiency of certain essential elements may cause dysfunction of pain inhibitory mechanisms. Insufficient levels of magnesium and selenium cause muscle pains. Deficiency of magnesium can cause chronic systemic inflammation, increase substance P levels and induce an increase in pro-inflammatory cytokines and C-reactive protein (CRP). Selenium has a protective role against ischemia (8).

Iron is necessary for enzymes in neurotransmitter production. Investigation of cerebrospinal fluid in fibromyalgia syndrome has shown a decrease in the concentration of serotonin, dopamine and norepinephrine (8). Moreover, as iron is a cofactor in dopamine and serotonin synthesis, it may have an effect in the etiopathogenesis of fibromyalgia (8,9). Therefore, the management of diet is very important for fibromyalgia patients in order to ameliorate inadequate intake of essential nutrients. When optimal nutrition is obtained, pain levels are usually decreased. Also, by consuming antioxidant-rich foods, it is possible to relieve fibromyalgia symptoms.

Researches about nutrition are necessary to reveal relationships between nutrition and fibromyalgia. The aim of our study is to assess the associations between dietary intake and biochemical parameters, clinical assessments of pain, sleep quality and current health status of patients who were diagnosed with fibromyalgia.

Methods

This was a prospective study conducted between April 2019 and September 2019 on patients with fibromyalgia (diagnosed with American College of Rheumatology 2010 Criteria), who were admitted to the physical medicine and rehabilitation clinics. Eighty-one patients with a disease duration of minimum 12 months aged between 18 and 65 years were included. The patients were selected according to the use of similar medical treatment and having similar exercise habits. Exclusion criteria included the presence of any disease which could affect biochemical parameters and clinical symptoms. The study protocol was approved by the bioethics and Gülhane Training and Research Hospital Research Committee with the number of 19/156 on April 30th of 2019, and all procedures were performed in compliance with the Helsinki Declaration. All patients were informed about the study and written informed consent was obtained. In patients' routine controls, data were recorded about their nutrition by using food consumption recording form, biochemical parameters including serum hemoglobin, ferritin, vitamin B_{12}, thyroid stimulating hormone, calcium, magnesium, folic acid, vitamin D, total protein, albumin, sedimentation, CRP levels. Twenty-four hours dietary recall was taken by investigator to determine daily nutrient intake of patients. Portion sizes and volumes were estimated with a portion size picture book including 120 photographs of foods, each with 3-5 different portion sizes (10). The BeBiS software version 7.2 was used to calculate daily intake of energy, macro and micronutrients (11). Dietary intakes of patients were assessed according to the Turkey-Specific Nutrition Guide (12). Clinical symptoms were evaluated by using the Short form of MacGill Pain Questionnaire (SFMPQ), Fibromyalgia Impact Questionnaire (FIQ) and Pittsburg Sleep Quality Index (PSQI).

Statistical Analysis

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) version 22.0 for Mac (SPSS Inc., Chicago, IL). Continuous variables were presented as mean ± standard deviation. Qualitative variables were presented as number and percentage. The Kolmogorov-Smirnov test was used to determine the normality of data distribution. Correlation analyses were done with the Pearson test. A value of $p<0.05$ was considered to be statistically significant.

Results

Main characteristics of the patients are given in Table 1. Most of the patients were female (90.1%) and most of them were married (82.7%). Education duration was generally low (1-5 years in 49.4% of the patients). Laboratory findings are given in Table 2. All parameters except 25-OH D were in normal range. The mean 25-OH D level was 22.8±14.1 ng/mL.

FIQ total, SFMPQ, and PSQI scores of the patients are given in Table 3. FIQ total score was 48.7±23.5, SFMPQ total pain rating index was 12.9±8.6, and PSQI-total was 9.7±4.5.

The correlation analysis between serum vitamin B_{12} and clinical symptoms showed a weak negative correlation with FIQ (r=-0.257, p=0.021), sleep duration (r=-0.317, p=0.004), sleep disturbance (r=-0.279, p=0.012), sleep quality (r=-0.235, p=0.035), and PSQI total score (r=-0.316, p=0.004). There was no correlation between other biochemical parameters and clinical symptoms.

The mean intakes of energy, carbohydrate, protein and fat were 1919.5±618.8 kcal, 212.2±94.7 g, 71.9±21.2 g, and 84.0±31.9 g, respectively. When daily energy percentage from carbohydrate, protein and fat were assessed according

to the Turkey-Specific Nutrition Guide, energy percentage from carbohydrate was over reference values in five (6.17%) patients, energy percentage from protein was over reference values in 10 (12.3%) patients and energy percentage from fat was over reference values in 60 (74.1%) patients. In addition, the contribution of saturated fat to energy was determined above the recommended level in 69 (85.2%) individuals. The correlation between FIQ, SFMPQ, macronutrients, and some micronutrients (which were significantly correlated) were shown in Table 4. Dietary energy, carbohydrate, protein, and percentage of energy from dietary protein were not correlated with FIQ and SFMPQ. The percentage of energy from dietary carbohydrate showed a moderate positive correlation with FIQ (r=0.383, p<0.001). Dietary fat showed moderate negative correlation with FIQ (r=-0.29, p=0.007). While dietary saturated fat had a moderate positive correlation with FIQ (r=0.361, p<0.001), dietary unsaturated fat had a weak negative correlation with FIQ (r=-0.228, p=0.041). Percentage of energy from dietary fat showed a negative moderate correlation with FIQ (r=-0.411, p<0.001) and a weak negative correlation with SFMPQ-visual analogue scale (VAS) subscore (r=-0.225, p=0.044). Dietary fiber displayed a moderate negative correlation with FIQ (r=-0.357, p<0.001), SFMPQ-present pain intensity (PPI) (r=-0.357, p<0.001), and SFMPQ-VAS (r=-0.419, p<0.001) subscores. In addition to dietary energy and above mentioned macronutrients, some vitamins and minerals (folic acid, calcium, phosphor, vitamin B1, vitamin B2, biotin, iron, zinc, and magnesium) showed a weak to moderate negative correlations with FIQ, SFMPQ-PPI, and SFMPQ-VAS subscores (as presented in Table 4).

Table 1. Main characteristics of patients

	Mean	SD
Age (years)	48.9	10.5
Gender	**n**	**%**
Female	73	90.1
Male	8	9.9
Education		
Illiterate	3	3.7
1-5 years	40	49.4
6-10 years	3	3.7
10-15 years	16	19.8
>15 years	19	23.5
Marital status		
Married	67	82.7
Single	14	17.3

SD: Standard deviation

Table 2. Laboratory findings of patients

Parameter	Mean	SD
Hemoglobin (g/dL)	13.2	1.1
ESR (mm/h)	15.7	10.6
CRP (mg/L)	3.4	4.4
Vitamin B_{12} (pg/dL)	327.8	205.7
Folic acid (ng/mL)	8.3	3.8
Ferritin (ng/mL)	31.7	30.1
Ca (mg/dL)	9.3	0.9
Mg (mg/dL)	2.1	0.7
25-OH D (ng/mL)	22.8	14.1
Total protein (mg/dL)	7.1	0.8
Albumin (mg/dL)	4.2	0.3
TSH (mU/L)	2.2	1.7

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TSH: Thyroid stimulating hormon, Ca: Calcium, Mg: Magnesium, SD: Standard deviation

Discussion

In this study of 81 patients who were diagnosed with fibromyalgia, results have shown some associations between biochemical parameters, dietary intake and clinical assessments of pain, sleep quality and current health status. The mean vitamin B_{12} level was in normal range and vitamin B_{12} levels showed a negative correlation with clinical scores such as FIQ and sleep scores. Although low vitamin B_{12} levels were reported with pain related pathologies before (13), studies including patients with fibromyalgia demonstrated no link between serum vitamin B_{12} levels and fibromyalgia (14,15). In a study by Regland et al. (16), cerebrospinal fluid vitamin B_{12} levels were correlated with fatigue and psychological ratings. This result was similar to the result in the current study notwithstanding sample differences. We suppose that more studies are necessary to firmly report a vitamin B_{12} effect on fibromyalgia symptoms.

Table 3. Fibromyalgia Impact Questionnaire total, Short form of MacGill Pain Questionnaire, and Pittsburg Sleep Quality Index scores of the patients

	Mean	SD
FIQ total	48.7	23.5
McGill sensory	10.1	6.3
McGill affective	2.9	3.1
Total pain rating index	12.9	8.6
McGill present pain intensity	3.1	1.0
McGill VAS	5.2	2.3
PSQI		
Sleep duration	1.1	1.0
Sleep latency	1.8	1.0
Sleep disturbance	1.9	0.8
Habitual sleep efficiency	0.8	1.1
Sleep medication use	0.2	0.7
Daytime dysfunction	1.7	1.0
PSQI-total	9.7	4.5

FIQ: Fibromyalgia Impact Questionnaire, PSQI: Pittsburg Sleep Quality Index, VAS: Visual analogue scale, SD: Standard deviation

Table 4. Correlation between Fibromyalgia Impact Questionnaire, Short form of MacGill Pain Questionnaire, macronutrients and some micronutrients

