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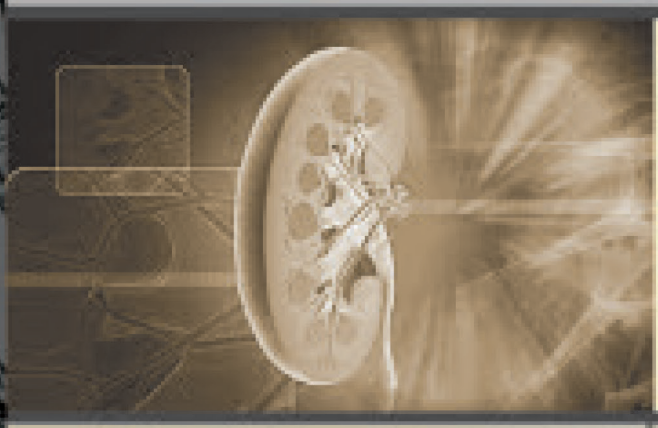

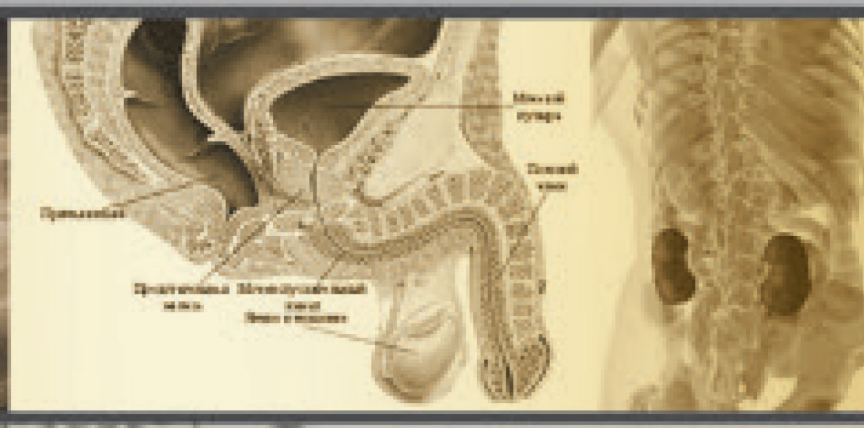

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ABOUT US

Journal of Urological Surgery is the official open access scientific publication organ of the Society of Urological Surgery. Journal of Urologic Surgery is being published in İstanbul, Turkiye. It is a double peer-reviewed journal published quarterly in March, June, September and December.

Journal of Urological Surgery is indexed in Web of Science-Emerging Sources Citation Index (ESCI), DOAJ, EBSCO, CINAHL, Research Bib-Academic Resource Index, Root Indexing, TUBITAK/ULAKBIM Turkish Medical Database, TurkMedline, Turkiye Citation Index.

The target audience of the journal includes physicians working in the fields of urology and all other health professionals who are interested in these topics.

The editorial processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE) (http://www.icmje.org) and the Committee on Publication Ethics (COPE) (http://publicationethics.org).

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Journal of Urological Surgery does not charge any fee for article submission or processing. Also manuscript writers are not paid by any means for their manuscripts.

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The Journal of Urological Surgery accepts invited review articles, research articles, brief reports, case reports, letters to the editor, and images that are relevant to the scope of urology, on the condition that they have not been previously published elsewhere. Basic science manuscripts, such as randomized, cohort, cross-sectional, and case control studies, are given preference. All manuscripts are subject to editorial revision to ensure they conform to the style adopted by the journal. There is a single blind kind of reviewing system.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (201, archived at http://www.icmje.org/).

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The Journal of Urological Surgery's editor and Editorial Board members are active researchers. It is possible that they would desire to submit their manuscript to the Journal of Urological Surgery. This may be creating a conflict of interest. These manuscripts will not be evaluated by the submitting editor(s). The review process will be managed and decisions made by editor-in-chief who will act independently. In some situation, this process will be overseen by an outside independent expert in reviewing submissions from editors.

Preparation of Manuscript

Manuscripts should be prepared according to ICMJE guidelines (http://www.icmje.org/).

Original manuscripts require a structured abstract. Label each section of the structured abstract with the appropriate subheading (Objective, Materials and Methods, Results, and Conclusion). Case reports require short unstructured abstracts. Letters to the editor do not require an abstract. Research or project support should be acknowledged as a footnote on the title page.

Technical and other assistance should be provided on the title page.

Title Page

Title: The title should provide important information regarding the manuscript's content.

The title page should include the authors' names, degrees, and institutional/professional affiliations, a short title, abbreviations, keywords, financial disclosure statement, and conflict of interest statement. If a manuscript includes authors from more than one institution, each author's name should be followed by a superscript number that corresponds to their institution, which is listed separately. Please provide contact information for the corresponding author, including name, e-mail address, and telephone and fax numbers.

Running Head: The running head should not be more than 40 characters, including spaces, and should be located at the bottom of the title page.

Word Count: A word count for the manuscript, excluding abstract, acknowledgments, figure and table legends, and references, should be provided not exceed 3000 words. The word count for an abstract should be not exceed 250 words.

Conflict of Interest Statement: To prevent potential conflicts of interest from being overlooked, this statement must be included in each manuscript. In case there are conflicts of interest, every author should complete the ICMJE general declaration form, which can be obtained at: http://www.icmje.org/coi_disclosure.pdf

Abstract and Keywords: The second page should include an abstract that does not exceed 250 words. For manuscripts sent by authors in Turkiye, a title and abstract in Turkish are also required. As most readers read the abstract first, it is critically important. Moreover, as various electronic databases integrate only abstracts into their index, important findings should be presented in the abstract.

Turkish abstract texts should be written in accordance with the Turkish Dictionary and Writing Guide of the Turkish Language Association.

Abstract

Objective: The abstract should state the objective (the purpose of the study and hypothesis) and summarize the rationale for the study.

Materials and Methods: Important methods should be written respectively.

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Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

Other types of manuscripts, such as case reports, reviews and others will be published according to uniform requirements. Provide at least 3 keywords below the abstract to assist indexers. Use terms from the Index Medicus Medical Subject Headings List (for randomized studies a CONSORT abstract should be provided (http://www.consort-statement.org).

After keywords in original research articles there must be a paragraph defining "What is known on the subject and what does the study add".

Original Research

Abstract length: Not to exceed 250 words. "What is known on the subject and what dos the study add" not exceed 100 words.

Article length: Not to exceed 3000 words.

Original researches should have the following sections:

Introduction: The introduction should include an overview of the relevant literature presented in summary form (one page), and whatever remains interesting, unique, problematic, relevant, or unknown about the topic must be specified. The introduction should conclude with the rationale for the study, its design, and its objective(s).

Materials and Methods: Clearly describe the selection of observational or experimental participants, such as patients, laboratory animals, and controls, including inclusion and exclusion criteria and a description of the source population. Identify the methods and procedures in sufficient detail to allow other researchers to reproduce your results. Provide references to established methods (including statistical methods), provide references to brief modified methods, and provide the rationale for using them and an evaluation of their limitations. Identify all drugs and chemicals used, including generic names, doses, and routes of administration. The section should include only information that was available at the time the plan or protocol for the study was devised on STROBE (http://www.strobe-statement.org/).

Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Statistically important data should be given in the text, tables and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

Results: Present your results in logical sequence in the text, tables, and figures. Do not present all the data provided in the tables and/or figures in the text; emphasize and/or summarize only important findings, results, and observations in the text. For clinical studies provide the number of samples, cases, and controls included in the study. Discrepancies between the planned number and obtained number of participants should be explained. Comparisons, and statistically important values (i.e. p value and confidence interval) should be provided.

Discussion: This section should include a discussion of the data. New and important findings/results, and the conclusions they lead to should be emphasized. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by the data. Do not repeat the findings/results in detail; important findings/results should be compared with those of similar studies in the literature, along with a summarization. In other words, similarities or differences in the obtained findings/results with those previously reported should be discussed.

Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

References

Cite references in the text, tables, and figures with numbers in parentheses. Number references consecutively according to the order in which they first appear in the text. Journal titles should be abbreviated according to the style used in Index Medicus (consult List of Journals Indexed in Index Medicus). Include among the references any paper accepted, but not yet published, designating the journal and followed by, in press. Authors are solely responsible for the accuracy of all references.

Examples of References:

1. List All Authors

Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 201, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

Case Reports

Abstract length: Not to exceed 100 words.

Article length: Not to exceed 1000 words.

Case Reports can include maximum 1 figure and 1 table or 2 figures or 2 tables.

Case reports should be structured as follows:

Abstract: An unstructured abstract that summarizes the case.

Introduction: A brief introduction (recommended length: 1-2 paragraphs).

Case Presentation: This section describes the case in detail, including the initial diagnosis and outcome.

Discussion: This section should include a brief review of the relevant literature and how the presented case furthers our understanding to the disease process.

Review Articles

Abstract length: Not to exceed 250 words.

Article length: Not to exceed 4000 words.

Review articles should not include more than 100 references. Reviews should include a conclusion, in which a new hypothesis or study about the subject may be posited. Do not publish methods for literature search or level of evidence. Authors who will prepare review articles should already have published research articles on the relevant subject. There should be a maximum of two authors for review articles.

Preparation of Manuscripts

The " Journal of Urological Surgery'' follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (International Committee of Medical Journal Editors - http://www.icmje.org /). Upon submission of the manuscript, authors are to indicate the type of trial/research and provide the checklist of the following guidelines when appropriate:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org /),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org /),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org /),

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org /),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.) (http://www.care-statement.org /

Images in Urological Surgery

Article length: Not to exceed 500 words.

Authors can submit for consideration an illustration and photos that is interesting, instructive, and visually attractive, along with a few lines of explanatory text and references. Images in Urology can include no more than 500 words of text, 5 references, and 3 figure or table. No abstract, discussion or conclusion are required but please include a brief title.

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Article length: Not to exceed 500 words.

Urological pathology can include no more than 500 words of text, 5 references, and 3 figure or table. No abstract, discussion or conclusion are required but please include a brief title.

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Letters to the Editor

Article length: Not to exceed 500 words.

Letters can include no more than 500 words of text, 5-10 references, and 1 figure or table. No abstract is required, but please include a brief title.

How I do?

Unstructured abstract: Not to exceed 50 words.

Article length: Not to exceed 1500 word.

Urologic Survey

Article length: Not to exceed 250 words.

Tables, Graphics, Figures, and Images

Tables: Supply each table on a separate file. Number tables according to the order in which they appear in the text, and supply a brief caption for each. Give each column a short or abbreviated heading. Write explanatory statistical measures of variation, such as standard deviation or standard error of mean. Be sure that each table is cited in the text.

Figures: Figures should be professionally drawn and/or photographed. Authors should number figures according to the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend that does not exceed 50 words. Use abbreviations only if they have been introduced in the text. Authors are also required to provide the level of magnification for histological slides. Explain the internal scale and identify the staining method used. Figures should be submitted as separate files, not in the text file. High-resolution image files are not preferred for initial submission as the file sizes may be too large. The total file size of the PDF for peer review should not exceed 5 MB.

Authorship

Each author should have participated sufficiently in the work to assume public responsibility for the content. Any portion of a manuscript that is critical to its main conclusions must be the responsibility of at least 1 author.

Contributor's Statement

All submissions should contain a contributor's statement page. Each manuscript should contain substantial contributions to idea and design, acquisition of data, or analysis and interpretation of findings. All persons designated as an author should qualify for authorship, and all those that qualify should be listed. Each author should have participated sufficiently in the work to take responsibility for appropriate portions of the text.

Acknowledgments

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Ethics

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On the other hand, short abstracts published in congress books that do not exceed 400 words and present data of preliminary research, and those that are presented in an electronic environment are not accepted pre-published work. Authors in such situation must declare this status on the first page of the manuscript and in the cover letter. (The COPE flowchart is available at: http://publicationethics.org).

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5. All authors participated in the study concept and design, analysis and interpretation of the data, drafting or revising of the manuscript, and have approved the manuscript as submitted. In addition, all authors are required to disclose any professional affiliation, financial agreement, or other involvement with any company whose product figures prominently in the submitted manuscript.

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The Review Process

Each manuscript submitted to the Journal of Urological Surgery is subject to an initial review by the editorial office in order to determine if it is aligned with the journal's aims and scope, and complies with essential requirements. Manuscripts sent for peer review will be assigned to one of the journal's associate editors that has expertise relevant to the manuscript's content. All manuscripts are single-blind peer reviewed. All accepted manuscripts are sent to a statistical and English language editor before publishing. Once papers have been reviewed, the reviewers' comments are sent to the Editor, who will then make a preliminary decision on the paper. At this stage, based on the feedback from reviewers, manuscripts can be accepted, rejected, or revisions can be recommended. Following initial peer-review, articles judged worthy of further consideration often require revision. Revised manuscripts generally must be received within 3 months of the date of the initial decision. Extensions must be requested from the Associate Editor at least 2 weeks before the 3-month revision deadline expires; the Journal of Urological Surgery will reject manuscripts that are not received within the 3-month revision deadline. Manuscripts with extensive revision recommendations will be sent for further review (usually by the same reviewers) upon their re-submission. When a manuscript is finally accepted for publication, the Technical Editor undertakes a final edit and a marked-up copy will be e-mailed to the corresponding author for review and to make any final adjustments.

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The video articles are prepared on urological surgeries by experts who have extensive experience and knowledge of certain advanced surgical techniques. Video article should introduce the clinical problem, describe the surgical solution, and present brief outcome of the technique or produce details in the video. This section is also intended to enable urologists to learn, evaluate, and apply new or complex surgical principles in their surgical practice.

All video article submissions should include all of the elements of original article (please label each section of the structured abstract with the appropriate subheading as objective, materials and methods, results and conclusion) or case report (please submit with a short unstructured abstract), and be presented with a video that demonstrates a novel or established surgical technique, or focuses on tips and tricks, and troubleshooting of common technical challenges. There is no minimum number of cases required, but priority is given to series with at least 8 cases. Videos are peer reviewed for relevance and overall scientific quality.

Video Presentation:

Authors who have a video that they wish to submit with their article are strongly encouraged to refer to the video within the body of the article, in the same way as a figure or table. All submitted files should properly labeled so that they directly relate to the video file's content. All names and institutions should be removed from all video materials. Please provide the file in one of recommended file formats with a preferred maximum size of 1 GB total and a maximum duration of 10 minutes. The resolution of the video should be at least 960 x 720 for 4:3 aspect ratio videos, and 1280x720 for 16:9 videos.. Videos can be larger than these dimensions, but not smaller. For larger video documents, please contact info@galenos.com.tr.

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The video should include audio narration explaining the procedure. All text and audio in the video must be in English. Audio must include narration in clear, grammatically correct English. Videos must be clear, in focus, and without excessive camera movement. Radiographs and other material must not contain any patient-identifiable information. A limited number of slides incorporated into the video may be included to provide details about the patient's history, clinical and laboratory findings.

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REVIEW
Andrology

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The Effectiveness of Genital Wart Treatments

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Abstract

Human papillomaviruses (HPV) are a family of DNA viruses that infect the epithelium. They cause benign proliferative lesions called anogenital warts. HPV infection is common in men and women and is the most common sexually transmitted infection. HPV infection can cause cervical, penile, anal, vaginal, vulvar and oropharyngeal cancers. Genital warts adversely affect the quality of life. It may cause anxiety, guilt, anger, and loss of self-esteem and may cause anxiety about the cancer risk. For the diagnosis, generally, visual inspection is enough. Different kinds of treatments have been reported. Genital wart treatments are generally painful, prolonged, hard for the patient to apply, and unfortunately often with recurrence of the lesions seen after treatment. Although many treatment methods are used, their superiority to each other is unclear. In this review, we investigate self-application treatments, clinical-based treatments and alternative treatments.

Keywords: Anogenital warts, condyloma acuminata, HPV

Introduction

Human papillomaviruses (HPV) are a family of DNA viruses that infect the epithelium (1). HPV infection is common in men and women and is the most common sexually transmitted infection. They cause benign proliferative lesions that called anogenital warts (AGW) (genital warts, condyloma acuminate, condylomas) (2,3) (Figures 1-3). There are more than 200 hundred variants of HPV (4). HPV is divided into two groups as low-risk noncarcinogenic and high-risk oncogenic types. HPV infections can cause cervical, penile, anal, vaginal, vulvar and oropharyngeal cancers (1). Ninety-nine percent of cervical cancers, 90% of anal cancers, 65% of vaginal cancers, 50% of vulvar cancers, 45-90% of oropharyngeal cancers are thought to be caused by HPV (4).

HPV can be transmitted through skin or mucosa contact. The most documented way of HPV infection is sexual transmission, but there are nonsexual courses reported for transmission. Fomites, fingers, mouth, skin contact, and self-inoculation are the reported ways of transmission. The transmission from mother to child is called a vertical transmission, and it is another way of transmission. Genital HPV in children and female virgins

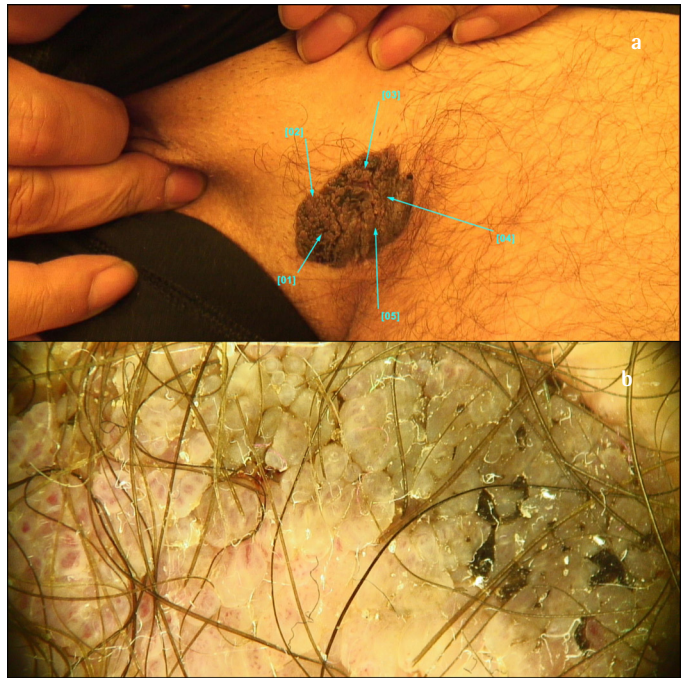

Figure 1a, b. Anogenital wart, dermoscopy

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(without sexual abuse, with low-risk HPV types) has also been reported. In a study, HPV DNA samples were collected from gynecological equipment. Gloves and colposcopy rooms may have a risk of HPV transmission (5). Condoms cover transvaginal ultrasound probes, but the risk of condom rupture may cause HPV transmission (6). Two gynecological laser surgeons were reported with HPV (+) tonsillar cancer that may show that particles in the air have transmission risk (7).

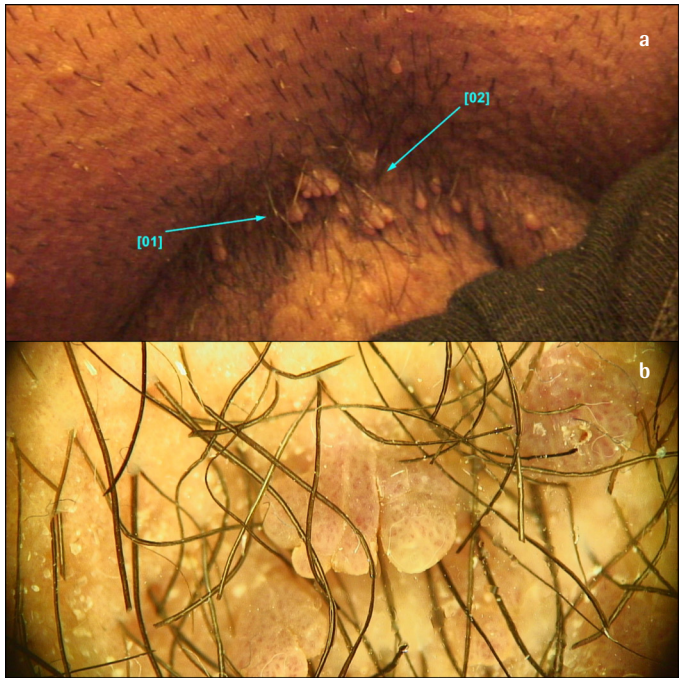

Figure 2a, b. Anogenital wart, dermoscopy

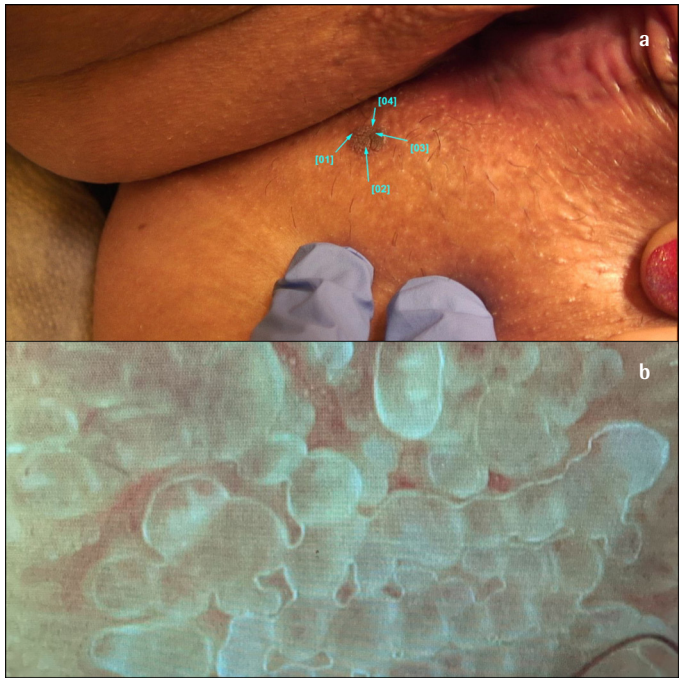

Figure 3a, b. Anogenital wart, dermoscopy

The most common HPV types seen in angenital verruca are HPV types 6 and 11. After HPV transmission, clinical presentation of symptoms is nearly 11-12 months among males and 5-6 months among females (8). In months, HPV infections mostly resolve spontaneously and are generally asymptomatic. The clearance time is approximately 6-24 months (cervical HPV in 9.4 months, genital HPV in men 7.5 months with oncogenic and non-oncogenic types) (9). HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 are carcinogenic (8).

The genital warts negatively affect health-related quality of life outcomes. It may cause anxiety, guilt, anger, and loss of self-esteem and causes anxiety about the cancer risk (10). Multiple partners, early start to sexual activity, smoking, sexually transmitted diseases, lack or delayed treatment, and disruption of skin integrity are risk factors for HPV infection.

Generally, visual inspection is enough for diagnosis. A good light is important for examination. Physical examinaiton of external genitalia, vagina, perineal and anorectal areas must be performed. If lesions are atypical, there is resistance to treatment, the diagnosis can be confirmed by biopsy (3,11).

Treatment

A wide range of treatment options are reported in the literature. Genital wart treatments are generally painful, prolonged, hard for the patient to apply, and unfortunately often recurrence of the lesions seen after treatment. Treatments generally depend on the physical destruction of the lesion because this recurrence can be easily seen. A treatment that has antiviral effects on human papillomavirus would give more success and lower recurrence rates. One more problem for the patient is several visits to the hospital that may need for treatment. This makes the treatments less cost effective and sparing time may be also difficult for the patient. Here, the treatments are discussed in three groups: self-application treatments, treatments applied in the hospital, and alternative medical wart treatments.

1.Self-application Treatments

1. a. Podophyllotoxin

Podophyllotoxin is a product prepared by separating nontherapeutic lignans and the mutagenic agent quercetin from podophyllin (12). Podophyllotoxin inhibits the proliferation of human skin keratinocytes by its antimitotic effect and cures genital HPV by inhibiting the proliferation of HPV-infected cells and destroying infected tissue (12,13). Podophyllotoxin has different forms: 0.15% cream, 3% cream and 5% solution and 5% gel. Cream form is suggested for vulvar and perianal warts because of its easy application (12). Side effects are itching, burning, tenderness, erythema, and erosion. Podophyllotoxin is contraindicated during pregnancy. Podophyllotoxin is a stable and safe product. Treatment is applied by the patient topically

twice a day at home for 3 consecutive days and after a 4 day break. If the treatment is not enough, it can be repeated for 4 weeks. Claesson et al. (12) compared the clinical efficacy of 0.3%, 0.15% cream forms of podophyllotoxin versus 0.5% solution. They found that the efficacy is similar and the tolerance is better with 0.15% cream. Strand et al. (14) compared 0.3%, 0.15% cream forms of podophyllotoxin with 0.5% solution. They found similar response rates but they also found that the effect of %0.15 cream is slower than other forms. Lacey et al. (15) mentioned that in the original warts treatment, podophyllotoxin solution 5% is superior to podophyllin and podophyllotoxin 0.15% cream. For all warts, podophyllotoxin solution was significantly better than podophyllin and similar to podophyllotoxin cream (15). The clearance rates of warts have been reported to be 36-83% for podophyllotoxin solution and 43-70% for podophyllotoxin cream. The recurrence rates with podophyllotoxin treatment were reported as 6-100% within 8-21 weeks after clearance (16).

1. b. Imiquimod 5% Cream

Imiquimod is a non-nucleoside heterocyclic amine, immune response modifying agent. Imiquimod induces several proinflammatory cytokines including interferon alpha, interleukin 1,6,8,12, tumor necrosis factor alpha, and other cellular proteins. It also induces the production of monocytes and macrophages. Imiquimod has antiviral and antitumor effects by enhancing the immune system without tissue destruction (17-19). Side effects are listed as itching, erythema, burning, irritation, tenderness, ulceration, erosion, pain, headache, and upper respiratory tract infections. In reports; complete response rate with imiquimod is 40% and the recurrence rate is 19% (18,19). Komericki et al. (13) compared imiquimod 5% cream with podophyllotoxin 5% solution. There was no statistically significant difference in the treatment results. In comparison with podophyllotoxin; the major disadvantage of imiquimod is the long treatment period (four months vs four weeks). Due to this fact, in the study of Komericki et al. (13); 6 (5 from imiquimod group) of the patients left the study and they believe that this is not only because of the side effects, long treatment period of imiquimod favors podophyllotoxin (20).

Edwards et al. (17) compared imiquimod 5%, 1% cream and vehicle. They found in their study imiquimed 5% cream was effective and safe. In this study 50% of patients using imiquimod 5% cream had total clearance and the recurrence rate was 13%.

Another study compared treatment options with 5% imiquimod cream 3 times a week, once daily, twice daily, and three times a day and found the optimal dosing 3 times a week. Although the other options were also effective, the side effects increased in these options and these applications showed no association with increased total wart clearance (21). In Arican et al. (22) study; 69.7% of the patients healed totally and female patients displayed earlier improvement than male patients. Garland et al. (23) compared the treatment durations with imiquimod 5% in female patients. They compared 4,8,12,16 weeks of treatment. The clearance rates were not significantly different (40.0%, 48.4%, 39.3% and 51.6%). They suggest that women with genital warts should be treated for 4 weeks and then followed for 12 to 16 weeks. This would help to decrease side effects, drug costs, and clinic visits. They suggest that following the cessation of treatment by a T-cell memory-mediated immune response, the effect of treatment goes on (23). In a meta-analysis of Elana et al. (24); they investigated the optimal application schedule for imiquimod 5% cream. They found that effect size was significantly higher in women than in circumcised men regardless of the drug application frequency, and the optimal application frequency of 5% imiquimod cream for all groups (women, circumcised and uncircumcised men) was 3 times a week. Drug penetration is the best in a keratinized and moist environment (24).

In a report of 7 women who used imiquimod cream during their pregnancy; all patients gave live births with no major complication and the mean birth weight was 3528 grams. Besides this, systemic absorption is reported as minimal (0.25-2.5%) in animal studies (25). Audisio et al. (26) reported 17 pregnant women treated with 5% imiquimod cream during pregnancy. In this retrospective case series 13 (76.4%) of 17 pregnant women provided a complete response. Yet, there is not enough data for recommending imiquimod cream during pregnancy, and imiquimod cream is category B during pregnancy.