	FIQ-total		McGill sensory		McGill affective		Total pain rating index		McGill present pain intensity		McGill VAS	
	r	p	r	p	r	p	r	p	r	p	r	p
Energy	-0.072	0.524	0.003	0.981	0.033	0.769	0.014	0.902	-0.026	0.815	-0.021	0.854
Cho	0.130	0.247	0.020	0.861	-0.043	0.704	-0.001	0.993	0.030	0.793	0.094	0.406
Cho %	**0.383**	**<0.001**	0.084	0.457	-0.103	0.358	0.054	0.829	0.123	0.276	0.203	0.070
Protein	-0.196	0.080	0.013	0.907	0.076	0.498	0.037	0.742	-0.045	0.692	-0.096	0.395
Protein %	-0.130	0.249	-0.042	0.710	0.034	0.766	-0.019	0.868	-0.012	0.918	-0.050	0.658
Fat	**-0.29**	**0.007**	-0.025	0.823	0.110	0.330	0.021	0.853	-0.106	0.345	-0.172	0.126
Fat %	**-0.411**	**<0.001**	-0.077	0.494	0.119	0.292	-0.014	0.902	-0.135	0.229	**-0.225**	**0.044**
Saturated fat	**0.361**	**<0.001**	0.105	0.350	-0.017	0.881	-0.083	0.460	-0.055	0.624	-0.123	0.274
Unsaturated fat	**-0.228**	**0.041**	0.015	0.891	0.158	0.158	0.068	0.545	-0.117	0.296	-0.173	0.123
Cholesterol	-0.213	0.056	-0.106	-0.344	0.013	0.907	-0.073	0.515	-0.018	0.871	-0.067	0.551
Fiber	**-0.358**	**<0.001**	0.111	0.325	0.116	0.302	0.123	0.274	**-0.357**	**<0.001**	**-0.419**	**<0.001**
Vitamin B1	**-0.246**	**0.027**	0.040	0.722	0.027	0.811	0.039	0.729	**-0.274**	**0.013**	**-0.320**	**<0.001**
Vitamin B2	**-0.393**	**<0.001**	**-0.221**	**0.047**	-0.083	0.464	-0.192	0.086	**-0.265**	**0.017**	**-0.356**	**<0.001**
Biotin	**-0.262**	**0.018**	-0.094	0.402	-0.053	0.641	-0.088	0.434	**-0.315**	**0.004**	**-0.384**	**<0.001**
Folic acid	**-0.405**	**<0.001**	0.003	0.979	0.100	0.374	0.038	0.735	**-0.276**	**0.013**	**-0.498**	**<0.001**
Vitamin C	-0.191	0.088	0.017	0.881	**0.232**	**0.037**	0.096	0.395	-0.118	0.293	**-0.287**	**0.009**
Calcium	**-0.473**	**<0.001**	**-0.237**	**0.034**	-0.124	0.269	-0.218	0.05	**-0.274**	**0.013**	**-0.418**	**<0.001**
Magnesium	**-0.259**	**0.020**	0.022	0.847	0.044	0.694	0.032	0.777	**-0.227**	**0.042**	**-0.335**	**0.002**
Phosphor	**-0.435**	**<0.001**	-0.122	0.277	-0.023	0.840	-0.098	0.385	**-0.263**	**0.018**	**-0.364**	**0.001**
Iron	**-0.323**	**0.003**	0.081	0.472	0.084	0.453	0.090	0.425	**-0.271**	**0.014**	**-0.390**	**<0.001**
Zinc	**-0.273**	**0.014**	-0.030	0.791	0.036	0.752	-0.009	0.935	-0.184	0.099	**-0.245**	**0.028**

SFMPQ: Short form of MacGill Pain Questionnaire, FIQ: Fibromyalgia Impact Questionnaire, VAS: Visual analogue scale, Cho: Carbohydrate

Vitamin D is also important in both inflammatory and pain pathways. We know an association between vitamin D deficiency and fibromyalgia, but in fact, little is known about its mechanism in fibromyalgia. A recent review showed that patients with fibromyalgia had low levels of vitamin D according to healthy controls (17). Literature shows contradictory results about the effect of vitamin D on pain or symptom control, with no clear results indicating the role of supplementation in the management of fibromyalgia. Although there are studies that found negative correlation between pain or tender points count and vitamin D levels, the remaining studies could not describe a correlation (18). In a study it was found that fibromyalgia patients with vitamin D levels ≤20 ng/mL to be more likely to have humor disruption, confusion, memory deterioration, sleep problems, palpitations and restless-leg syndrome (19). In addition, vitamin D supplements are reported to improve disease symptoms in patients with fibromyalgia (20,21). In the current study, the mean vitamin D level was 22.8±14.1 ng/mL and thirty patients showed vitamin D insufficiency. However, there was no correlation between serum vitamin D levels and clinical symptoms.

The hypothesis about connection between dietary patterns and fibromyalgia symptoms has directed clinicians to investigate the effects of different diets on fibromyalgia symptoms (8). Raw vegetarian diet, low FODMAPs diet, hypocaloric diet, monosodium glutamate- and aspartame-free diet are some of the dietary patterns which have been studied to date and results on pain, quality of life and sleep are contradictory. A study showed that a pure vegetarian, raw diet provided significant improvements in fibromyalgia symptoms (pain, physical performance, function and quality of life) (22,23). Another study reported that after a three-months vegan diet, there were significant improvements in pain scores, health assessment questionnaire scores, general health questionnaire, quality of sleep and morning stiffness (24). In a randomized controlled trial, it was shown that lacto-vegetarian diet combined with core stabilization exercises in patients with fibromyalgia who had low back pain provided pain reduction and body composition improvement (25). In another study, it was shown that a gluten-free diet improved all symptoms including pain, tender points, function, gastrointestinal complaints and fatigue (26). Despite the fact that there are studies in the literature about diet-

symptom association, few studies investigated macronutrient and micronutrient content of the diet. In the current study, we found dietary energy percent from carbohydrate, fat, and fiber association with FIQ and SFMPQ.

Fibromyalgia and obesity are very closely associated pathologies and obesity and carbohydrate-rich diets are potential factors that may affect the severity of symptoms, pain, and disease activity in fibromyalgia syndrome (27,28). We also found similar results in the current study. The percent of energy from carbohydrate showed a moderate positive correlation with FIQ. To date, some investigators tended to enlighten the possible relation between glucose metabolism and pain, but there is no significant result yet (29). In the current study, interestingly the percent of energy from fat showed a moderate negative correlation with FIQ and dietary fat showed a moderate negative correlation with FIQ. However, when we reanalyzed fat content considering saturated and unsaturated fat, saturated fat showed a moderate positive correlation while unsaturated fat showed a weak negative correlation with FIQ. We suggest that, according to this result, saturated fat content of diet may be the factor which worsens symptoms of the patient. Intake of saturated fat is increasing day by day due to processed food and fast food consumption. Diets containing excessive saturated fat are suspected to cause chronic diseases due to chronic low degree inflammation (30-33).

Plant-enriched diets are reported to increase nitric oxide levels which may help to relieve pain in fibromyalgia patients (8). In the current study, the amount of dietary fiber showed a moderate negative correlation with FIQ, SFMPQ-VAS and SFMPQ-PPI. Different from other dietary content, fiber showed a correlation with SFMPQ-VAS and SFMPQ-PPI and this gives a rise to the thought that increasing fiber content of diet may help relieving pain.

Redox balance changes in cells due to nutritional deficiencies like iron, magnesium, iodine, melatonin, zinc, selenium and branched chain amino acids can have a potential role in fibromyalgia symptoms (34). Although magnesium and selenium are suspected ions in physiopathology and symptom severity of fibromyalgia, a review showed that magnesium and malic acid use did not significantly change pain ratings or depressive symptoms in patients with fibromyalgia (35). While some authors reported that serum levels of selenium and magnesium were not significantly different from controls (36), another study showed a decrease in magnesium and zinc levels, but no significant difference in selenium levels. Also, serum magnesium and zinc levels were associated with clinical parameters, indicating a possible role of these two elements in fibromyalgia etiopathogenesis (37). However, this study did not investigate nutritional deficiency or low magnesium or zinc dietary intake. In the current study, we evaluated dietary intake of magnesium and found that dietary magnesium showed a weak negative correlation with FIQ and SFMPQ-VAS. As it can be realized from the above mentioned results, cross-sectional or interventional studies show contradictory results.

In addition to study methodology, included patients in the current study were given nutrition advice according to dietary recalls. To the best of our knowledge, the current study is the first on the relationship between nutrition, biochemical parameters and clinical symptoms in fibromyalgia patients. The cross-sectional design can be interpreted as the limitation of this study. There are also strengths of the study. Large sample size and comprehensive assessment of patients with multiple questionnaires are the strengths of the study. Well-designed clinical trials about the effect of the dietary interventions on fibromyalgia patients are necessary in order to understand more details about the potential benefits from nutrition.

Conclusion

The current study results suggest that a healthy diet habit consisting of low saturated fat, carbohydrates and higher fiber, vitamins and minerals (folic acid, calcium, phosphor, vitamin B1, vitamin B2, vitamin B_{12}, biotin, iron, magnesium, zinc) may provide an improvement in fibromyalgia symptoms. We also suggest that dietary assessment and interventions should be a part of the management of patients with fibromyalgia.

Ethics

Ethics Committee Approval: The study protocol was approved by the bioethics and Gülhane Training and Research Hospital Research Committee with the number of 19/156 on April 30th of 2019, and all procedures were performed in compliance with the Helsinki Declaration.