1. c. Sinecathecins

Green tea (leaves of Camellia sinensis, Theaceae) has many favorable effects such as anti-inflammatory, anti-oxidative, anti-mutagenic, anti-carcinogenic, and cardioprotective effects. Preventing type 2 diabetes and osteoblast differentiation are other effects of green tea extracts. Green tea extract contains polyphenols (e.g., catechin, epicatechin, epigallocatechin (EGC), and their gallates), teanin, caffeine, and polysaccharides, many of which are thought to be responsible for the beneficial health effects. By blocking the mitotic signal transduction pathway, it has antitumor effects. With these effects and anti-inflammatory properties, green tea extracts have been successful for treating warts. The ointment should be used 3 times a day until the lesions heal for a maximum of 16 weeks. Sinecathecins are not suitable for use on internal warts and during pregnancy (27,28). Side effects such as local skin reactions (itching, erythema), intensity, balanitis, herpes simplex, lymphadenitis, dysuria, rash, hyperkeratosis, skin discoloration, pain, and allergic dermatitis have been reported (28,29). Gross et al. (28) found that the 15% ointment preparation was more effective than the 10% cream formulation and both of them were superior to placebo.

They found higher clearance rates in uncircumcised men and suggested that the lower degree of keratinization and semi-occlusive effect may cause these higher clearance rates. They found clearance rates 61% and recurrence rate of 10.6% for 15% ointment (28). Tatti et al. (30) found clearance rates higher in women, but the difference was small. They associated this with higher keratinization of the penis. Tzellos et al. (31) found both forms of Polyphenon E (15%,10%) effective, safe, cost-effective and well tolerated. Both forms have low recurrence rates (31).

2. Clinical Based Treatments

2. a. Cryotherapy

Cryotherapy (CRYO) destroys warts by cold-induced cytolysis. It is liquid nitrogen and can be used as a spray or cryoprobe, and it is a very common treatment technique (32). The adverse effects are pain, erythema, swelling, exudation, blistering, ulceration, and post-inflammatory pigmentation (32,33).

In a review that discussed the efficacy and safety of CRYO for patients with AGW, it was mentioned that CRYO has a similar effect as trichloroacetic acid (TCA), imiquimod, and podophyllin and slightly less effect than electrosurgery (32). The disadvantage of CRYO is that the treatment effectiveness depends on the user, and this is a limitation for deciding the effectiveness of the treatment (32). Pontini et al. (33) investigated the efficacy of topical nitriding complex solution (NZCS) versus cryotherapy for treating AGWs. They found that the treatment efficacy in NZCS was slightly higher, and this difference was statistically significant. Not only was the efficacy higher but also the number of recurrences after one month was lower in the NZSC (18.4%) than the CRYO group (38.1%) ($p=0.0356$) and tolerability to NZCS was better (33). Rodriguez et al. (34) investigated cryotherapy plus low dose oral isotretinoin vs cryotherapy treatment. In their study with the isotretinoin group, both faster treatment success was achieved and recurrence was less frequent. Cryotherapy is safe during pregnancy. An important advantage of cryotherapy is that anesthesia is unnecessary (35). In clinical studies clearance rates were reported as 44-87% and recurrence rates reported as 12-42% in 3 months of follow-up. CO_2 laser was found to be more effective than CRYO; electrosurgery was found to be slightly more effective than CRYO and TCA and podophyllin showed similar effects with CRYO (32-38).

2. b. Trichloroacetic Acid (TCA)

TCA treats AGW by causing chemical coagulation, protein denaturation, and cell death of tissue proteins. TCA can be used in different concentrations between 60 and 90%. TCA treatments are generally performed in hospitals up to 3 times weekly and the applications go on until the warts heal (39,40). Sodium bicarbonate 5% is a neutralizing agent for TCA and it should stay with TCA for safeness. Generally, a superficial ulcer occurs and it heals without scarring. With TCA, clearance rates are reported as 56-94% and recurrence rates as 36% (36,41,42). The side effects are pain, itching, irritation, erythema, erosion, and ulceration. Anggraini et al. (43) compared 1%, 5 5%-fluorouracil creams and 90% TCA and found that the effectiveness was similar. The response was earlier (at week 2) in the TCA group in their study. Recanati et al. (44) compared cantharidin versus TCA and found that cantharidin was more effective (100%, 66%), the cantharone group healed with less scar and needed less treatment for heeling. Trichloroacetic acid is not absorbed from the mucous membranes and skin, so it can be safely used for pregnant women (35).

2. c. Surgical Treatment

There are several different surgical techniques for the treatment of AGW. Excision, electrosurgery, and laser treatments are the most recommended surgical treatments.

2.c1. Laser Treatment

In a review, both ablative lasers [CO_2 and Erbium YAG (Er yag)] and nonablative lasers were mentioned as effective, but the number of treatment sessions was found to be lower with ablative lasers than nonablative [Pulsed Dye (PDL) and NDYag] lasers. When nonablative lasers are compared, patients with neodymium-doped yttrium aluminum garnet (NDYag) laser treatments need lower number of sessions for clearance. Combining keratolytic agents with laser treatments may help in rapid clearance times (45). The combination of PDL with interferon alpha or bleomycin may cause higher efficacy but because of side effects this combination can be used as second-line treatment (46,47). On the other hand; applying a moisturizing cream before NDYag laser treatments may lead to deeper penetration and higher response rates (48). For patients with darker skin types; NDyag would be a better choice. Among lasers; PDL seems safer and can be preferred first choice if possible (49). The side effects of laser treatments are listed as pain, hemorrhage, crust formation, blisters, hyperpigmentation, hematoma, second bacterial infection, persistent erythema, hypertrophic or atrophic scar formation, ulceration, recurrent anal fissures, and perianal dermatitis (45-49). In pregnancy, the studies did not show adverse effects related to laser therapy (35). The advantage of laser treatment is that widespread warts can be treated in a single session. With PDL treatment response rates are 0-100% and recurrence rates are 0-30%, with NDyag treatment complete remission rates vary between 9.1% and 100%, recurrence rates vary between 0 and 10, with CO_2 laser treatment complete remission rates are different between 59.15% and 100%, and recurrence rates are between 0 and 40.8% (45-49).

2.c.2. Excision

There are a smaller number of studies on scissor excision. When the lesions are small, exophytic, pedunculated, or single, scissor excision can be a choice. Handley et al. (50,51) found that scissor excision plus electrocautery of anogenital warts under general anesthesia were safe for prepubertal children. The side effects of this treatment are scarring, pain, and hypohyperpigmentation. For scissor excision 89-100% clearance rates were reported and 19-29% of recurrence rates were reported (50-52).

2.c.3. Electrocautery and Surgery

Electrosurgical units show their effects of destroying the wart lesion by thermal coagulation and burning. The tissue that is desiccated is afterward removed by curettage. For small lesions on the penis shaft, vulva, or rectum, this technique is effective but for large lesions because of scar formation, this technique is not recommended. Because electrosurgery is a painful procedure, local anesthesia for small lesions and general anesthesia is required for a large number of lesions (53). The side effects are pain and scar formation. Electrocautery treatment is contraindicated in patients who have cardiac pacemakers (54,55). In pregnancy, there are not enough reports about electrocautery or surgery. Electrocautery or scissor excision may be preferred primarily in cases where laser treatments cannot be reached or when the pathological investigation is required (35). The clearance rates of this procedure have been reported as 94-100%, whereas recurrence rates as 22% (56).

2.c.4. Transurethral Resection

Urinary tract and bladder HPV infections may rarely be seen. Immunsuppression and anogenital condylomas are risk factors for isolated urinary tract involvement (57-59). Sarier et al. (57) reported a case of HPV type 45 (+) condyloma acuminata of the bladder in a renal transplant recipient. By transurethral resection (TUR), they removed multiple warty lesions inside the bladder. They did control cystoscopy in the third and sixth postoperative months and did not see recurrence. Condyloma arising inside the bladder is a risk factor for developing squamous cell carcinoma (SCC) (58). For this reason, urological examination is important for patients who are immunosupressed and have anogenital condylomas (57-59).

Alternative Medical Wart Treatments

3. a. 5-Fluorouracil

5-fluorouracil blocks thymidylate synthase and inhibits DNA synthesis. It is available in 5% cream form (60). The side effects of 5-fluorouracil treatment are pain, burning, inflammation, and ulceration (60). In a review with 988 patients 5% fluorouracil cream was found to be superior to placebo, but the authors found the evidence level for this treatment weak in these studies (60). During pregnancy 5-fluorouracil treatment is not recommended (35).

3. b. Interferon

Interferon has immune-boosting effects and promotes the healing of virally infected cells. By this therapy not only the lesions seen by the naked eye but also infected cells can be treated, which may lead to lower recurrence rates (61,62). The side effects of interferon are flu-like symptoms, such as headache, nausea, vomiting, fatigue, and myalgia, elevated liver enzymes, bone marrow suppression, bronchospasms, and depression, and pain is also reported with intralesional injections (61-64). In a meta-analysis with 1500 case interferon therapy was found to be superior to placebo (61). During pregnancy, interferon is not recommended (35). Interferon therapy for anogenital warts is controversial and expensive; it can be a choice for resistant cases.

3. c. Photodynamic Therapy

Using 5-aminolevunic acid (ALA) and photodynamic therapy (PDT) is a noninvasive technique. It is an effective treatment for proliferative diseases, inflammatory diseases such as psoriasis, acne, infectious diseases such as verruca vulgaris, condyloma acuminate, and cutaneous leishmaniasis (65). PDT uses photoensitizer, light, and oxygen to destroy the target tissue cells. 5-aminolevunicacid metabolizes to active protoporphyrin IX, which photoensitization. The 635 nm red light is clinically used because of its absorption rate and penetration depth. With photodynamic therapy, cell death occurs by apoptosis and necrosis and this causes the destruction of HPV-infected cells (65-67). The major side effects are pain, bleeding, and secondary infection. Xie et al. (65-67) concluded that ALA-PDT is a safe and effective treatment for condyloma acuminate with lower recurrence rates. ALA-PDT especially has advantages for urethral and anal canal warts. With ALA-PDT, subclinical latent infections around the lesions can be treated. PDT is expensive and it can be an option for resistant cases and for areas that are hard to treat such as the urethra and anal canal (65-67). There are insufficient data on the efficacy and safety of photodynamic therapy in pregnancy (35).

3. d. Ingenol Tebutate

Ingenol tebutate stimulates the inflammatory response and neutrophil infiltration and by this way stimulates cell death in proliferating keratinocytes. The major side effect reported is local skin irritation (68,69).

3. e. Injectable Immunotherapy

Intralesional antigens led to an immune response and by this way wart resolution can occur. The most common injectable immunotherapy agents are candida antigen, mumps-measles-rubella vaccines, mycobacterial antigen, and HPV vaccines.

Intralesional candida antigen and measles, mumps, and rubella vaccine (MMR) were found to be more effective than cryotherapy. They do not only treat the injected lesion but are also effective in distant lesions from the injected lesion. The side effects are reported as mild injection site pain, flu-like symptoms and within very few reports a short-term myalgia, erythema and local swelling (70-79).

3. f. Human Papilloma Virus (HPV) Vaccine

HPV vaccines target high-risk HPV types in the prevention of associated cancers. Although they do not target common warts, there are studies that found them effective for treating extragenital warts. Although there are not sufficient studies with a large number of patients, it may be an option for recalcitrant warts, even in immunosuppressed patients (80-85).

3. g. Vitamin D

Vitamin D analogs are used in the treatment of warts both topical and intralesional. In a study comparing intralesional vitamin D, candida antigen, and saline, intralesional vitamin D treatment was found to be superior. On the other hand; when compared with CRYO, the efficacy was found to be similar. There is not enough data on the use of topical vitamin D but it may be more comfortable in terms of side effects (86-90). The side effects are listed as pain at injection site, redness, and swelling (86-90).

3. h. Bleomycin

Intralesional bleomycin treatment has been used on resistant warts. The most common dosing schedule was using 1 U/mL solution, up to 1-2 mL per treatment. It can be up to 4 times at 2-3-week intervals. The side effects are scar formation and hyperpigmentation and flagellate hypopigmentation (91).

3.ı. Retinoids

Retinoids are vitamin derivates. They have effects on epithelial differentiation and proliferation and may also have an immunomodulatory inhibitory effect on HPV replication. They can be used topically and systemically in HPV treatment. Even though oral etretinate was found to be the most efficient agent, oral isotretinoin studies are higher in number. In studies; topical tretinoin has the least efficiency. The side effects are cheilitis, xerosis, xerostomia, conjunctivitis, xeropthalmia, epistaxis, desquamation, retinoid dermatitis, photosensitivity, pruritus, local irritation, fatigue, hair loss, arthralgia, myalgia, hypertriglyceridemia, hypercholesterolemia, and elevated liver function tests. The retinoids are in category X during pregnancy. Clearence rates are reported as 100% with etretinate, and 56% with isotretinoin, and the patients in the studies were resistant cases (92).

Genital Wart Differential Diagnosis

In differential diagnosis, pearly penile papules, Fordyce spots, acrochordons, condylomata lata of syphilis, molluscum contagiosum, granuloma annulare, lichen nitidus, lichen planus, seborrheic keratosis, epidermal nevus, lymphangioma circumscriptum, lymphogranuloma venereum, angiokeratoma Bowenoid papulosis, and squamous cell carcinoma can be listed (Figure 4-9) (39).

Figure 4. Buschke-Löwenstein, dermoscopies

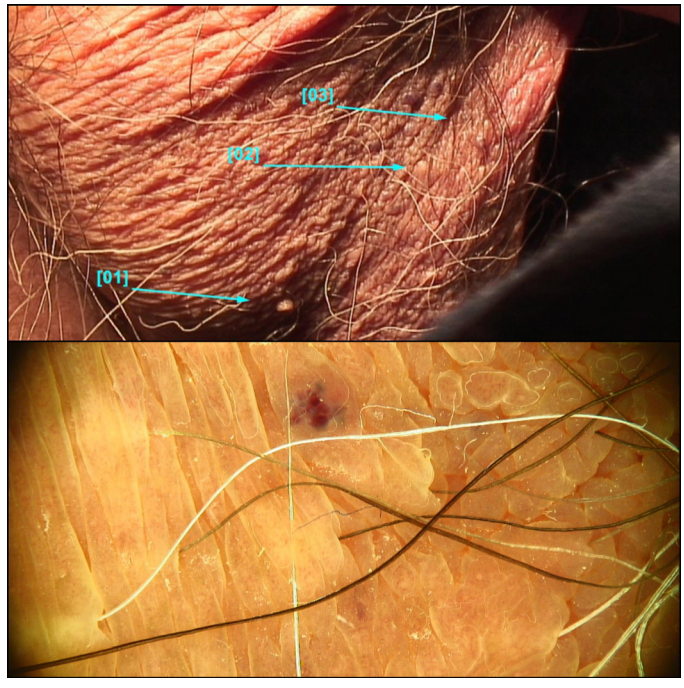

Figure 5. Angiokeratoma dermoscopy

Exophytic cauliflower-like growth lesion, which has a tendency to infiltrate adjacent tissue, is called Buschke-Lowenstein (93-95). It is generally associated with HPV 6,11 and is mostly seen in immunosuppressed patients. It is locally aggressive, has potential for destructive growth and malignant transformation. Computarised tomography and magnetic resonance imaging are necessary because of malignancy transferals and adipose tissue growth tendency. The gold standard treatment is excision.

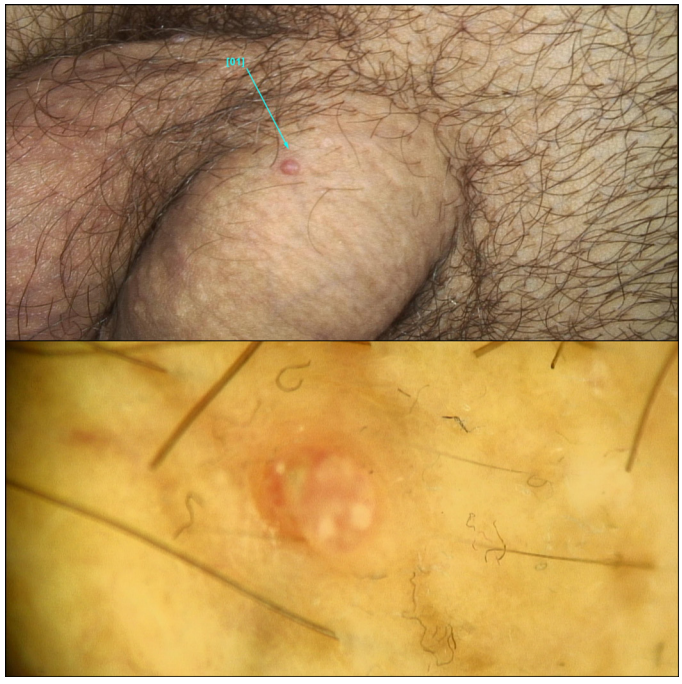

Figure 6. Molluscum contagiosum dermoscopy

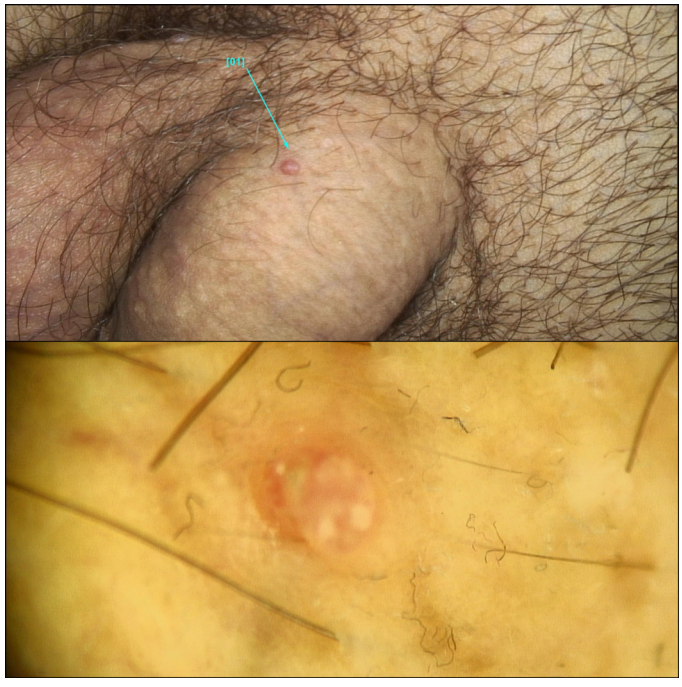

Figure 7. Pearly penile papules, dermoscopies

Cryotherapy, Co_2 laser, electrocauterisation, intralesional bleomycin, intralesional 5-FU, radiation therapy, chemotherapy, imiquimod 5% cream are other treatment options (94-96).

Prevention

Reducing the number of sexual partners, using condoms, and HPV vaccines (11-12 years for boys and girls) are important factors in the prevention of HPV infections. Cigaret smoking

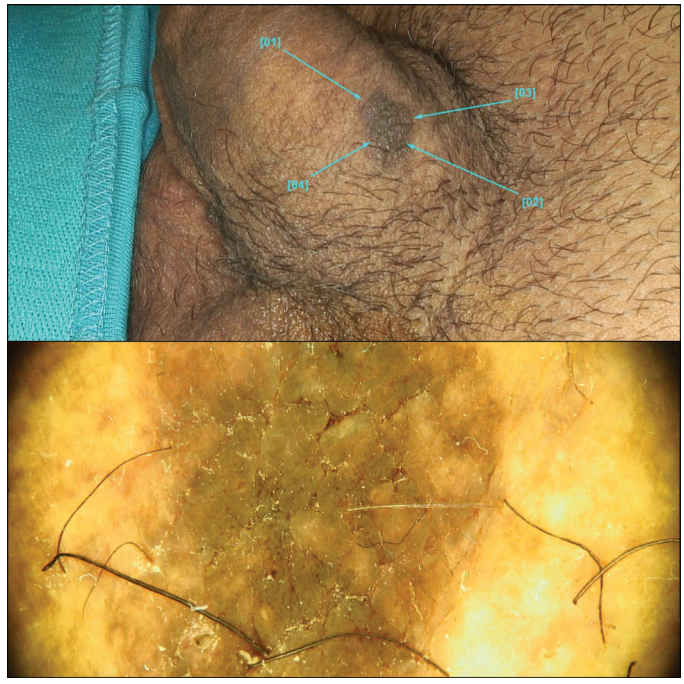

Figure 8. Seborrheic keratosis dermoscopy

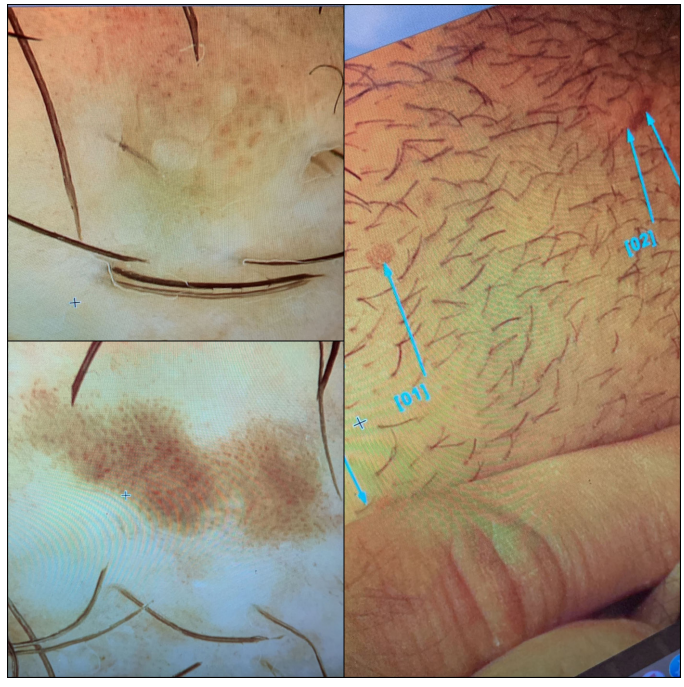

Figure 9. Genital melanosis, anogenital wart, dermoscopies

is associated with a high risk of genital warts, but there is no evidence that cigaret cessation improves treatment success (96,97).

Conclusion

HPV may cause cancers in the cervix, vagina, vulva, anus, penis, and oropharynx. Apart from the cancers it causes, the difficulties during the treatment also disrupt the psychology of the patient. Although many treatment methods are used, their superiority to each other is unclear. When deciding the treatment option, the patient's preference, the physicians' experience, access to the device, cost, localization, and size of the lesion should be evaluated. Although there are many treatment methods, it seems that the best way is to provide adequate training to teach prevention and vaccination. Large-scale studies are needed to determine treatment algorithms.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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References

1. Dunne EF, Park IU. HPV and HPV-associated diseases. Infect Dis Clin North Am 2013;27:765-778.
2. Delmonte S, Benardon S, Cariti C, Ribero S, Ramoni S, Cusini M. Anogenital warts treatment options: a practical approach. G Ital Dermatol Venereol 2020;155:261-268.
3. Gilson R, Nugent D, Werner RN, Ballesteros J, Ross J. 2019 IUSTI-Europe guideline for the management of anogenital warts. J Eur Acad Dermatol Venereol 2020;34:1644-1653.
4. Petca A, Borislavschi A, Zvanca ME, Petca RC, Sandru F, Dumitrascu MC. Non-sexual HPV transmission and role of vaccination for a better future (Review). Exp Ther Med 2020;20:186.
5. Gallay C, Miranda E, Schaefer S, Catarino R, Jacot-Guillarmod M, Menoud PA, Guerry F, Achtari C, Sahli R, Vassilakos P, Petignat P. Human papillomavirus (HPV) contamination of gynaecological equipment. Sex Transm Infect 2016;92:19-23.
6. Woodhall S, Ramsey T, Cai C, Crouch S, Jit M, Birks Y, Edmunds WJ, Newton R, Lacey CJ. Estimation of the impact of genital warts on health-related quality of life. Sex Transm Infect 2008;84:161-166.
7. Rioux M, Garland A, Webster D, Reardon E. HPV positive tonsillar cancer in two laser surgeons: case reports. J Otolaryngol Head Neck Surg 2013;42:54.
8. La Rosa G: Papillomavirus. In: Global Water Pathogen Project. Rose JB and Jiménez-Cisneros B (eds) (Meschke JS and Girones R (eds) Part 3 Viruses). Michigan State University, E. Lansing, MI, Unesco, 2016.
9. Park IU, Introcaso C, Dunne EF. Human Papillomavirus and Genital Warts: A Review of the Evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis 2015;61 Suppl 8:849-855.
10. Camargo CC, D'Elia MPB, Miot HA. Quality of life in men diagnosed with anogenital warts. An Bras Dermatol 2017;92:427-429.
11. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021;70:1-187.
12. Claesson U, Lassus A, Happonen H, Hogström L, Siboulet A. Topical treatment of venereal warts: a comparative open study of podophyllotoxin cream versus solution. Int J STD AIDS 1996;7:429-434.
13. Komericki P, Akkilic-Materna M, Strimitzer T, Aberer W. Efficacy and safety of imiquimod versus podophyllotoxin in the treatment of anogenital warts. Sex Transm Dis 2011;38:216-218.
14. Strand A, Brinkeborn RM, Siboulet A. Topical treatment of genital warts in men, an open study of podophyllotoxin cream compared with solution. Genitourin Med 1995;71:387-390.
15. Lacey CJ, Goodall RL, Tennvall GR, Maw R, Kinghorn GR, Fisk PG, Barton S, Byren I; Perstop Pharma Genital Warts Clinical Trial Group. Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. Sex Transm Infect 2003;79:270-275.
16. Werner RN, Westfechtel L, Dressler C, Nast A. Self-administered interventions for anogenital warts in immunocompetent patients: a systematic review and meta-analysis. Sex Transm Infect 2017;93:155-161.
17. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, Hougham AJ, Schmitt KA. Self-administered topical 5% imiquimod cream for external anogenital warts. HPV Study Group. Human PapillomaVirus. Arch Dermatol 1998;134:25-30.
18. Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM Jr. Treatment of genital warts with an immune-response modifier (imiquimod). J Am Acad Dermatol 1998;38:230-239.
19. Beutner KR, Tyring SK, Trofatter KF Jr, Douglas JM Jr, Spruance S, Owens ML, Fox TL, Hougham AJ, Schmitt KA. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. Antimicrob Agents Chemother 1998;42:789-794.
20. Gilson R, Nugent D, Bennett K, Dore CJ, Murray ML, Meadows J, Haddow LJ, Lacey C, Sandmann F, Jit M, Soldan K, Tetlow M, Caverly E, Nathan M, Copas AJ. Imiquimod versus podophyllotoxin , with and without human papillomavirus vaccine, for anogenital warts: the HIPvac factorial RCT. Health Technol Assess 2020:24:1-86.
21. Fife KH, Ferenczy A, Douglas JM Jr, Brown DR, Smith M, Owens ML; HPV Study Group. Treatment of external genital warts in men using 5% imiquimod cream applied three times a week, once daily, twice daily, or three times a day. Sex Transm Dis 2001;28:226-231.
22. Arican O, Guneri F, Bilgic K, Karaoglu A. Topical imiquimod 5% cream in external anogenital warts: a randomized, double-blind, placebo-controlled study. J Dermatol 2004;31:627-631.
23. Garland SM, Waddell R, Mindel A, Denham IM, McCloskey JC. An open-label phase II pilot study investigating the optimal duration of imiquimod 5% cream for the treatment of external genital warts in women. Int J STD AIDS 2006;17:448-452.
24. Gotovtseva EP, Kapadia AS, Smolensky MH, Lairson DR. Optimal frequency of imiquimod (aldara) 5% cream for the treatment of external genital warts in immunocompetent adults: a meta-analysis. Sex Transm Dis 2008;35:346-351.

25. Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. Reprod Toxicol 2006;21:1-2.

26. Audisio T, Roca FC, Piatti C. Topical imiquimod therapy for external anogenital warts in pregnant women. Int J Gynaecol Obstet 2008;100:275-276.

27. Lin JK, Liang YC. Cancer chemoprevention by tea polyphenols. Proc Natl Sci Counc Repub China B 2000;24:1-13.

28. Gross G, Meyer KG, Pres H, Thielert C, Tawfik H, Mescheder A. A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. J Eur Acad Dermatol Venereol 2007;21:1404-1412.

29. Stockfleth E, Beti H, Orasan R, Grigorian F, Mescheder A, Tawfik H, Thielert C. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. Br J Dermatol 2008;158:1329-1338.

30. Tatti S, Swinehart JM, Thielert C, Tawfik H, Mescheder A, Beutner KR. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. Obstet Gynecol 2008;111:1371-1379.

31. Tzellos TG, Sardeli C, Lallas A, Papazisis G, Chourdakis M, Kouvelas D. Efficacy, safety and tolerability of green tea catechins in the treatment of external anogenital warts: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2011;25:345-353.

32. Bertolotti A, Dupin N, Bouscarat F, Milpied B, Derancourt C. Cryotherapy to treat anogenital warts in nonimmunocompromised adults: Systematic review and meta-analysis. J Am Acad Dermatol 2017;77:518-526.