Informed Consent: All patients were informed about the study and written informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Fast track anesthesia for lumbar discectomy in outpatient basis: A retrospective observational study

Mehmet Özgür Özhan[1], Mehmet Burak Eşkin[2], Ceyda Çaparlar[3], Bülent Atik[4], Mehmet Anıl Süzer[1], Uğur Gönç[5]

[1]*Cankaya Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey*

[2]*University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Turkey*

[3]*University of Health Sciences Turkey, Yildirim Beyazit Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey*

[4]*Balikesir University Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Turkey*

[5]*Cankaya Hospital, Clinic of Orthopedics and Traumatology, Ankara, Turkey*

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Corresponding Author:
Mehmet Burak Eşkin, MD, University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Turkey
burakeskin@hotmail.com

ORCID:
orcid.org/0000-0001-6781-9334

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ABSTRACT

Aims: The use of short acting anesthetics has introduced a fast track anesthesia concept that allows the transfer of the patients from the operating room directly to the ward without a need for an observation in the post anesthesia care unit. The aim of this study was to evaluate whether fast tracking had an effect on the duration of hospital discharge after lumbar discectomy (LD) under general anesthesia (GA) between October 2017 and April 2018.

Methods: Medical records of 252 American Society of Anesthesiologists physical status 1-2 patients were enrolled in this retrospective and observational study. The primary aim was to determine the patients who were eligible for fast tracking and to compare the duration of hospital discharge between fast track eligible and ineligible patients. The secondary aim was to identify the factors that prevented fast tracking and early hospital discharge. The value of $p<0.05$ was considered statistically significant.

Results: More patients were eligible for fast tracking than those who were not eligible [176 (69.8%) vs. 76 (30.2%), p=0.012]. The duration of hospital discharge was lower in fast track eligible patients compared to ineligible patients (14.5±7.5 hours vs 17.8±7.3 hours; p=0.009). Pain was the most common cause of fast track ineligibility and delay in hospital discharge (42.1% and 64.5%; $p<0.05$).

Conclusions: GA using short acting anesthetics could increase fast track eligibility which reduced the duration of hospital discharge after outpatient LD. Postoperative pain should be considered as a limiting factor for fast tracking and early hospital discharge.

Introduction

The developments in the anesthetic and surgical techniques facilitated early recovery after the surgery and introduced the "fast track anesthesia" concept in practice (1). According to the concept, the patients are assessed for the fast track eligibility in the operating room (OR) immediately after awakening from general anesthesia (GA). Eligible patients are transferred from the OR directly to the ward (phase 2 recovery area) without a need for an observation in the phase 1 recovery area of the post-anesthesia care unit (PACU) which is called "PACU bypass" (1,2). It has been reported that fast tracking is associated with a reduced length of hospital stay which increases patient's satisfaction and cost-saving in the health care (1-3).

In the past, fast tracking was preferred generally for anesthetic managements including monitored anesthetic care (MAC), neuraxial anesthesia, or GA using only supraglottic airway devices that did not necessitate endotracheal intubation with the use of neuromuscular blocking agents (NMBAs) (4).

However, in recent years, the introduction of newer anesthetics with a short duration of action and immediate-acting reversal agents has made fast tracking after GA possible (5-7).

We have been using fast tracking in our anesthesia practice for three years in certain outpatient surgeries under GA that enables the discharge of patients in less than 24 hours after the surgery. One of these outpatient surgeries is lumbar discectomy (LD) which is the most common surgical practice in the neurosurgery (8). LD necessitates endotracheal intubation with the use of NMBA when they are performed under GA due to a prone positioning. The aim of this study was to evaluate whether fast tracking had an effect on the duration of hospital discharge after LD under GA.

Methods

Study Design

This observational and retrospective study was conducted in a tertiary hospital after obtaining ethics committee approval (Gülhane Training and Research Hospital, date: 06/05/2018; protocol no: 18/148). Data were retrospectively collected from the hospital's computerized database, medical and anesthesia files of all adult patients who underwent elective LD under GA for lumbar disc hernia between October 2017 and April 2018. The inclusion criteria were as follows: Being American Society of Anesthesiologists (ASA) physical status 1-2 and undergoing elective one level LD for the treatment of a lumbar disc hernia performed by a single neurosurgeon under GA. Exclusion criteria were undergoing urgent surgery, having a history of a neurological impairment, having obstructive sleep apnea, having difficult airway management, the presence of insufficient data, and being lost to follow-up in the perioperative period. Informed consent was not obtained from patients due to the retrospective design of the study. The study followed the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Anesthetic Technique

The routine anesthetic protocol for the outpatient LD under GA was as follows: GA was induced using IV propofol (2-2.5 $mgkg^{-1}$), fentanyl (1 μgkg^{-1}), and rocuronium (0.6 $mgkg^{-1}$) and maintained using a total intravenous (IV) anesthesia (TIVA) technique based on IV infusions of propofol (3-6 $mgkg^{-1}$ h^{-1}) combined with remifentanil (1-2 μgkg^{-1} h^{-1}). Infusion doses were adjusted to keep the mean arterial blood pressure and heart rate in ± 20 of baseline levels. At the end of the surgery, a subcutaneous wound infiltration was performed on the surgical incision site using a local anesthetic mixture containing 100 mg of lidocaine 2% and 25 mg of bupivacaine 0.5%. GA was discontinued. Sugammadex (2-4 $mgkg^{-1}$) was given for the reversal of the NMBA and the patients were extubated. Fast track eligibility was evaluated using the White's Fast Track scoring system (Table 1) (4). The patients with a score >12 were considered to be eligible for fast tracking and were transferred from the OR directly to the phase 2 recovery area (the ward). This was called PACU bypass. Ineligible patients were followed in the PACU where their treatments were continued. The patients were discharged from the PACU to the ward according to the modified Aldrete scoring system. A score >9 was considered to be eligible for the transfer from PACU to the ward (Table 1) (9).

Postoperative Follow-up Period

A multi-modal analgesic (MMA) regimen was used throughout the perioperative period including preoperative IV tenoxicam (10 mg), intraoperative IV paracetamol (10 $mgkg^{-1}$) and tramadol (1 $mgkg^{-1}$), postoperative IV patient controlled analgesia (IV-PCA) using tramadol, IV paracetamol (10 $mgkg^{-1}$ with six hours intervals, up to a total daily dose of 3000 mg), and oral diclofenac sodium (75 mg with 24 hours intervals). Pain was evaluated using a Visual Analogue Scale (VAS) and IV pethidine (0.5 $mgkg^{-1}$) was given when VAS score >3. Postoperative nausea and vomiting were treated using IV ondansetron (4 mg). The Post Anesthetic Discharge Scoring System Discharge was used to evaluate the eligibility for discharge from the hospital (Table 2) (10).

Data Collection

All medical data were reviewed in detail to obtain: 1) demographic characteristics including gender, age, ASA physical status, co-morbidity, and body mass index, 2) recovery times: a) the duration of the operation (min), b) time to be eligible for PACU by-pass in fast tracked patients (min), d) the duration of PACU care for non- fast tracked patients (min), e) time to hospital discharge (hours), 3) number and rate of patients who were fast tracked and discharged from hospital with respect to outpatient surgery (discharge time <24 hours), 5) factors preventing fast tracking and/or discharge from hospital in outpatient setting, 6) complications.

Outcome Measure Criteria

The primary outcome measure was to determine the patients who were eligible for fast tracking and to compare the duration of hospital discharge between fast track eligible and ineligible patients. The secondary outcome measure was to identify the factors that prevented fast tracking and early hospital discharge.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 21 (IBM SPSS Inc, Chicago, IL) pocket program. Descriptive statistics were calculated for continuous variables as mean and standard deviation (mean±SD), and for categorical variables as frequency distribution and percentage (n, %). The Pearson's

Table 1. White's fast track scoring system and modified Aldrete scoring system

White's fast track scoring system*	Score	Modified Aldrete scoring system**	Score
Physical activity		**Activity**	
Able to move all extremities under command	2	Moves all four extremities	2
Weakness in some movements of extremities	1	Moves only two extremities	1
Unable to move all extremities	0	Unable to move any extremities	0
Respiratory stability		**Respiration**	
Able to deep breathe	2	Able to deep breath with free cough	2
Tachypneic, but with free cough	1	Dyspnea with limited breathing	1
Dyspnea without free cough	0	Apnea	0
Hemodynamic stability		**Circulation (BP)**	
BP below the 15% of baseline MAP	2	20 mm Hg higher than baseline anesthetic level	2
BP between 15-30% of baseline MAP	1	20-50 mm Hg higher than baseline anesthetic level	1
BP higher than 30% below baseline MAP	0	>50 mm Hg higher than baseline anesthetic level	0
Level of consciousness		**Consciousness**	
Awake and orientated	2	Fully awake with orientation	2
Arousable with minimal stimulation	1	Arousable on calling	1
Respond to tactile stimulation only	0	Unresponsive	0
Oxygen saturation status		**Oxygen saturation**	
Maintains SpO_2>90% on room air	2	SpO_2>92% on room air without O_2 supplement	2
Requires oxygen supplement (nasal prongs)	1	Requires supplemental O_2 to maintain SpO_2>90%	1
SpO_2<90% with oxygen supplement	0	SpO_2<90% with O_2 supplement	0
Postoperative pain assessment			
No pain or mild discomfort	2		
Moderate to severe pain requires IV analgesics	1		
Persistent and severe pain	0		
Postoperative emetic symptoms			
None or mild nausea without active vomiting	2		
Transient nausea and vomiting or retching	1		
Persistent moderate or severe nausea and active vomiting	0		

MAP: Mean arterial pressure, BP: Blood pressure, IV: Intravenous
*Adapted from the reference 4.
A score >12 was considered to be eligible for fast tracking.
**Adapted from the reference 9.
A score >9 was considered to be eligible for the transfer from post-anesthesia care unit

chi-square (χ^2) and Fisher's exact tests were used to test the difference in distributions of categorical variables between the groups. Normality of distribution for continuous variables was assessed with the Kolmogorov-Smirnov test. The distribution of the non-parametric variables in groups was assessed with the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

Results

Medical records of 312 patients were analyzed. Sixty patients were excluded from the study due to the partially missing data (n=48), and to the loss to follow up (n=12). The remaining 252 patients were included in the analysis (Figure 1). There were 138 female and 114 male patients with a mean age of 46.2±9.8 years. Two groups were identified after matching the data regarding the fast track availability following surgery: the Fast Track group (group FT) included patients who were eligible for fast tracking and transferred from the OR to the ward. The PACU group included patients who were not eligible for fast tracking and transferred from the OR to the PACU.