33. Pontini P, Mastorino L, Gaspari V, Granger C, Ramoni S, Delmonte S, Evangelista V, Cusini M. A Multicentre, Randomised Clinical Trial to Compare a Topical Nitrizinc® Complex Solution Versus Cryotherapy for the Treatment of Anogenital Warts. Dermatol Ther (Heidelb) 2020;10:1063-1073.

34. Reyna-Rodríguez IL, Chavez-Alvarez S, Garza-Rodríguez V, Franco-Marquez R, Gonzalez-Martinez G, Ocampo-Candiani J, Villarreal-Martinez A. Cryotherapy plus low-dose oral isotretinoin vs cryotherapy only for the treatment of anogenital warts: a randomized clinical trial. Arch Dermatol Res 2021;313:815-827.

35. Sugai S, Nishijima K, Enomoto T. Management of Condyloma Acuminata in Pregnancy: A Review. Sex Transm Dis 2021;48:403-409.

36. Sherrard J, Riddell L. Comparison of the effectiveness of commonly used clinic-based treatments for external genital warts. Int J STD AIDS 2007;18:365-368.

37. Stefanaki C, Katzouranis I, Lagogianni E, Hadjivassiliou M, Nicolaidou E, Panagiotopoulos A, Anyfantakis V, Bethimoutis G, Rallis E, Antoniou C, Katsambas A. Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. Int J STD AIDS 2008;19:441-444.

38. Gilson RJ, Ross J, Maw R, Rowen D, Sonnex C, Lacey CJ. A multicentre, randomised, double-blind, placebo controlled study of cryotherapy versus cryotherapy and podophyllotoxin cream as treatment for external anogenital warts. Sex Transm Infect 2009;85:514-519.

39. Karnes JB, Usatine RP. Management of external genital warts. Am Fam Physician 2014;90:312-318.

40. Fein LA, Marbin SJ. Condylomata acuminata of the neovagina in a transgender woman treated with trichloroacetic acid. Int J STD AIDS 2020;31:1011-1013.

41. Godley MJ, Bradbeer CS, Gellan M, Thin RN. Cryotherapy compared with trichloroacetic acid in treating genital warts. Genitourin Med 1987;63:390-392.

42. Lotfabadi P, Maleki F, Gholami A, Yazdanpanah MJ. Liquid nitrogen cryotherapy versus 70% trichloroacetic acid in the treatment of anogenital warts: A randomized controlled trial. Iran J Dermatol J 2016;18: 151-155.

43. Anggraini I, Hoemardani AS, Nilasari H, Indriatmi W. Randomised controlled trial of 1% and 5% 5-fluorouracil creams compared with 90% trichloroacetic acid solution for anogenital wart treatment. Int J STD AIDS 2020;31:849-858.

44. Recanati MA, Kramer KJ, Maggio JJ, Chao CR. Cantharidin is Superior to Trichloroacetic Acid for the Treatment of Non-mucosal Genital Warts: A Pilot Randomized Controlled Trial. Clin Exp Obstet Gynecol 2018;45:383-386.

45. Iranmanesh B, Khalili M, Zartab H, Amiri R, Aflatoonian M. Laser therapy in cutaneous and genital warts: A review article. Dermatol Ther 2021;34:e14671.

46. Pollock B, Sheehan Dare R. Pulsed dye laser and intralesional bleomycin for treatment of resistant viol hand warts. Lasers Surg Med 2002;30:135-140

47. Dobson JS, Harland CC. Pulsed dye laser and intralesional bleomycin for the treatment of recalcitrant cutaneous warts. Lasers Surg Med 2014;46:112-116.

48. Alshami MA, Mohana MJ. Novel Treatment Approach for Deep Palmoplantar Warts Using Long-Pulsed 1064-nm Nd:YAG Laser and a Moisturizing Cream Without Prior Paring of the Wart Surface. Photomed Laser Surg 2016;34:448-455.

49. Komericki P, Akkilic M, Kopera D. Pulsed dye laser treatment of genital warts. Lasers Surg Med 2006;38:273-276.

50. Khawaja HT. Podophyllin versus scissor excision in the treatment of perianal condylomata acuminata: a prospective study. Br J Surg 1989;76:1067-1068.

51. Handley JM, Maw RD, Horner T, Lawther H, Bingham EA, Dinsmore WW. Scissor excision plus electrocautery of anogenital warts in prepubertal children. Pediatr Dermatol 1991;8:243-245,248-249.

52. Bonnez W, Oakes D, Choi A, d'Arcy SJ, Pappas PG, Corey L, Stoler MH, Demeter LM, Reichman RC. Therapeutic efficacy and complications of excisional biopsy of condyloma acuminatum. Sex Transm Dis 1996;23:273-276.

53. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol 2012;5:25-36.

54. Leung L. Hyfrecation for recalcitrant nongenital warts. J Family Med Prim Care 2013;2:141-144.

55. Thurgar E, Barton S, Karner C, Edwards SJ. Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation. Health Technol Assess 2016;20:1-486.

56. Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts: a randomised clinical trial comparing podophyllin, cryotherapy, and electrodesiccation. Genitourin Med 1990;66:16-19.

57. Sarier M, Ozel E, Duman I, Yuksel Y, Demirbas A. HPV type 45-positive condyloma acuminata of the bladder in a renal transplant recipient. Transpl Infect Dis 2017;19.

58. Samarska IV, Epstein JI. Condyloma Acuminatum of Urinary Bladder: Relation to Squamous Cell Carcinoma. Am J Surg Pathol 2019;43:1547-1553.

59. Sarier M, Ceyhan AM, Sepin N, Ozel E, Inal MM, Kukul E, Soylu A. HPV infection in urology practice. Int Urol Nephrol 2020;52:1-8.

60. Batista CS, Atallah AN, Saconato H, da Silva EM. 5-FU for genital warts in non-immunocompromised individuals. Cochrane Database Syst Rev 2010;2010:CD006562.

61. Westfechtel L, Werner RN, Dressler C, Gaskins M, Nast A. Adjuvant treatment of anogenital warts with systemic interferon: a systematic review and meta-analysis. Sex Transm Infect 2018;94:21-29.

62. Yang J, Pu YG, Zeng ZM, Yu ZJ, Huang N, Deng QW. Interferon for the treatment of genital warts: a systematic review. BMC Infect Dis 2009;9:156.

63. Friedman-Kien A. Management of condylomata acuminata with Alferon N injection, interferon alfa-n3 (human leukocyte derived). Am J Obstet Gynecol 1995;172:1359-1368.

64. Syed TA, Ahmadpour OA. Human leukocyte derived interferon-alpha in a hydrophilic gel for the treatment of intravaginal warts in women: a placebo-controlled, double-blind study. Int J STD AIDS 1998;9:769-772.

65. Ao C, Xie J, Wang L, Li S, Li J, Jiang L, Liu H, Zeng K. 5-aminolevulinic acid photodynamic therapy for anal canal condyloma acuminatum: A series of 19 cases and literature review. Photodiagnosis Photodyn Ther 2018;23:230-234.

66. Zhao W, Shan XF, Wang CL, Liu XZ, Li Z, Xiao HL, Li ZW, Zheng RT, Hou JL, Tian HQ. Topical 5-aminolevulinic acid photodynamic therapy for intra anal-rectal warts. J Dermatolog Treat 2020;31:241-244.

67. Xie J, Ao C, Li J, Jiang L, Liu H, Zeng K. 5-aminolevulinic acid photodynamic therapy for condyloma acuminatum of urethral meatus. J Dermatolog Treat 2019;30:714-717.

68. Dika E, Vaccari S, Fanti PA, Patrizi A. Ingenol mebutate: an unconventional treatment proposal. Dermatol Ther 2016;29:72.

69. Schopf RE. Ingenol mebutate gel is effective against anogenital warts - a case series in 17 patients. J Eur Acad Dermatol Venereol 2016;30:1041-1043.

70. Maronn M, Salm C, Lyon V, Galbraith S. One-year experience with candida antigen immunotherapy for warts and molluscum. Pediatr Dermatol 2008;25:189-192.

71. Attwa E, Elawady R, Salah E. 'Cryo-immuno-therapy' is superior to intralesional Candida antigen monotherapy in the treatment of multiple common warts. J Dermatolog Treat 2021;32:1018-1025.

72. Hodeib AAE, Al-Sharkawy BG, Hegab DS, Talaat RAZ. A comparative study of intralesional injection of Candida albicans antigen, bleomycin and 5-fluorouracil for treatment of plane warts. J Dermatolog Treat 2021;32:663-668.

73. Nofal A, Nofal E, Yosef A, Nofal H. Treatment of recalcitrant warts with intralesional measles, mumps, and rubella vaccine: a promising approach. Int J Dermatol 2015;54:667-671.

74. Na CH, Choi H, Song SH, Kim MS, Shin BS. Two-year experience of using the measles, mumps and rubella vaccine as intralesional immunotherapy for warts. Clin Exp Dermatol 2014;39:583-589.

75. Chauhan PS, Mahajan VK, Mehta KS, Rawat R, Sharma V. The Efficacy and Safety of Intralesional Immunotherapy with Measles, Mumps, Rubella Virus Vaccine for the Treatment of Common Warts in Adults. Indian Dermatol Online J 2019;10:19-26.

76. Agrawal C, Vyas K, Mittal A, Khare AK, Gupta LK. A Randomized double Blind Controlled Study Comparing the Efficacy of Intralesional MMR Vaccine with Normal Saline in the Treatment of Cutaneous Warts. Indian Dermatol Online J 2018;9:389-393.

77. Zamanian A, Mobasher P, Jazi GA. Efficacy of intralesional injection of mumps-measles-rubella vaccine in patients with wart. Adv Biomed Res 2014;3:107.

78. Abd El-Magiud EM, Abd El-Samea GM, Gaber HD. Intralesional injection of measles, mumps, and rubella vaccine versus cryotherapy in treatment of warts: A randomized controlled trial. Dermatol Ther 2020;33:e13257.

79. Shaheen MA, Salem SA, Fouad DA, El-Fatah AA. Intralesional tuberculin (PPD) versus measles, mumps, rubella (MMR) vaccine in treatment of multiple warts: a comparative clinical and immunological study. Dermatol Ther 2015;28:194-200.

80. Yang MY, Son JH, Kim GW, Kim HS, Ko HC, Kim MB, Lim KM, Kim BS. Quadrivalent human papilloma virus vaccine for the treatment of multiple warts: a retrospective analysis of 30 patients. J Dermatolog Treat 2019;30:405-409.

81. Ling YK. Human papillomavirus vaccine for the treatment of recalcitrant extragenital warts. J Am Acad Dermatol 2017;76:159.

82. Nofal A, Marei A, Ibrahim AM, Nofal E, Nabil M. Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. J Am Acad Dermatol 2020;82:94-100.

83. Ferguson SB, Gallo ES. Nonavalent human papillomavirus vaccination as a treatment for warts in an immunosuppressed adult. JAAD Case Rep 2017;3:367-369.

84. Kost Y, Zhu TH, Blasiak RC. Clearance of recalcitrant warts in a pediatric patient following administration of the nine-valent human papillomavirus vaccine. Pediatr Dermatol 2020;37:748-749.

85. Bossart S, Imstepf V, Hunger RE, Seyed Jafari SM. Nonavalent Human Papillomavirus Vaccination as a Treatment for Skin Warts in Immunosuppressed Adults: A Case Series. Acta Derm Venereol 2020;100:adv00078.

86. Kareem IMA, Ibrahim IM, Mohammed SFF, Ahmed AA. Effectiveness of intralesional vitamin D3 injection in the treatment of common warts: Single-blinded placebo-controlled study. Dermatol Ther 2019;32:e12882.

87. Fathy G, Sharara MA, Khafagy AH. Intralesional vitamin D3 versus Candida antigen immunotherapy in the treatment of multiple recalcitrant plantar warts: A comparative case-control study. Dermatol Ther 2019;32:e12997.

88. Imagawa I, Suzuki H. Successful treatment of refractory warts with topical vitamin D3 derivative (maxacalcitol, 1alpha, 25-dihydroxy-22-oxacalcitriol) in 17 patients. J Dermatol 2007;34:264-266.

89. Egawa K, Ono T. Topical vitamin D3 derivatives for recalcitrant warts in three immunocompromised patients. Br J Dermatol 2004;150:374-376.

90. Zainab Z, Malik NA, Malik S, Mashhood A, Obaid S, Aftab K, Mumtaz M, Pervaiz A, Syed Z. Role Of Intralesional Vitamin-D In Viral Wartse. J Ayub Med Coll Abbottabad 2021;33:598-601.

91. Bik L, Sangers T, Greveling K, Prens E, Haedersdal M, van Doorn M. Efficacy and tolerability of intralesional bleomycin in dermatology: A systematic review. J Am Acad Dermatol 2020;83:888-903.

92. Oren-Shabtai M, Snast I, Lapidoth M, Sherman S, Noyman Y, Mimouni D, Hodak E, Levi A. Topical and Systemic Retinoids for the Treatment of Genital Warts: A Systematic Review and Meta-Analysis. Dermatology 2021;237:389-395.

93. Nieves-Condoy JF, Acuña-Pinzón CL, Chavarría-Chavira JL, Hinojosa-Ugarte D, Zúñiga-Vázquez LA. Giant Condyloma Acuminata (Buschke-Lowenstein Tumor): Review of an Unusual Disease and Difficult to Manage. Infect Dis Obstet Gynecol 2021;2021:9919446.

94. Purzycka-Bohdan D, Nowicki RJ, Herms F, Casanova JL, Fouéré S, Béziat V. The Pathogenesis of Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor): An Overview. Int J Mol Sci 2022;23:4547.

95. Russano F, Russo I, Del Fiore P, Di Prata C, Mocellin S, Alaibac M. Bleomycin-based electrochemotherapy for the treatment of a Buschke-Löwenstein tumor (perianal giant condyloma) in an HIV-positive kidney transplant recipient: A case report. Oncol Lett 2022;24:466.

96. Hansen BT, Hagerup-Jenssen M, Kjaer SK, Munk C, Tryggvadottir L, Sparén P, Liaw KL, Nygård M. Association between smoking and genital warts: longitudinal analysis. Sex Transm Infect 2010;86:258-262.

97. Foerster V, Khangura S, Severn M. HPV vaccination in men: a review of clinical effectiveness, cost-effectiveness, and guidelines [Internet]. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health 2017. https://europepmc.org/article/nbk/nbk470470?report=printable&client=bot

ORIGINAL RESEARCH
General Urology

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How An Emergency Can Effect Urological Emergencies: COVID-19

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What's known on the subject? and What does the study add?

During the pandemic period, the number of consultations requested from the urology department decreased, as the number of admissions to the emergency department (ED). On the other hand, the number of hospitalizations in the urology ward of patients consulted from the ED has increased. In our study, it was determined that the highest decrease in consultations requested due to renal colic, while the number of consultations requested due to urinary tract infection increased. The results obtained from this study are important in terms of revealing which urological emergencies are affected.

Abstract

Objective: Coronavirus disease-2019 (COVID-19) has caused many changes in the health services since its inception. The change in the functioning of the emergency services and the decrease in admissions have also changed the form of consultations requested from the urology clinic. This study aims to reveal how the consultations requested from the urology clinic of a large hospital were affected during the COVID-19 period.

Materials and Methods: In our study, one year before and after March 10, 2020, was divided into two groups as "pre-covid" and "covid era". The gender, age, reason for consultation, result, date and time, hospitalization status of the patients were examined.

Results: A total of 2018 consultations, 1242 in the pre-COVID period and 776 during the COVID period, were analyzed in the study. Although renal colic was the most common reason for consultation in both periods, its number and rate decreased significantly during the COVID period [384 (30.9%) vs. 165 (21.3%), p≤0.0001]. Proportionally, more patients were hospitalized during the COVID period [196 (15.8%) vs. 161 (20.7%), p=0.02]. In both periods, the most common reason for hospitalization was hematuria, but the difference was not statistically significant [26 (29.5%) vs. 20 (27.8%), p=0.261].

Conclusion: COVID-19 has turned all health parameters upside down and has been one of the biggest factors affecting public health since the day it started. While the density and form of consultation requested from the urology clinic changed during the pandemic period, the hospitalization rates increased, so urology clinics should adapt accordingly for possible pandemic waves or epidemics in the future.

Keywords: Urology, emergencies, COVID-19

Introduction

No one could have predicted that a disease that emerged in China in December 2019 could affect the world in so many ways. The coronavirus disease-2019 (COVID-19) outbreak, which was declared a pandemic in March 2020, is perhaps the most important event of the 21st century (1). According to official authorities, COVID-19 has caused 6.3 m deaths, but some sources even claim that the estimated global excess mortality rate is three times greater (2). This serious situation has deeply affected the social, economic, and cultural lives of individuals, especially in the area of health. In Turkiye, the first case was reported on March 10, 2020, and since then, more than seven million people have contracted the virus and more than 64 thousand have died (3,4). Because of the rapid transmission of COVID-19 in social environments, various measures have been taken, both at governmental and individual levels, including quarantine, transportation restriction, closure of non-essential workplaces, and interruption of formal education (5). These conditions have also substantially changed the provision of health services.

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With the beginning of the pandemic, an increasing number of patients presented to emergency departments (ED) with respiratory distress and required hospitalization. Different from their daily routine operations, EDs became the first gateway to which patients with COVID-19 presented. However, ED visits due to other health reasons were delayed because of social and personal isolation measures. Therefore, compared with the pre-pandemic period, there was a 50% decrease in ED presentations (6).

This study aimed to reveal the effects of the COVID-19 pandemic on consultations requested from the urology clinic of a large hospital receiving more than one million ED visits per year and provide data that will assist in the management of health services in future pandemics or diseases that may affect public health.

Materials and Methods

In this study, all consultations requested from ED to the urology clinic at Bursa Yüksek İhtisas Training and Research Hospital between March 10, 2019, and March 10, 2021, were screened through the hospital information management system. The data belonging to the year before March 10, 2020, when the first case and quarantine measures were announced in Turkiye, were grouped as the "pre-COVID-19 period," and those belonging to one year starting from the beginning of the pandemic period were grouped as "the COVID-19 period." Each group was evaluated over four quarters of three months, with Q1, Q2, Q3, and Q4 representing the pre-COVID-19 period and Q5, Q6, Q7, and Q8 representing the COVID-19 period. The fifth quarter (Q5) reflected the first effects of the pandemic. In Turkiye, national restrictions and quarantines were implemented from March 21, 2020, to June 1, 2020, and from November 17, 2020, to March 10, 2021 (7). Various restriction measures were applied at the national level during the Q5, Q7, and Q8 quarters of the pandemic time.

All the consulted patients, regardless of age, were included in the study. To ensure the homogeneity of the data and exclude the possible urological side effects of COVID-19, patients who were positive for COVID-19 according to the polymerase chain reaction test performed at the time of presentation to ED were excluded from the study. The patients' gender, age, reason for consultation, results, date and time of presentation, and hospitalization status was evaluated. Consultation hours were divided into three groups: 08:00-16:00, 16:00-24:00, and 24:00-08:00. The study was approved by the ethics committee of the hospital with the decision number 2011-KAEK-25 2021/07-30 (Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee). Informed consent was not obtained because the study was planned retrospectively.

Statistical Analysis

The data were analyzed with the Shapiro-Wilk test to determine whether they showed a normal distribution. The results were presented as mean ± standard deviation, minimum, and maximum, or frequency and percentage values. Normally distributed data were compared with the Independent Samples t-test or One-Way analysis of variance. The Bonferroni test was used as a multiple comparison method. Categorical variables between the groups were compared using Pearson's chi-square test. Statistical significance was defined as $p<0.05$. IBM SPSS ver. 25.0 was used to perform statistical analyses and construct graphs.

Results

A total of 2.018 consultations, 1.242 in the pre-COVID-19 period and 776 during the COVID-19 period, were included in the study. During the pandemic, the number of consultations requested from the ED to the urology clinic decreased by 37% ($p<0.0001$). Especially in the first three months of the pandemic, the number of consultations requested decreased by 48.7% compared to the same period a year before (371 versus 190). When the same periods of the two years were compared, the difference decreased to 12.2% over time. Demographic data and consultation characteristics are shown in Table 1. No significant difference was found between the groups in terms of the mean age and gender. However, the mean age of the inpatients was found to be higher than the patients treated in the outpatient setting (57.23±19.1 vs. 53.4±21.1, $p=0.002$). In both periods, most consultations were requested between 16:00 and 24:00.

Table 1. Demographic data and clinical outcomes of the patients

	Pre-COVID-19 period	COVID-19 period	p-value
Consultations (n)	1.242	776	
Age (mean, min-max)	53.7 (5-97)	54.5 (5-96)	>0.05
Sex			>0.05
• Male	961 (77.4%)	599 (77.2%)	
• Female	281 (22.6%)	177 (22.8%)	
Time of consultation			
• 08:00-16:00	487 (39.2%)	269 (34.7%)	0.04
• 16:00-24:00	566 (45.6%)	364 (46.9%)	>0.05
• 24:00-08:00	189 (15.2%)	143 (18.4%)	>0.05
Consultation results			
• Outpatient treatment	974 (78.4%)	582 (75%)	>0.05
• Admission to the inpatient urology ward	196 (15.8%)	161 (20.7%)	0.004
• Admission to other wards	72 (5.8%)	33 (4.3%)	>0.05
Outcomes of patients admitted to the urology ward			>0.05
• Medical treatment	108 (55.1%)	89 (55.3%)	
• Operation	88 (44.9%)	72 (44.7%)	

COVID-19: Coronavirus disease-2019, min-max: Minimum-maximum

However, in the pre-COVID-19 period, more consultations were requested during daytime hours (8:00-16:00, p=0.04).

Reasons for requesting consultation are showed in Table 2. In both periods, the most common reason for consultation was renal colic. During the COVID-19 period, there was a statistically significant decrease in both the number and ratio of patients presenting with renal colic (p<0.0001). Ureteral stones were detected in 182 (47.4%) and 98 (59.4%) patients presenting with renal colic in the pre-COVID-19 and COVID-19 periods, respectively, and the difference was statistically significant (p=0.01). Similarly, the number of patients consulted for urological problems secondary to orthopedic trauma significantly decreased during the COVID-19 period (p=0.05). Consultations requested due to hematuria, urinary tract infection (UTI), and postrenal acute kidney injury proportionally increased during the COVID-19 period. The distribution of the six most common reasons for urological consultations is given in Figure 1 according to the quarterly evaluation.

Table 2. Reasons for urological consultations

Reasons for urological consultation	Pre-COVID-19 period	COVID-19 period	p-value
Renal colic	384 (30.9%)	165 (21.3%)	<0.0001
Acute scrotum	238 (19.2%)	138 (17.8%)	>0.05
Gross hematuria	167 (13.4%)	133 (17.1%)	0.023
Urinary tract infection	126 (10.1%)	130 (16.8%)	<0.0001
Urinary retention	122 (9.8%)	69 (8.9%)	>005
Urological trauma	55 (4.4%)	30 (3.9%)	>0.05
Orthopedic trauma	46 (3.7%)	12 (1.5%)	0.005
Postrenal acute kidney injury	36 (2.9%)	44 (5.7%)	0.002
Incidental mass	12 (1%)	8 (1%)	>0.05
Fournier's gangrene	7 (0.6%)	3 (0.4%)	>0.05
Priapism	2 (0.2%)	5 (0.6%)	>0.05
Penile fracture	2 (0.2%)	3 (0.4%)	>0.05
Anuria	2 (0.2%)	2 (0.3%)	>0.05
Other	43 (3.5%)	34 (4.4%)	>0.05
Total	1242	776	

COVID-19: Coronavirus disease-2019

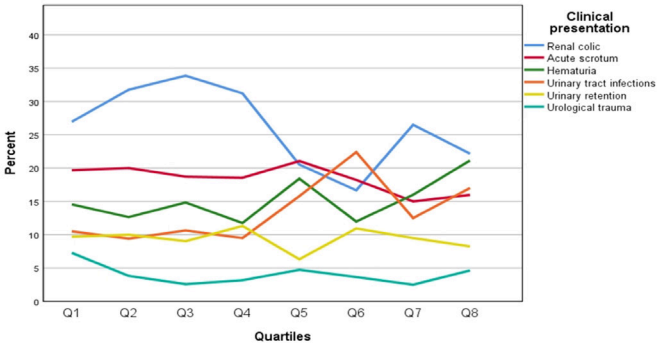

Figure 1. Six most common reasons for urological consultations according to their quartile distribution

While 196 (15.8%) of the consulted patients were admitted to the urology ward in the pre-COVID-19 period, 161 (20.7%) were hospitalized during the COVID-19 period. Proportionally, more patients were hospitalized during the COVID-19 period (p=0.02). Eighty-eight (44.9%) of the 196 patients hospitalized in the pre-COVID-19 period underwent surgery: 26 (29.5%) for the investigation and treatment of the etiology of hematuria, 14 (15.9%) for renal colic (bilateral ureteral stone, ureteral stone in a solitary kidney, etc.), and 13 (14.8%) for acute scrotum (testicular torsion, testicular trauma, etc.). During the COVID-19 period, 72 (44.7%) of the 161 patients who were admitted to the wards underwent surgery [20 (27.8%) for the investigation and treatment of the etiology of hematuria, 17 (23.6%) for acute scrotum, and 16 (22.2%) for renal colic]. No significant difference was found between the two periods in terms of the interventions performed (p=0.396).

Discussion

With the unavoidable spread of COVID-19, there was an unprecedented, rapid transformation in healthcare services. Standard healthcare parameters have rapidly changed, with most health services being allocated to patients with COVID-19. Under these circumstances, EDs and wards and intensive care beds were rearranged to primarily provide ventilation support for these patients. Many countries have taken quarantine measures to prevent the pandemic from spreading rapidly, and the health systems of some countries were overburdened by increasing demands (8). In addition to social measures, strict isolation measures were applied because of the fear of contracting an unknown disease. As a result, the demand of individuals for standard health services decreased. In a previous study, it was reported that the average daily outpatient clinic admissions decreased by 71% with the implementation of isolation measures (9). This decrease was also seen in ED presentations. In a study conducted in Germany, it was shown that ED visits decreased by 38% following isolation measures (10). In another study, it was shown that ED presentations decreased by 42% between March 29 and April 25, 2020, compared to the same period of the previous year (11). Similarly, in our hospital, the annual average number of ED presentations decreased from 1,201,614 in the pre-COVID-19 period to 716,989 during the COVID-19 period, indicating a 40% reduction.

Along with the decrease in the number of patients presenting to the ED, the number of consultations requested from ED also decreased. Both the restriction of access to the hospital due to quarantine conditions and the absence of truly non-urgent

consultations reduced the number of consultations requested from the urology clinic during this period (12). In our study, the number of consultations requested from the urology clinic decreased by 37% compared to the previous year (1.242 vs. 776, p<0.0001). In another study conducted in Turkiye, it was reported that there was a 72% decrease in consultations made by ED (13). When the reasons for consultations were examined, it was observed that the highest decrease was seen in the number of consultations made for renal colic (57%, 384 vs. 164, p<0.0001). Although the rate of consultations due to UTI significantly increased compared to the previous year, there was no significant difference between the number of infections requiring hospitalization, contrary to the expectation of severe UTI due to delayed hospital visits [38 (30.2%) vs. 32 (24.6%) p=0.539]. Similarly, many studies have reported a decrease in the number of patients presenting to hospitals with trauma under quarantine conditions (6,10). In parallel with this decrease, studies have also shown an 85% decrease in the number of patients referred to the urology clinic because of trauma (13). In our study, the proportion of the patients consulted for urological trauma secondary to orthopedic trauma significantly decreased (p=0.005), although the number of those consulted for primary urological trauma decreased, the difference was not statistically significant (p>0.05).

During the COVID-19 period, urological operations were mostly performed due to trauma, testicular torsion, penile fracture, massive hematuria, Fournier's gangrene, etc. according to the European Association of Urology guidelines (14). Under the pandemic conditions, the primary goal was to protect patients against COVID-19 transmission. However, in our study, the proportion of patients requiring hospitalization increased compared with the pre-pandemic period (15.8% vs. 20.7%, p=0.004). In a previous study, a similar increase was observed, which was attributed to the limitations concerning outpatient clinic examinations and postponement of elective operations, resulting in the exacerbation of urological diseases (15). Similarly, in another study, there was an increase in the rate of consultations resulting in invasive procedures (12). However, Alkis et al. (16) reported that the rate of invasive interventions decreased by 3% in consultations made by ED.

Study Limitations

The most important limitation of our study concerns its single-center nature. Another limitation is that some patients may have presented to nearby hospitals because of the fear of contamination since our hospital was designated as a reference COVID-19 care center in and around Bursa during the pandemic period. Despite this, we examined the effect of the COVID-19 period on urological emergencies with the largest number of patients and the longest timeframe in the literature. Our study is also important since it contributes to the knowledge pool on COVID-19 to minimize the impact of similar pandemic waves or other future pandemics on urological emergencies.