Primary outcome measures: Of a total 252 patients, more patients were found eligible for fast tracking: group FT (n=176, 69.8%) vs. group PACU (n=76, 31.2%), (p=0.012). The demographic characteristics were similar between the groups (p>0.05) (Table 3). The number and rate of patients who were discharged from the hospital in an outpatient basis (length of hospital stay <24 hours) were higher than those patients who were discharged after 24 hours after surgery [221 (87.7%) vs. 31 (12.3%), p=0.006]. The mean time to be discharged from the hospital (time to Post Anesthesia Discharge Scoring System score ≥9) was lower in the group FT compared to the group PACU (14.5±7.5 hours vs. 17.8±7.3 hours; p=0.009). The rate of patients who were discharged in <24 hours was not statistically different between the groups (88.1% vs. 86.8%; p=0.881) (Table 3).

Secondary outcome measures: When assessing factors which prevented fast tracking, it was found that postoperative

pain was the leading factor (42.1%). It is followed by unconsciousness (21.1%), hemodynamic instability (15.8%), postoperative nausea and vomiting (13.1%), and desaturation (7.9%), (p=0.001) (Table 4). The factors that prevented outpatient hospital discharge were as follows: pain (64.5%), PONV (29.0%), and hemodynamic instability (6.5%) (p=0.001, Table 4). Three patients in group FT and one patient in group PACU were readmitted after hospital discharge due to intractable pain (1.7% vs. 1.3%; p=0.563). There were no complications observed related to the surgical procedure.

Discussion

The results of this study demonstrated that the majority of lumbar discectomies (87.7%) could be performed in an outpatient basis with a PACU by-pass availability of 69.8% under GA. Numerous studies have reported that 49.9% to 99.8% of patients undergoing LD are discharged at the same-day of the surgery (11-13). Fast tracking provides earlier discharge from hospital as reported in many studies (1-8).

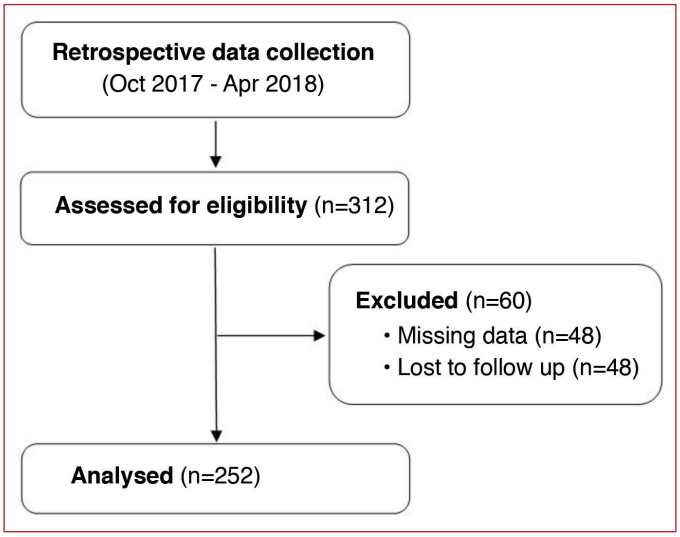

Figure 1. The study flow chart

Since the first report by Lubarsky (14) in 1996, fast track anesthesia has been expanded in all types of surgeries. MAC, regional anesthesia, and GA using supraglottic airway devices have been frequently used in fast track anesthesia. The use of NMBAs for endotracheal intubation has limited fast tracking due to the residual neuromuscular block after the procedures. However, the introduction of anesthetics with a short duration of action has facilitated early recovery from GA in those procedures. We used a TIVA technique based on propofol and remifentanil for the maintenance of anesthesia, a combination of a hypnotic with a short duration of action and an ultra-short acting opioid. It is well-known that interaction between propofol and remifentanil results in decreased propofol doses required for anesthesia (15). Additionally, the use of sugammadex has made a big contribution to the early recovery from GA by rapid reversal of non-depolarizing neuromuscular blockade induced by rocuronium (6,7,16).

In this study, it was observed that the most important factor which prevented fast tracking was postoperative pain rather than unconsciousness and respiratory failure. Previous studies reported that 80% of patients suffered from acute postoperative pain after the spinal surgery and 80% of them described the pain as severe (17). Inadequate postoperative analgesia is associated with delayed recovery, ambulation and hospital discharge, excessive use of narcotic analgesics, increase of opioids- related side-effects, and development of chronic pain. MMA is considered to be the most effective method for

Table 2. Post Anesthetic Discharge Scoring System

Parameter	Score*
Vital signs	2=Lower than the 20% of preoperative value 1=Between 20% and 40% of preoperative value 0=Higher than the 40% preoperative value
Activity and mental status	2=Oriented and has a steady gait 1=Oriented or has a steady gait 0=Neither oriented nor has a steady gait
Pain, nausea and/or vomiting	2=None or minimal 1=Moderate, required treatment was given 0=Severe, requires treatment
Surgical bleeding	2=Minimal 1=Moderate 0=Severe
Intake and output	2=Has had oral intake of fluids and voided 1=Has had oral intake of fluids or voided 0=Neither oral intake nor voiding

MAP: Mean arterial pressure
*Adapted from the reference 10.
A score >9 was considered to be eligible for the hospital discharge

Table 3. Comparison of demographic characteristics and perioperative data between the groups

Parameters/Groups	Group FT (n=176)	Group PACU (n=76)	p*
Gender (female/male) (%)	55.7%/44.3%	52.6%/38.4%	0.750
Age (years)	41.2±11.1	43.4±12.3	0.272
ASA physical status (1/2) (%)	85.8%/14.2%	84.2%/15.8%	0.579
Body mass index (kgm^{-2})	26.2±1.3	27.3±2.1	0.716
Duration of surgery (min)	135.2±15.0	131.9±12.8	0.251
Time to discharge from OR into ward (min)	7.8±2.5	31.3±2.9	0.001
Time to PADSS score ≥9 (hrs)	14.5±7.5	17.8±7.3	0.009
Hospital discharge time <24 hours (%)	88.1%	86.8%	0.881
Unanticipated hospital admission n, (%)	3 (3.4%)	1 (2.6%)	0.563

ASA: American Society of Anesthesiologists, OR: Operating room, PADSS: Post Anesthesia Discharge Scoring System, FT: Fast track, PACU: Post anesthesia care unit
Values are presented as mean±standard deviation, numbers and/or proportion (n, %).
*p<0.05 was considered as statistically significant

Table 4. The factors preventing fast tracking and hospital discharge in outpatient basis

	Pain	Unconsciousness	Hemodynamic instability	PONV	Desaturation	p*
Fast tracking n, (%)	32 (42.1)	16 (21.1)	12 (15.8)	10 (13.1)	6 (7.9)	0.001
Hospital discharge n, (%)	20 (64.5)	0 (0.0)	2 (6.5)	9 (29.0)	0 (0.0)	0.001

PONV: Postoperative nausea and vomiting
Values are presented as mean±standard deviation, numbers and/or proportion (n, %).
*p<0.05 was considered as statistically significant

the treatment of postoperative pain. MMA combines analgesic medications and techniques targeting different mechanism and actions in the peripheral and/or central nervous system (18). Our MMA regimen consisted of three components: a) pre-emptive analgesia using non-steroidal anti-inflammatory drugs (NSAIDs), b) intraoperative administrations of NSAIDs and tramadol, a centrally acting synthetic opioid medication with a lower risk of respiratory depression, in combination with a local anesthetic wound infiltration, c) postoperative IV/oral NSAIDs and IV tramadol PCA. Pethidine was used only as rescue analgesic to minimize adverse effect. Many combinations of drugs and techniques were described, but there is a lack of evidence regarding optimal MMA after lumber discectomy (17,18).

An interesting finding was the similar rate of same-day hospital discharge for both fast tracked and not fast tracked patients despite the reduced length of stay in FT group. It might be attributable to the use of different scoring systems for the assessment of fast tracking (White's Fast Track Scoring System) and for the hospital discharge (Post Anesthetic Discharge Scoring System). However, the factors which prevented both fast tracking and early hospital discharge were same in these scoring systems. We think that the treatments for pain and hemodynamic disturbances postponed the hospital discharge time beyond to 24 hours in both groups. In a study by Song et al. (19), it was reported that the time to discharge was shorter in the fast track group, but the total numbers of nursing interventions and nursing hours were not different between the fast tracked and not fast tracked patients.

This study has several limitations. First, the retrospective nature of the study might have resulted in significant bias that affected the results. To prevent this disadvantage, we used the same criteria for inclusion and exclusion from the study during the data collection period. Data were obtained from multiple sources including anesthesia files, patient files, and electronic medical records to reduce recall bias. A single neurosurgeon performed all interventions. The patient files with insufficient data were excluded. Second, the lack of using bispectral index and monitoring of the neuromuscular junction compelled to adjust the dose of TIVA infusions according to the vital parameters rather than monitoring of the anesthetic depth (20,21). Another limitation was the exclusion of patients with obstructive sleep apnea and morbid obesity. Although recent studies have reported that those patients can be safely operated as outpatients, we still exclude them in the assessment for fast tracking to prevent further risks associated with the respiratory system (22,23).

Conclusion

In conclusion, lumber discectomies can be performed in outpatient manner with fast track eligibility under GA when appropriate patient selection criteria with short-acting anesthetics

drugs are used. Postoperative pain has to be considered as one of the main factors impairing fast track eligibility and hospital discharge. Therefore, MMA regimens should be routinely implemented in ambulatory surgery.

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Ethics

Ethics Committee Approval: The study was approved by the ethics committee of Gülhane Training and Research Hospital, Turkey (06/05/2018; 18/148).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.Ö.Ö., Design: M.Ö.Ö., Data Collection or Processing: M.Ö.Ö., Analysis or Interpretation: C.Ç., B.A., M.A.S., U.G., Literature Search: M.B.E., Writing: M.Ö.Ö., B.A., M.A.S., U.G.

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Endovascular treatment of intracranial aneurysms: A single center experience

Gökhan Yüce, Mustafa Taşar

University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Radiology, Ankara, Turkey

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Corresponding Author:
Gökhan Yüce MD, University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Radiology, Ankara, Turkey
drgkhann85@gmail.com

ORCID:
orcid.org/0000-0003-3546-7965

Keywords: Intracerebral aneurysms, endovascular treatment, detachable coil, flow diverter stent

ABSTRACT

Aims: Intracranial aneurysms (IA) are vascular anomalies that are mostly detected by life threatening complications such as intracerebral hematoma or subarachnoid hemorrhage. Recently endovascular treatments have become the major treatment modality. In this study, our objectives were to describe the clinical data of the patients with treated IAs, to evaluate the success rate of two treatment modalities [coil embolization and flow diverter stents (FDS)], and to document common complications.

Methods: The patients who were admitted to our tertiary center and underwent endovascular treatment (with coil embolization/FDS) in the interventional radiology unit between December 2018 and October 2019 were enrolled. The clinical data of the patients including aneurysm size, subtype, location, treatment modality, and pre and post procedural complications were analyzed retrospectively.

Results: Eighteen of 37 patients (48.6%) were male and 19 (51.3%) were female. The median age was 54 (minimum-maximum; 12-77) years. There was no predisposing factor in the clinical history except four patients. Regarding the aneurysm subtypes, 89% of IAs were saccular and 11% were fusiform. The most common localization was internal carotid artery (48%). Ten patients were admitted with ruptured aneurysm and twenty seven were asymptomatic and unruptured. Four patients died in the mean follow-up of nine months. Two patients had intervention-related complication (hemiparesis and hydrocephalus).

Conclusions: IAs can be effectively treated with endovascular techniques since cure rates are high and complications rates are reasonably low. Coil, FDS or both can be used in selected cases of ruptured or unruptured aneurysms.

Introduction

Intracranial aneurysms (IA) have been the focus of attention for both clinicians and experimental studies since they have versatile properties. IAs are vascular anomalies that are mostly detected with complications such as intracerebral hematoma, subarachnoid hemorrhage (SAH) or hydrocephalus. Mortality rate of IA complications have decreased from 30-33% to 10% in the last decade indicating that important and rapid steps have been taken in the field of treatment. Although surgical clipping was the gold standard treatment method in the past, endovascular treatment became an alternative to surgical treatment with the development of coil systems (1,2).

Endovascular treatment of IA started with the use of latex balloons and pushable coils. However, their uses were associated with significant complications which leaded to the development of detachable coil systems (3). In aneurysms treated by the detachable coils, despite total occlusion, relapse may develop due to mechanical failure or re-growth of the residual neck (3,4). Another method used in endovascular therapy is flow diverter stents (FDS). FDSs decrease the blood flow, change the transmural gradient of the vessel wall, and induce intra-aneurysmal thrombosis (5). Unlike the coated stents, the pores in the FDS allow the passage of adequate amounts of blood and by that way, the main artery line along with the thin perforating branches remains open (6). Although the introduction of this device is relatively new, experience is rapidly increasing. However, the choice of the best endovascular procedure and indications for the use of FDSs are still a matter of debate and deserve to be discussed.

There are previous reports in the literature but few of them comprehensively investigated the clinical and technical aspects of using those two separate techniques. The clinical properties of patients, selected treatments and technical difficulties may vary among centers according to the expertise of the specialists and interpretation of local or international guidelines.

Herein this study, our purpose was to document our single center experience in endovascular treatment of IAs. Our primary objectives were to describe the demographic and clinical data of the patients with IA (aneurysm subtypes, locations and size), to evaluate the success rate of two treatment modalities (coil embolization and FDS), and also to document the complications that we came across in the routine clinical practice.

Methods

In this study, the patients who were admitted to our tertiary center's neurosurgery department and underwent endovascular treatment (with coil embolization/FDS) in the interventional radiology unit between December 2018 and October 2019 were enrolled. The demographic and clinical data together with the images of the procedures were analyzed retrospectively. Local Ethics Committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital approved the study protocol (approval number: 2020-59) in accordance with the principles of the Declaration of Helsinki.

Diagnostic digital subtraction angiography (DSA) (Infinix, Canon Medical Systems, Japan) was performed in all patients when they applied to our interventional radiology division. Routine blood tests, chest radiography and electrocardiography had been performed for each patient before the intervention and data were recorded retrospectively from the patient files. In our center, the routine clinical practice based on the clinical guidelines is to start dual antiplatelet therapy, including acetylsalicylic acid (100 mg-once a day) and clopidogrel (75 mg-once a day) at least five days before the procedure for patients who are planned to undergo FDS. Endovascular embolization of aneurysms was performed using detachable coils (Axium, Meditronics, Ireland) and stents (FRED®, Tokyo, Japan) in the DSA system. The procedure was performed under general anesthesia in all patients. According to the aneurysm localization, after the catheterization of the vertebral or internal carotid artery, the appropriate working position was determined and a 'road map' was made by contrast agent injection. Then, the desired area was reached through the catheter by the help of the appropriate length microcatheter (Headway microvention, California, USA) guidewires. Varying number of coils [Axium Prime coils (extra soft), Meditronics, Ireland] and/or stents were used, depending on the size and morphology of the aneurysms.

Statistical Analysis

The Statistical Package for the Social Sciences, version 25 (Inc., Chicago, IL, USA) was used for the statistical analysis. Descriptive analysis was made to identify the baseline characteristics of the patients. Mean, standard deviation, and range were used to describe continuous variables. Categorical variables were described as number and percentage. Median was used to describe non-parametric variables.

Results

Eighteen of 37 patients (48.6%) were male and 19 (51.3%) were female. The median age was 54 years (minimum-maximum; 12-77). In 33 of 37 patients (89.1%), there was no predisposing factor for IA in the clinical history. Ten patients had ruptured whereas twenty seven had unruptured IA. All patients with unruptured IA, who had no vasospasm during the procedure, were followed up in the neurosurgery intensive care unit in the post intervention period until they were clinically stabilized. They were discharged provided that no intervention-related complication developed in three days. The patients with ruptured IA were intubated and sedated until the intracranial pressure returned to normal and the neurological condition began to improve. All patients with ruptured IA received nimodipine treatment in order to reduce vasospasm (10 mg/24 hours intravenous then 6x60 mg oral for 21 days).

When aneurysm subtypes were evaluated, 89% of IAs (33 patients) were saccular and 11% (four patients) were fusiform (Table 1). The mean aneurysm size was 6.4±2.9 mm (minimum and maximum sizes were 3.2 and 15 mm, respectively). Among four patients with fusiform aneurysms, one was a 22-year-old male patient with a history of skull base fracture that had been diagnosed after a traffic accident that occurred two months before the admission and had required hospitalization for few weeks. The second patient had a 2.5 cm sized pseudoaneurysm detected in the cavernous segment of left internal carotid artery, which was diagnosed two months after a cranial trauma (Figure 1). The third patient with fusiform aneurysm was a 12-year-old male patient who had a history of transcranial operation for craniopharyngioma two years before the admission with IA. In the fourth patient, fusiform enlargement was detected in the supraclinoid segment of the right internal carotid artery during preoperative evaluation for recurrent bleeding.

Regarding the localizations of aneurysms, internal carotid artery aneurysms constituted the most common type (48.6%). The least common localizations were the posterior cerebral artery and vertebral artery aneurysms. Ten (27%) of the patients were admitted to neurosurgery with ruptured aneurysm whereas 27 (83%) patients were admitted with an unruptured aneurysm (Table 1).

In 32 of 37 (86.4%) patients, endovascular treatment was successfully performed without any significant complication. Detachable coil was placed in 16 and FDS was used in 19 patients whereas two patients required both (Table 1). The recorded indication for FDS was mainly treating complex wide

necked saccular or fusiform IA. Four patients (10.8%) died due to vasospasm and infection. In a patient with a wide-necked aneurysm in the M2 segment of the middle cerebral artery, branch loss occurred after implanting FDS. That patient had left hemiparesis in the postoperative period and was referred to the physical therapy center after discharge. In another patient who was admitted with a ruptured aneurysm in the M2 segment of the middle cerebral artery and underwent coil embolization, hydrocephalus findings (neurological worsening, severe enlargement in the 3rd ventricle and lateral ventricles in the brain tomography) appeared two days after the treatment. That patient required external ventricular drainage which was removed after clinical and radiological improvement on the postoperative 7th day. In a patient who had asymptomatic non-ruptured left internal carotid artery supraclinoid segment aneurysm, FDS was implanted. Fifteen days after the stent implantation, the patient was readmitted with an intraparenchymal hematoma in the left parietooccipital region. During the follow-up period, the patient died due to secondary infections. Endovascular treatments of two cases were shown on Figure 1 and 2.