Conclusion

Since the day it was initiated, COVID-19 has caused all health parameters to change radically and has become one of the greatest factors affecting public health. During the pandemic period, the proportion and number of patients consulted for UTI increased. Similarly, the possibility of hospitalization increased during the pandemic period. The results obtained from this study are important in terms of revealing which urological emergencies have been affected and to what extent in the presence of restrictions imposed due to pandemic conditions.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of the hospital with the decision number 2011-KAEK-25 2021/07-30 (Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee).

Informed Consent: Informed consent was not obtained because the study was planned retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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References

1. World Health Organization. WHO director-General's opening remarks at the media briefing on COVID-19-11 march 2020. World Health Organization. 2020 [cited 2021 October 2]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard 2022 [cited 2022 July 14]. Available from: https://covid19.who.int/.
3. Demirbilek Y, Pehlivantürk G, Özgüler ZÖ, Alp Meşe E. COVID-19 outbreak control, example of ministry of health of Turkey. Turk J Med Sci 2020;50:489-494.
4. Worldometer. Coronavirus cases 2021 [Available from: https://www.worldometers.info/coronavirus/.
5. Parmet WE, Sinha MS. Covid-19 - The Law and Limits of Quarantine. N Engl J Med 2020;382:e28.
6. Boserup B, McKenney M, Elkbuli A. The impact of the COVID-19 pandemic on emergency department visits and patient safety in the United States. Am J Emerg Med 2020;38:1732-1736.

7. Wikipedia. Timeline of the COVID-19 pandemic in Turkey 2021 [Available from: https://en.wikipedia.org/wiki/Timeline_of_the_COVID-19_pandemic_in_Turkey.
8. Thu TPB, Ngoc PNH, Hai NM, Tuan LA. Effect of the social distancing measures on the spread of COVID-19 in 10 highly infected countries. Sci Total Environ 2020;742:140430.
9. Ferahman S, Dural AC, Aydin H, Sahbaz NA, Akarsu C, Peker KD, Donmez T, Karabulut M. Analysis of general surgery outpatient clinic admissions and operations during COVID-19 pandemic in Turkey: Reactions of 12728 patients. Bratisl Lek Listy 2020;121:475-480.
10. Slagman A, Behringer W, Greiner F, Klein M, Weismann D, Erdmann B, Pigorsch M, Möckel M; AKTIN Emergency Department Registry; German Forum of University Emergency Departments (FUN) in the Society of University Clinics of Germany E.V.. Medical Emergencies During the COVID-19 Pandemic. Dtsch Arztebl Int 2020;117:545-552.
11. Hartnett KP, Kite-Powell A, DeVies J, Coletta MA, Boehmer TK, Adjemian J, Gundlapalli AV; National Syndromic Surveillance Program Community of Practice. Impact of the COVID-19 Pandemic on Emergency Department Visits - United States, January 1, 2019-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:699-704.
12. Motterle G, Morlacco A, Iafrate M, Bianco M, Federa G, Xhafka O, Zattoni F, Prayer-Galetti T. The impact of COVID-19 pandemic on urological emergencies: a single-center experience. World J Urol 2021;39:1985-1989.
13. Bozkurt O, Sen V, Irer B, Sagnak L, Onal B, Tanidir Y, Karabay E, Kaya C, Ceyhan E, Baser A, Duran MB, Suer E, Celen I, Selvi I, Ucer O, Karakoc S, Sarikaya E, Ozden E, Deger D, Egriboyun S, Ongun S, Gurboga O, Asutay MK, Kazaz IO, Yilmaz IO, Kisa E, Demirkiran ED, Horsanali O, Akarken I, Kizer O, Eren H, Ucar M, Cebeci OO, Kizilay F, Comez K, Mercimek MN, Ozkent MS, Izol V, Gudeloglu A, Ozturk B, Akbaba KT, Polat S, Gucuk A, Ziyan A, Selcuk B, Akdeniz F, Turgut H, Sabuncu K, Kaygisiz O, Ersahin V, Kahraman HI, Guzelsoy M, Demir O; Study Group of the Society of Urological Surgery. Nation-wide analysis of the impact of Covid-19 pandemic on daily urology practice in Turkey. Int J Clin Pract 2021;75:e13735.
14. Ribal MJ, Cornford P, Briganti A, Knoll T, Gravas S, Babjuk M, Harding C, Breda A, Bex A; GORRG Group; Rassweiler JJ, Gözen AS, Pini G, Liatsikos E, Giannarini G, Mottrie A, Subramaniam R, Sofikitis N, Rocco BMC, Xie LP, Witjes JA, Mottet N, Ljungberg B, Rouprêt M, Laguna MP, Salonia A, Bonkat G, Blok BFM, Türk C, Radmayr C, Kitrey ND, Engeler DS, Lumen N, Hakenberg OW, Watkin N, Hamid R, Olsburgh J, Darraugh J, Shepherd R, Smith EJ, Chapple CR, Stenzl A, Van Poppel H, Wirth M, Sønksen J, N'Dow J; EAU Section Offices and the EAU Guidelines Panels. European Association of Urology Guidelines Office Rapid Reaction Group: An Organisation-wide Collaborative Effort to Adapt the European Association of Urology Guidelines Recommendations to the Coronavirus Disease 2019 Era. Eur Urol 2020;78:21-28.
15. Gallioli A, Albo G, Lievore E, Boeri L, Longo F, Spinelli MG, Costantino G, Montanari E, De Lorenzis E. How the COVID-19 Wave Changed Emergency Urology: Results From an Academic Tertiary Referral Hospital in the Epicentre of the Italian Red Zone. Urology 2021;147:43-49.
16. Alkis O, Baser A, Caglayan MS, Teke K, Avci IE, Yasar A, Keskin E, Yuksekkaya M, Celen S, Ozlulerden Y, Olcucu MT, Ucar M, Guzel A, Asutay MK, Bahceci T, Oncel HF. The Impact of COVID-19 Pandemic on Urological Emergencies, 8 Months Results of a Multicenter Retrospective Study From Turkey. Sisli Etfal Hastan Tip Bul 2022;56:49-54.

ORIGINAL RESEARCH
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Metabolic Syndrome and Benign Prostatic Hyperplasia/Which Component of Metabolic Syndrome Is Related to Benign Prostatic Hyperplasia?

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What's known on the subject? and What does the study add?

One of the most prevalent disorders affecting men in their old age is benign prostatic hyperplasia (BPH). Prostatic enlargement and lower urinary tract symptoms are its defining features. The main risk factors for the development of BPH are recognized to be aging, inflammation, and a hormonal imbalance. The etiology of BPH is not well understood. Additionally, current research indicates that metabolic conditions such hyperinsulinemia, dyslipidemia, and obesity may contribute to the emergence of BPH. Our goal was to assess the relationship between BPH and each metabolic syndrome (MS) feature and identify which feature carries the greatest risk for BPH development. This is the first study in the literature to investigate the risk between BPH and MS with each metabolic syndrome component separately and independently of each other. We discovered at the study's conclusion that there was no difference in BPH prevalence between MS components. We came to the conclusion that while none of the MS components by themselves enhance the likelihood of BPH, when these metabolic problems combine to form a syndrome, BPH becomes more common.

Abstract

Objective: Our objective was to evaluate the association of benign prostatic hyperplasia (BPH) with each component of metabolic syndrome (MS), and determine which component plays the major risk for developing BPH.

Materials and Methods: This cross-sectional observational study was performed on 203 male patients aged over 50, who came to the internal medicine outpatient clinics just for a check-up with/without any known disease. Forty-three of them were healthy control patients and the rest had only 1 criterion of MS. They were searched for the presence of BPH.

Results: BPH prevalence ranged between 45.5-65.6% in the subgroups, there was no statistically significant difference in the presence of BPH between these groups. There was a slight positive correlation between glucose level and prostate volume. Triglyceride levels were positively correlated with Q_{max} and negatively correlated with the grade of hypertrophy. There was also a slight positive correlation between systolic blood pressure and prostate volumes, grade of hypertrophy, and IPSS scores.

Conclusion: BPH prevalence was not different between MS components. We concluded that none of the MS components increase the occurrence of BPH by itself but when those metabolic disorders come together and form a syndrome, the prevalence of BPH increases.

Keywords: Metabolic syndrome, benign prostatic hyperplasia, hyperglycemia, hypertension, dyslipidemia, obesity.

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Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases of men in their elderly age. It is characterized by hyperplasic nodules in the prostate gland, prostatic enlargement, and the presence of lower urinary tract symptoms (LUTS). Aging, inflammation, and hormonal imbalance between androgens and estrogen are known as the main risk factors for developing BPH; however, the cause of BPH is not well defined. Recent studies have also shown that metabolic disorders such as hyperinsulinemia, dyslipidemia, and obesity may play a role in the development of BPH (1,2).

Metabolic syndrome (MS) is defined as a combination of hypertension, impaired glucose metabolism, abdominal obesity, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C) (3). According to the International Diabetes Foundation (IDF)-5 definition, metabolic syndrome is present if abdominal obesity (waist circumference over 94 cm for men or 80 cm for women) + two or more of the following four criteria are met: fasting blood sugar over 100 mg/dL, fasting triglyceride (TG) level greater than 150 mg/dL, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women), and blood pressure over 130/85 mmHg. Similar to BPH, with increasing age, MS is seen more frequently (4). Some studies in the literature give an impulse to an association between MS and prostatic hyperplasia and LUTS (5-8). It is unclear whether MS triggers BPH or whether these two phenomena simply occur together because of aging. In some of these studies, it was shown that this risk is positively associated with the number of MS components. However, there are also some studies conflicting with this relationship (9,10). Furthermore, studies performed on Asian populations have shown a null or even inverse association between MS and BPH and/or its related LUTS (11-15).

In this study, our objective was to evaluate the association of BPH with each component of MS, and determine which component plays the major risk for developing BPH, whether one pathology is responsible for this risk or does the risk occur when 3 or more components get together and named as MS.

Materials and Methods

This is a cross-sectional and observational study that was performed on 203 male patients aged over 50 years, who came to the Internal Medicine outpatient clinics between the years 2015-2018 just for a check-up with/without any known disease. The study was approved by our hospital's non-interventional clinical research ethics committee (University of Health Sciences Turkiye, Kartal Dr. Lütfi Kırdar Training and Research Hospital Ethics Committee - decision no: 89513307/1009/409, dated: 10.02.2015). Informed consent was obtained from all the patients.

Patients with a history of prostatic malignancy, those taking 5 alfa reductase inhibitor medications that decrease prostate volume, or patients who had surgery related to the urinary bladder or prostate were excluded from the study. For the inclusion criteri, patients must have just one component of MS (not more than 1 component). According to these components, the patients were divided into five groups [Group 1: just having abdominal obesity, Group 2: just having blood pressure over 130/85 mmHg, Group 3: just having fasting triglyceride (TG) level greater than 150 mg/dL, Group 4: just having fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL, Group 5: just having fasting blood sugar over 100 mg/dL]. Patients that have more than 1 criterion were excluded. In addition, there was a control group composed of healthy volunteers without any diagnosed disease and without having any criteria for MS.

These patients involved in the study were later examined by urologists for the existence of BPH. The following measurements were recorded: waist circumference, height, weight, body mass index, blood pressure, lipid profile, fasting blood glucose, urea, creatinine, prostate-specific antigen (PSA), prostate volume, and urine specimen. The drugs used by these patients were recorded. The prostate gland was evaluated by digital rectal examination, and ultrasound was used to measure the prostate volume. To specifying the severity of LUTS, the International Prostate Symptom Score (IPSS) was used. With the total score changing from 0 to 35 points, patients who had 0-7, 8-19, and 20-35 points were classified as mild, moderate, and severely symptomatic respectively. Uroflowmetry was performed for each patient to detect the Q_{max} value. In men who had a serum PSA concentration of more than 4.0 ng/mL and/or a suspected digital rectal examination, prostate biopsy was performed. PSA levels ≥4 µg/L, prostate volume ≥40 ccs, digital rectal examination result ≥ grade 1, Q_{max} ≤15 mL/sn, or IPSS >7 (at least having one of them) were considered as having BPH.

Statistical Analysis

SPSS version 24 software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical Inc. Mean, SD, median, minimum, maximum, frequency, and percentage values were used as descriptive statistics. The distribution of the variables was evaluated using the Kolmogorov-Smirnov test. In continuous variables, for non-parametric data Mann-Whitney U test, and parametric data Independent Samples t-test were used. The chi-square test was used for categorical variables. Pearson correlation analysis for parametric variables and Spearman correlation analysis for non-parametric variables were applied to examine the relationships between them. A p-value <0.05 was considered statistically significant.

Results

The prevalence of BPH ranged between 45.5-65.6% in the groups, there was no statistically significant difference between these groups. Also, there was not any statistically meaningful difference in prostate volumes, PSA levels, digital examination results, IPSS scores, and Q_{max} values between these groups (Table 1).

According to the correlation coefficient between BPH parameters and MS syndrome parameter, there was a slight positive correlation between glucose levels and prostate volumes. Triglyceride levels were positively correlated with Q max and negatively correlated with the grade found in digital rectal examination. There was also a slight positive correlation between systolic blood pressure and prostate volumes, IPSS scores, and rectal examination grading of the patients.

When these patients were grouped as having BPH (n=117) or not having BPH (n=86), statin usage in BPH (-) patients were 4.7%, whereas in BPH (+) patients it was %0 (p=0.0.13). There was no statistical difference in anti-hypertensive and anti-diabetic drug usage percentages between patients.

A prostate biopsy was wanted from 13 patients. One of them did not accept biopsy. In four patients, prostate adenocarcinoma was detected (Patient 1: 65 years old +high triglyceride, patient 2: 62 years old + low HDL, patient 3: 63 years old + abdominal obesity, patient 4: 71 years old + low HDL).

Among their follow-up, 1 patient was diagnosed with angiomyolipoma (61 years old + high blood pressure), and 1 patient was diagnosed with renal cell ca (65 years old +low HDL).

Discussion

Metabolic syndrome is a combination of cardiovascular and metabolic risk factors. The association between MS and BPH was first observed by Hammarsten et al (7). In their study, prostate volume was significantly higher in patients with BPH with MS compared with those without MS. After this study, several authors have supported a possible link between MS and BPH (5-8,16-18), but some others did not confirm this association (9-15).