Of all patients, only two had a prior history of endovascular treatment. The indication for the second intervention was filling of the aneurysm sac in both. Both FDS and coil embolization were performed in one patient as redo intervention, and only FDS was installed in the other.

Discussion

IA mostly present with complications or can be completely asymptomatic. Therefore, their actual incidence can be difficult to determine. In the study by Meyer et al. (7), rupture rate was reported as 1-8%. SAH is the most common clinical presentation form of IA and it is an important health problem due to its high mortality and morbidity (8). In our study, ten of thirty seven patients were admitted with ruptured and complicated IA.

Table 1. Demographic and clinical characteristics of the patients

Age years (median; minimum-maximum)	54 (12-77)		
Aneurysm size mm (mean±SD)	6.4±2.9		
Aneurysm subtype (number)	Saccular: 33 Fusiform: 4		
Aneurysm localization (number/%)	ICA-supraclinoid 12 (32.4%) ICA-cavernous 6 (16.2%) MCA-M1 segment 4 (10.8) MCA-bifurcation 2 (5.4%) MCA-M2 segment 2 (5.4%) Anterior communicating artery 9 (24.3%) Vertebral artery 1 (2.7%) Posterior cerebral artery 1 (2.7%)		
Unruptured/ruptured aneurysm (number)	27/10		
Treatment modality, complication and exitus (number)	**Modality**	**Complication**	**Exitus**
	Coil only 16	1 Hydrocephalus	3
	FDS only 19	1 Hemiparesis	1
	Coil+FDS 2	None	0

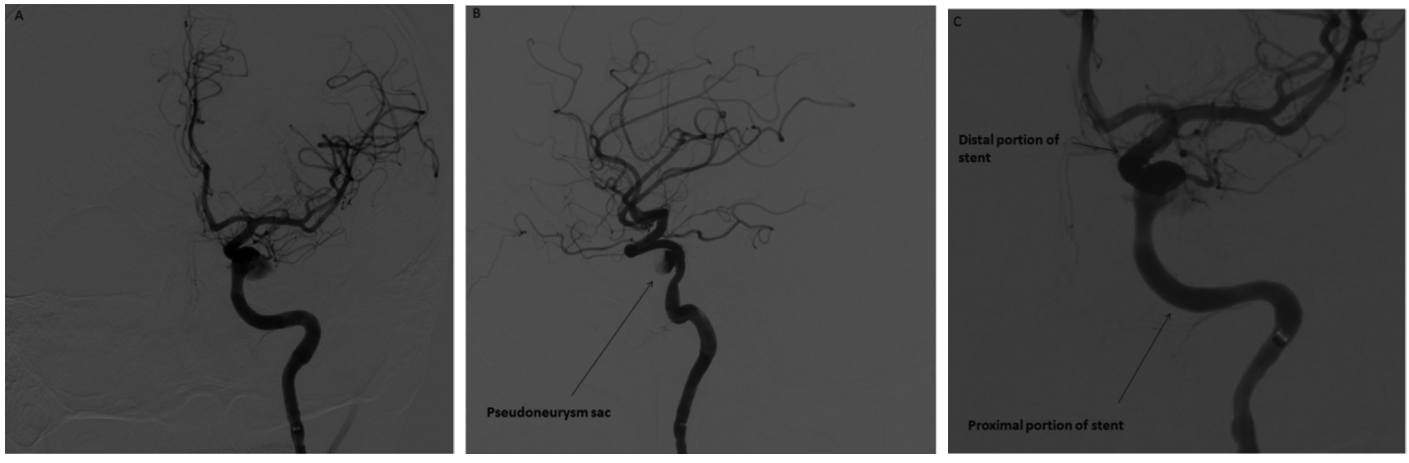

Figure 1. Preoperative lateral (a) and anteroposterior (b) angiographic image of a wide neck internal carotid artery aneurysm and post interventional (c) angiographic image shows stagnation of contrast agent within the aneurysm sac after stent replacement

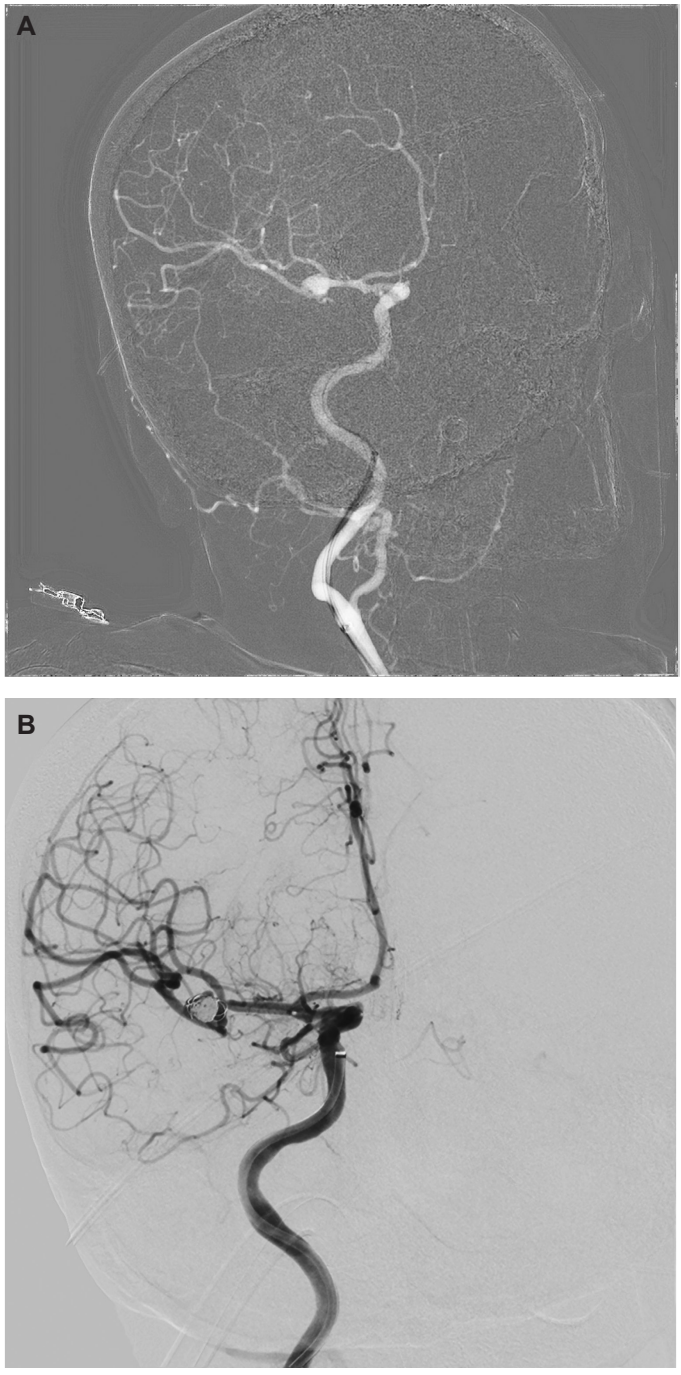

Figure 2. Preoperative angiographic image of a saccular aneurysm in the right MCA superior-inferior truncus bifurcation (a) angiographic image after coil embolization shows the effective volume reduction of the aneurysm sac (b)

IA can be classified as saccular (berry) or non-saccular. Saccular aneurysm, which is the most common type, looks like sacs or berries sticking out of a side of a blood vessel wall. Most of these saccular aneurysms have a “neck” region that may or may not be visualized during surgery (9,10). Saccular aneurysms are associated with growth and rupture. The “fusiform” (dissecting) aneurysm is less common than the saccular aneurysm and looks like the blood vessel is expanded in all directions (11,12). In our study, 89% of IAs (33 patients) were saccular and 11% (four patients) were fusiform. All patients with fusiform subtype had a predisposing factor such as cranial operation or previous trauma.

Coiling or clipping are accepted treatment options for endovascular treatment of both ruptured and unruptured aneurysm. After coiling or stent implantation, only 22-36% of the aneurysm volume can be filled (13). Two factors, which are the aneurysm size and neck width, determine the degree of volume reduction. There are publications indicating that endovascular treatment is less effective in wide-necked and giant aneurysms (14). In our study, 26 of the IAs were wide-necked. Three of four patients who died after endovascular treatment had wide-necked aneurysms. Moreover, two patients who required recurrent intervention also had wide-necked aneurysms. Those findings support the previous reports indicating that prognosis gets worse as the neck widens. In our study group, the mean aneurysm size was 6.4 mm. Ten patients had small-sized aneurysm (<4 mm), 22 had medium-sized (4-10 mm) and 5 had large aneurysms (>10 mm).

The possible complications of coil embolization method were the need for recanalization and coil compaction in large series (14,15). The rate of recanalization was reported as 33.6% and the rate of re-treatments was 20.7% in the study of Raymond et al. (15) including 383 aneurysms. In that aforementioned study, it was stated that the rate of contrast filling and baseline aneurysm size greater than 10 mm were the major determinants of recurrence after endovascular coil embolization. In our study, coil embolization was performed in 18 of 37 aneurysms (16 patients underwent only coil placement whereas 2 had both coil and FDS). During the median follow-up of six months (minimum-maximum; 4-15 months), none of the aneurysms had contrast filling within the neck.

FDS have greatly changed the landscape of IA therapy and are now considered first-line therapy for selected lesions. Its mechanisms of action are based on the internal change in hemodynamic parameters both in the main artery and within the aneurysm sac (16,17). Also, the indentations along the stent act as a nidus for endothelial cell growth in the neck of the aneurysm that results in exclusion of the aneurysm from the circulation. In our study, a total of 19 patients were implanted with a FDS (15 saccular, 4 fusiform aneurysms). Antiplatelet therapy was started in all patients before the procedure. As a complication, one patient was admitted due to intraparenchymal hematoma on the 15th postoperative day and died due to secondary infections whereas another patient had hemiparesis due to loss of feeder branches. Remaining seventeen patients who received FDS treatment did not have any significant complication during the follow-up period.

Long-term follow-up after endovascular treatment is important to evaluate the stability of the treatment and to detect early recurrence. In many studies, it has been reported that at least two controls should be performed within the first year after endovascular treatment (4). Although DSA is the gold standard diagnostic method for the follow-up of these patients, it is a more invasive and expensive procedure compared to MRA. We performed the first control after the procedure in our center in the 3rd month by the DSA. However, the patient was advised to have an earlier control visit in case any neurologic symptom developed or the aneurysm neck was not completely occluded in the first intervention.

The limitations of our study were small number of patients and limited follow-up period. Prospective studies should be conducted to determine the best treatment approach in different subtypes, localizations and clinical scenarios.

Conclusion

IAs can be effectively treated with endovascular techniques since cure rates are high and complications rates are reasonably low. Coil, FDS or both can be used in selected cases of ruptured or unruptured aneurysms. Wide neck aneurysms constitute a technical challenge for the radiologists and have worse prognosis regarding to recurrence and need for additional therapy.

Ethics

Ethics Committee Approval: Local Ethics Committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital approved the study protocol (approval number: 2020-59) in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Fitz-hugh-curtis syndrome: A rare disease in the differential diagnosis of acute abdomen

Ahmet Burak Çiftci[1], Sönmez Ocak[1], Abdullah Taylan[2]

[1]University of Health Sciences Turkey, Samsun Training and Research Hospital, Clinic of General Surgery, Samsun, Turkey

[2]University of Health Sciences Turkey, Samsun Training and Research Hospital, Clinic of Radiology, Samsun, Turkey

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Corresponding Author:
Ahmet Burak Çiftci, MD, University of Health Sciences Turkey, Samsun Training and Research Hospital, Clinic of General Surgery, Samsun, Turkey
drburakciftci@yahoo.com

ORCID:
orcid.org/0000-0002-1814-4008

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ABSTRACT

Fitz-Hugh-Curtis syndrome (FHCS) is defined as peritoneal capsule inflammation of the liver. This disease is thought to be a complication of an ascending genital infection. A young sexually active woman was admitted to our emergency department with an acute right upper quadrant abdominal pain and diagnosed as FHCS via computed tomography examination. She was treated conservatively with adequate antibiotherapy. This syndrome should be kept in mind in the differential diagnosis of acute abdominal pain diseases to avoid unnecessary surgery.

Introduction

Fitz-Hugh-Curtis syndrome (FHCS) is a rare syndrome which is characterized by perihepatic inflammation associated with an ascending genital infection. The diagnosis is difficult and it may be misdiagnosed as it may present like many other disorders like acute cholecystitis, right pyelonephritis, pneumonia and even acute appendicitis (1,2). First in 1930, Curtis described adhesions of the anterior surface of the liver, called "violin-string" adhesions, in patients with coincident residual gonococcal tubal disease (3). Four years later, Fitz-Hugh described clinical characteristics of this syndrome (4). Although it is first reported in the literature in 1930's, the disease is still insufficiently known among general surgeons and thus unnecessary surgery can be made on the clinical ground. So, we aimed to present a young woman who was diagnosed as FHCS and treated medically at our clinic.

Presentation of Case

A 33-year-old female patient was admitted to the emergency department with a severe right upper and lower abdominal pain

which was exacerbated by movement, breathing and coughing for the past one week. In her medical history, she had a missed abortus one month ago and she had a treatment for vaginal infection at the same time.

On physical examination, tenderness was found in the right lower and upper abdominal quadrant. Abdominal defense and rebound was also positive. Routine blood tests demonstrated white blood cell count of 8100/mm^3 and hemoglobin of 10.8 gr/dL, and biochemical parameters including liver and renal function tests were also normal. With a preliminary diagnosis of acute abdomen, the abdominal computed tomography (CT) was requested. CT revealed transient hepatic attenuation difference with periportal edema and free fluid in the pelvis, and pelvic fat inflammation is also seen (Figure 1, 2). On CT imaging, the appendix vermiformis, and gall bladder were normal. With these findings, patient was hospitalized for follow-up and treatment. Next day of admission, a control abdomen ultrasonography (USG) was requested. USG showed normal appendix and gall bladder, but ovaries were enlarged, inflamed and had a cystic appearance. With these findings, preliminary diagnosis was made of FHCS secondary to pelvic inflammatory disease (PID). And thus, the medical treatment consisting of ceftriaxone, metronidazole and doxycycline therapy was given, which was derived from the International Union against Sexually Transmitted Infections guideline for PID (5). In the follow-up, the patient recovered well and was discharged on the 7th day of hospitalization.

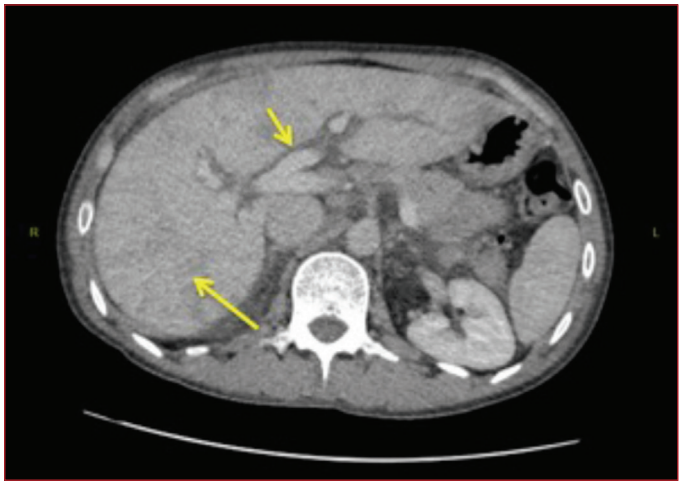

Figure 1. Heterogeneus attenuation pattern in liver parenchyma and periportal halo sign, mild periportal edema

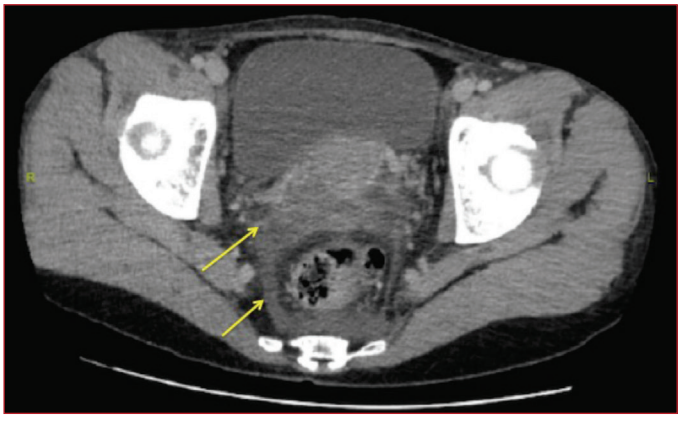

Figure 2. Free fluid in the pouch of Douglas, pelvic fat inflammation and heterogeneous cystic appearance of the ovaries

Discussion

FHCS is an uncommon condition of the perihepatic capsule inflammation secondary to PID (1). The mechanism of the inflammation is thought to result from the direct intraperitoneal spread of infection towards the perihepatic region from initial pelvic inflammation (6).

Most FHCS patients are sexually active women at childbearing age, who apply to emergency room because of acute pain and tenderness in the right upper abdomen. Because of the physical findings and pain characteristics, it can be difficult to distinguish from acute cholecystitis, sometimes acute appendicitis and the other form of peritonitis (1,2). As in our case, the patient was a young woman at childbearing age and she had a severe acute right upper and lower quadrant abdominal pain and tenderness. So, the first impression of diagnosis was acute cholecystitis or appendicitis. However, CT and USG revealed no gall bladder and appendiceal pathologies. In addition to these imaging findings, liver function tests, bilirubin levels and blood leukocyte counts were also normal. So, despite undergoing an emergency surgery, it was decided to start with a medical treatment. And in our case with the proper treatment, the symptoms were resolved immediateley and no surgical interventions were needed.

In FHCS, the patient's medical history is very important. The prevalence of PID, a history of treatment of sexually transmitted disease or a gynecologic intervention should raise suspicion of this disease (2). Our patient had also a history of a missed abortus and vaginal infection treatment one month ago and she had vaginal discharge as described before.

In the past, the diagnosis was made by showing the perihepatic adhesions via open or laparoscopic surgery and the treatment was made by adhesiotomy. But now, with the development of imaging strategies and antibiotherapy regimens, it can be diagnosed and treated by non-invasive methods (1,6). Contrast enhanced CT is widely accepted as diagnostic method and it provides accurate diagnosis. On CT scan, free fluid in the pouch of Douglas, pelvic fat inflammation, enlarged and inflamed ovaries with a heterogeneous cystic appearance can be reported. In addition to pelvic findings, multiple hypodense periportal halos and decreased parenchymal attenuation of the liver parenchyma and therefore nutmeg liver appearance are also suggestive of the diagnosis of FHCS (6,7). Our patient had all of these imaging findings. And FHCS was diagnosed rapidly. On the other hand, surgical treatment can be preferred only for

cases that were unresponsive to antibiotic therapy. Laparoscopic adhesiolysis can be preferred in such cases (1,2).

Conclusion

FHCS should be kept in mind in the differential diagnosis of acute abdominal pain diseases especially in sexually active women at childbearing age. We hope with this case report that physicians notice this rare syndrome and so unnecessary surgery and diagnostic tools were avoided.

Ethics

Informed Consent: Consent form was filled out by the participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Endovascular extraction of a disconnected port-A catheter from inferior vena cava in a patient with chronic bilateral occlusion of femoroiliac veins: A case report

Alireza Rai[1], Mohammadreza Sobhiyeh[2]

[1]Kermanshah University of Medical Sciences, Imam Ali Hospital, Clinical Research Development Center, Clinic of Cardiology, Kermanshah, Iran

[2]Kermanshah University of Medical Sciences, Imam Reza Hospital, Clinical Research Development Center, Clinic of Vascular and Endovascular Surgery, Kermanshah, Iran

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Corresponding Author:
Mohammadreza Sobhiyeh, MD, Kermanshah University of Medical Sciences, Imam Reza Hospital, Clinical Research Development Center, Clinic of Vascular and Endovascular Surgery, Kermanshah, Iran
mreza.sobhiyeh@yahoo.com

ORCID:
orcid.org/0000-0002-7333-1316

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ABSTRACT

Catheter detachment from a port may be seen due to various reasons, including operator errors, subsequent catheter manipulation during endovascular procedures, and trauma. For catheter removal, various tools including loop snare or basket catheter may be used with access via femoral or jugular veins. In this paper, we report the removal of a detached port-A catheter using a snare catheter from a jugular venous access in a patient with ilio-femoral venous occlusion. The main reason for reporting this case is the central venous catheter migration immediately after insertion and total occlusion of bilateral ilio-femoral veins due to unsuccessful manipulations previously.

Introduction

Percutaneously implanted venous port catheters provide permanent access for intravenous therapy and can be used for several years if handled correctly (1). Dislodgement of the catheter may be seen due to manipulation or trauma in less than 3% of patients (2). In cases of central venous catheter migration to the heart or inferior vena cava (IVC), endovascular retrieval using a snare is usually attempted through a jugular or femoral or subclavian access (3,4). We report a case of a dislocated and migrated port-A catheter into the IVC in a young woman immediately after its implantation.

Presentation of Case

A 36-year-old woman with a previous history of rectal cancer received a port-A catheter in her right jugular vein for chemotherapy in 2017 at another hospital. Directly after implantation, the catheter was non-functional. Subsequent chest X-ray revealed a dislocated catheter migrated into the

right atrium (Figure 1). No further information was available about the details of the primary operation and the reason for unsuccessful retrieval of the catheter by interventional technique through bilateral femoral veins access. The patient had undergone unsuccessful attempts for extracting the catheter in an urban tertiary health care center twice. She was under oral anticoagulation with warfarin thereafter. The cause of anticoagulant therapy was bilateral development of iliofemoral vein thrombosis after two times of unsuccessful manipulations. The patient was referred to our hospital in 2018 for the extraction

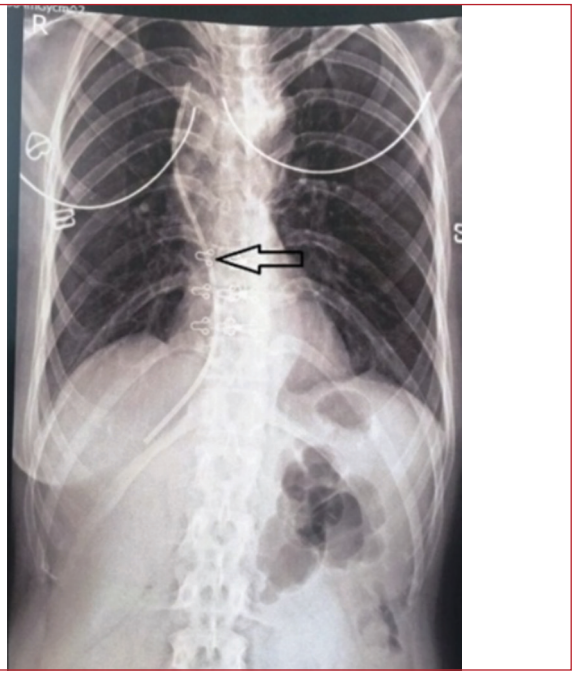

Figure 1. The port-A-catheter was dislodged in inferior vena cava and right atrium

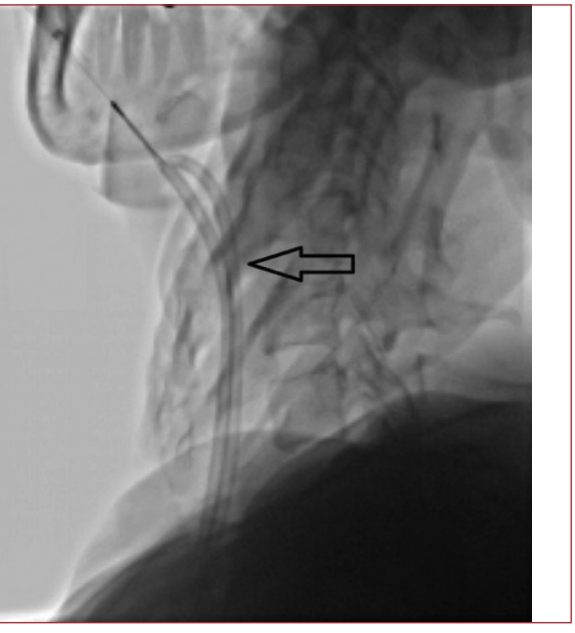

Figure 2. The port-A-catheter was captured and removed successfully

of the foreign body and discontinued the oral anticoagulation due to newly developed gastrointestinal bleeding. The preoperative clinical and sonography assessment showed a bilateral occlusion of ilio-femoral veins. This finding was also noted on the previous venography as well as a partial recanalized occlusion of IVC below the renal veins. Because of the risk of bleeding and contraindication for oral anticoagulation, we did not intend to puncture the femoral veins and recanalization of the iliocaval tract as the first option. Instead, we planned to capture the catheter by snaring through right internal jugular vein (IJV). After cannulating the right IJV under ultrasound guidance, the catheter was removed with a large loop snare. During the withdrawal the catheter was folded and stuck to the sheath's introducer tip (Figure 2). We stopped pulling back the catheter and tried to remove it together with the sheath. However, due to the bulk of folded catheter, it was impossible to extract the catheter through puncture hole. To avoid damaging the IJV, a 1.5 centimeter incision under local anesthesia was made at the entry site of sheath (included cutaneous and subcutaneous fat) due to fibrosis and the catheter was removed successfully.

Discussion

Implantation of a port system is indicated if drugs are to be administered over a longer period of time (5). Although the catheter placement is relatively safe, several potential complications can occur including catheter dislodgement, catheter malposition, catheter compression and catheter fracture (2). The dislodged catheter scan migrates along the blood stream to the superior vena cava, the right atrium, the right ventricle, the main pulmonary artery or its branches (3,4). The risk factors for intravascular thrombus formation in case of catheter migration include endothelial injury, hemodynamic flow changes within vessel and partial stasis (5,6). Anti-coagulation therapy alone may not prevent thrombus formation in the presence of a dislodged catheter. Before the procedure, color Doppler ultrasound of the femoral and jugular veins was initially done bilaterally, and also simple thoracic and abdominal radiography was obtained to determine definite catheter location.

Several percutaneous extraction techniques of dislocated or fragmented cardiovascular catheters like loop snare, a forceps, a guide wire and a basket catheter have been suggested (4). Use of loop snare is relatively safe and the most often reported technique (3). Our initial strategy was to snare and pull back the catheter through the right IJV access. In case of failure of the right and left jugular veins, we were prepared to use a femoral access and recanalize the iliac and infra renal IVC to increase the possibility of endovascular extraction of the catheter. We succeed in retrieval with triple-loop snare through the right IJV. The problem in this case was mainly one-year persistence of the catheter. Also, bilateral occlusion of the ilio-femoral

vein excluded the chance of procedure exclusion. However, the dislocated catheter could not pass through the sheath or pulled out together with it, so a small incision (cutaneous and subcutaneous fat) was needed to avoid vessel injury.

In our reported case, due to two times of unsuccessful manipulation, thrombosis developed and the catheter was remained one year in the right atrium and IVC that led to fibrin sheath formation around the catheter and it was removed after one year. Our experience is that the dislocated catheter in the heart or IVC can easily be grasped using a loop snare even long after implantation. Nevertheless, the fibrin sheath around the catheter may hamper its extraction and can cause damage to vessel wall. Therefore, extraction of migrated catheter of IJV route is feasible, but the presence of thrombosis and fibrin sheath may reduce the chance of successful intervention.

Conclusion

Intravascular migration of central catheter is sometimes associated with severe and rare complications of indwelling intravenous catheters such as IVC thrombosis, that the anti-coagulation administration alone cannot prevent catheter thrombosis. Therefore, after central catheter migration, immediately should be retrieved by experience interventional center.

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Ethics

Informed Consent: Consent form was filled out by the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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The mistake has been made inadvertently. “University of Sains Malaysia” expression in the first page, author institutions section has been corrected as “Universiti Sains Malaysia”.

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ORIGINAL ARTICLES

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