The pathogenetic mechanisms of the association between MS and BPH are not well known. Clinical studies corroborate the role of chronic inflammation as a possible factor (19). In addition, the role of the impaired immune response has recently been emphasized in BPH pathogenesis (19).

Studies up to now related to this article have all been performed in patients diagnosed with MS. As it is known, it is a combination of metabolic disorders. There has been no study

Table 1. Clinical features of patients with different components of MS and the control group

	Control group (n=43)	Abdominal obesity (n=29)	High glucose level (n=38)	Low HDL cholesterol level (n=28)	Hipertension (n=32)	High triglyceride level (n=33)	p-value
BPH prevalence (n, %)	**25 (58%)**	**18 (62.1%)**	**23 (60.5%)**	**15 (53.3%)**	**21 (65.6%)**	**15 (45.5%)**	**0.646**
Age	60.5±8.0	59.9±0.6	60.4±6.8	57.5±6.5	63.4±7.3	57.9±5.4	0.016
Prostate volume (cc)	33.0±16.0	36.4±20.2	38.3±16.5	30.9±11.3	37.9±17.8	32.4±17.7	0.344
PSA (µg/L)	1±0.6	1.24±0.7	0.95±0.5	0.85±0.65	1.1±0.8	0.8±0.5	0.676
IPSS score	6.5±4.1	6.9±4.8	7.4±5.3	5.9±3.9	7.2±3.9	6.0±4.4	0.658
Q_{max} (mL/sn)	19.9±8.7	18.2±7.8	21.8±11.2	20.6±8.5	21.4±10.2	22.5±9.0	0.521
PVR (post void residual volume) (cc)	33±12	39±20	34±15	48±20	35±5	39±18	0.512
Glukoz (mg/dL)	93.3±7.4	99.0±7.2	142.4±46.8	96.1±8.8	96.4±8.0	97.6±6.2	0.000
HDL cholesterol (mg/dL)	53.7±9.1	51.2±9.6	52.2±11.3	35.9±3.1	53.2±8.9	47.5±6.2	0.000
Triglyceride (mg/dL)	100.6±31.2	92.7±28.5	108.7±34.6	114.8±27.0	104.2±26.8	230.7±61.8	0.000
LDL cholesterol (mg/dL)	149.0±37.7	142.8±43.8	157.9±35.0	123.8±29.3	152.7±30.1	161.4±38.8	0.001
Total cholesterol (mg/dL)	222.6±43.2	212.5±46.3	231.5±39.0	182.8±32.1	226.8±33.6	254.9±40.8	0.000
Systolic blood pressure (mm/Hg)	123.7±4.9	126.6±4.6	124.9±5.6	122.4±6.1	134.7±9.8	123.2±4.6	0.000
Diastolic blood pressure (mm/Hg)	77.6±4.7	79.8±2.5	78.2±4.6	78.9±3.9	80.6±6.7	77.5±4.2	0.035
Waist circumference	85.9±2.5	99.2±3.2	86.8±2.8	86.6±3.5	87.4±2.2	86.0±2.1	0.791

on the relationship between each component of metabolic syndrome separately and the BPH. We do not know whether a component of MS is responsible for this or is it just because of inflammation and aging. It is still unclear which metabolic disorder makes those men more prone to BPH.

In our study, we grouped patients according to their metabolic disorders. Patients having more than one criterion for MS were excluded at the beginning. Therefore, the patients included in the study were not MS patients. They were the patients having only one metabolic disorder, which was a component of MS.

There was not any correlation between these groups and BPH prevalence. In groups with abdominal obesity, high glucose levels, and high blood pressure, BPH prevalence was higher than in the control group, but this was not statistically significant.

In the patients that do not have BPH, statin usage was significantly higher. There are some studies in the literature that statin usage has a protective effect on BPH. This result also supports that BPH prevalence is lower in patients using a statins.

With these results, we thought that none of the MS parameters separately increase the risk of BPH, but when they come together and form the syndrome, with the contribution of increased inflammation, aging, and co-existence of metabolic disorders, including hyperinsulinemia, this makes MS patients more prone to BPH occurrence. The role of inflammation and inflammatory mediators should be overviewed once more for this process. It is impossible to say that BPH prevalence is increased in hypertension, or in hyperglycemia or in dyslipidemia. Also, we can not say that obesity is an independent risk factor for BPH. None of the determinants of MS is solely responsible for the risk of BPH existence. All these risk factors should be evaluated together. We should consider increased BPH prevalence when patients have a diagnosis of MS.

Study Limitations

Low number of patients was a limitation of this study. This is because of the difficulties in forming these separate groups that only have 1 MS component. Although we could not find a statistically significant relationship between MS parameters and BPH, studies having a larger number of patients are needed on this subject.

Conclusion

BPH prevalence was not different between MS components. We concluded that none of the MS components increase the occurrence of BPH by itself. But by looking at the results of previous studies, we concluded that when these metabolic disorders come together and form a syndrome, the prevalence of BPH increases.

Ethics

Ethics Committee Approval: The study was approved by our hospital's non-interventional clinical research ethics committee (University of Health Sciences Turkiye, Kartal Dr. Lütfi Kırdar Training and Research Hospital Ethics Committee - decision no: 89513307/1009/409, dated: 10.02.2015).

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A.T., E.Ç., Ö.K., M.K., K.F.N., Concept: B.A.T., Y.Ö., K.F.N., Design: B.A.T., E.Ç., Ö.K., M.K., Y.Ö., K.F.N., Data Collection or Processing: B.A.T., E.Ç., Ö.K., M.K., K.F.N., Analysis or Interpretation: B.A.T., Y.Ö., K.F.N., Literature Search: B.A.T., K.F.N., Writing: B.A.T., K.F.N.

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References

1. Nandeesha H, Koner BC, Dorairajan LN, Sen SK. Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia. Clin Chim Acta 2006;370:89-93.
2. Lee S, Min HG, Choi SH, Kim YJ, Oh SW, Kim YJ, Park Y, Kim SS. Central obesity as a risk factor for prostatic hyperplasia. Obesity (Silver Spring) 2006;14:172-179.
3. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-2752.
4. Churilla JR, Fitzhugh EC, Thompson DL. The Metabolic Syndrome: How Definition Impacts the Prevalence and Risk in U.S. Adults: 1999-2004 NHANES. Metab Syndr Relat Disord 2007;5:331-342.
5. Hammarsten J, Högstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. Eur Urol 2001;39:151-158.
6. Jiang M, Strand DW, Franco OE, Clark PE, Hayward SW. PPARγ: a molecular link between systemic metabolic disease and benign prostate hyperplasia. Differentiation 2011;82:220-236.
7. Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1:157-162.
8. Abdollah F, Briganti A, Suardi N, Castiglione F, Gallina A, Capitanio U, Montorsi F. Metabolic syndrome and benign prostatic hyperplasia: evidence of a potential relationship, hypothesized etiology, and prevention. Korean J Urol 2011;52:507-516.
9. De Nunzio C, Aronson W, Freedland SJ, Giovannucci E, Parsons JK. The correlation between metabolic syndrome and prostatic diseases. Eur Urol 2012;61:560-570.

10. Vignozzi L, Gacci M, Maggi M. Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. Nat Rev Urol 2016;13:108-119.

11. Jeong JH, Kim ET, Kim DK. Association of metabolic syndrome and benign prostate enlargement in young korean males. Korean J Urol 2011;52:757-762.

12. Eom CS, Park JH, Cho BL, Choi HC, Oh MJ, Kwon HT. Metabolic syndrome and accompanying hyperinsulinemia have favorable effects on lower urinary tract symptoms in a generally healthy screened population. J Urol 2011;186:175-179.

13. Ohgaki K, Hikima N, Horiuchi K, Kondo Y. Association between metabolic syndrome and male lower urinary tract symptoms in Japanese subjects using three sets of criteria for metabolic syndrome and International Prostate Symptom Score. Urology 2011;77:1432-1438.

14. Park YW, Kim SB, Kwon H, Kang HC, Cho K, Lee KI, Kim YJ, Lee JH. The relationship between lower urinary tract symptoms/benign prostatic hyperplasia and the number of components of metabolic syndrome. Urology 2013;82:674-669.

15. Kim JH, Doo SW, Yun JH, Yang WJ. Lower likelihood of having moderate-to-severe lower urinary tract symptoms in middle-aged healthy Korean men with metabolic syndrome. Urology 2014;84:665-669.

16. Parsons JK, Carter HB, Partin AW, Windham BG, Metter EJ, Ferrucci L, Landis P, Platz EA. Metabolic factors associated with benign prostatic hyperplasia. J Clin Endocrinol Metab 2006;91:2562-2568.

17. Rohrmann S, Smit E, Giovannucci E, Platz EA. Associations of obesity with lower urinary tract symptoms and noncancer prostate surgery in the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2004;159:390-397.

18. Corona G, Gacci M, Maseroli E, Rastrelli G, Vignozzi L, Sforza A, Forti G, Mannucci E, Maggi M. Clinical correlates of enlarged prostate size in subjects with sexual dysfunction. Asian J Androl 2014;16:767-773.

19. Fibbi B, Penna G, Morelli A, Adorini L, Maggi M. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. Int J Androl 2010;33:475-488.

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The Effect of Obturator Nerve Blockade on Oncological Outcomes of Patients with Lateral Wall Localized Non-Muscle Invasive Bladder Cancer

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What's known on the subject? and What does the study add?

Prior research has established that transurethral resection of bladder tumors (TUR-BT) is the standard approach for non-muscle invasive bladder cancer (NMIBC), particularly those localized to the lateral wall. During this procedure, the stimulation of the obturator nerve can trigger adductor muscle contractions, potentially leading to complications like incomplete tumor resection, inadequate muscle tissue sampling, and bladder perforation. Obturator nerve blockade has been proposed as a method to mitigate these complications by preventing undesirable adductor muscle spasms. Various techniques, including ultrasound guidance, have been explored for obtaining effective obturator nerve blockade. This study contributes to the existing knowledge by investigating the impact of combining spinal anesthesia with ultrasound-guided obturator nerve blockade on oncological outcomes in patients with lateral wall localized NMIBC. The results demonstrate several key findings that add to the understanding of this topic. First, the combination of spinal anesthesia and obturator nerve blockade is associated with lower rates of tumor recurrence and progression compared to spinal anesthesia alone. Additionally, patients who underwent this combined approach had higher rates of complete resection and adequate detrussor muscle sampling in surgical specimens. These findings underscore the potential benefits of incorporating obturator nerve blockade into TUR-BT procedures for lateral wall localized NMIBC, enhancing patient outcomes and reducing perioperative complications.

Abstract

Objective: To investigate the effect of obturator nerve blockade on oncological outcomes of patients with a diagnosis of lateral wall localized non-muscle invasive bladder cancer.

Materials and Methods: One hundred six patients diagnosed with lateral wall localized non-invasive bladder cancer were evaluated between January 2015 and March 2020 in this retrospective, cross-sectional observational study. The patients were divided into two groups: patients receiving only spinal anesthesia and those receiving spinal anesthesia combined with ultrasound-guided obturator nerve blockade. Oncological outcomes of the groups were compared statistically.

Results: We observed recurrent tumors in 25 patients (45.5%) in Group 1 and 11 patients (21.6%) in Group 2. Additionally, we observed tumor progression in eight patients (14.5%) in Group 1 and two patients (3.9%) in Group 2. We observed statistical significance in differences between groups regarding tumor size, recurrence rate, adequate muscle tissue sampling, ability for complete resection, and persistent obturator reflex. The efficacy rate of obturator blockade was 92.1% in Group 2. One-year recurrence-free survival (RFS) was 98.0% and 5-year RFS was 23.5% for Group 1, while for Group 2, they were 97.4% and 57.2%, respectively.

Conclusion: The obturator reflex is a common and challenging reflex that may cause major complications and result in unintended consequences, such as incomplete resection or tumor recurrence with transurethral resection of bladder tumors. In this study, we demonstrated that combining spinal anesthesia with obturator nerve blockade for lateral wall localized non-muscle invasive bladder cancer may prevent tumor recurrence and reduce peroperative complications.

Keywords: Bladder cancer, non-muscle invasive bladder cancer, obturator nerve blockade, adductor contraction, bladder perforation, and nerve block

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Introduction

Bladder cancer is the sixth most common cancer in men in the United States (1). Transurethral resection of bladder tumor (TUR-BT) is an initial diagnostic and therapeutic procedure for non-muscle invasive bladder cancer (NMIBC). The most common complications related to tumor resection include minor bleeding and irritative symptoms in the early postoperative period. Major complications, including uncontrolled hematuria and bladder perforation, may occur in approximately 5% of cases (2).

The obturator nerve is located near the inferolateral bladder wall, and it arises from the anterior rami of the second, third, and fourth lumbar nerves, descends through the psoas major and emerges from the psoas major medial border. The nerve then crosses into the pelvis at the level of the sacroiliac joint. At this point, it courses close to the wall of the bladder (3). TUR-BT localized close to the lateral side of the bladder may stimulate the obturator nerve and trigger adductor contraction, possibly causing inadvertent bladder perforation or an incomplete resection due to the hindrance of the tumor resection. However, spinal anesthesia combined with obturator nerve blockade in the obturator canal may be effective in preventing the adductor spasm (4). Various strategies are recommended to prevent undesirable adductor contractions due to obturator nerve stimulation. For instance, the incidence of obturator nerve stimulation can be reduced through attention to technical strategies, decreasing the intensity of energy, avoiding overdistention of the bladder and using anesthetic paralysis or giving general anesthesia during the resection of lateral wall-localized tumors to decrease the obturator reflex response (5-7).

Most bladder cancers (70-75%) are NMIBC during the initial diagnosis, and tumor recurrence is more common in NMIBC. Nearly 30% of patients have tumor recurrence within the first 3 months of having TUR-BT, and 50% of patients have a recurrent tumor at the 1-year follow-up (8). The major causes of recurrent tumor have been reported to be residual tumor tissue due to an incomplete resection or inability to obtain adequate muscle tissue during TUR-BT (9). The obturator reflex that occurs during TUR-BT may increase the risk of incomplete resection of the tumor, inability to sample the muscle tissue or tumour dissemination via bladder perforation.

In this study, we investigated the effect of obturator nerve blockade on oncological outcomes in patients undergoing TUR-BT for lateral wall-localized NMIBC.

Materials and Methods

We designed a retrospective cross-sectional observational study that was conducted between January 2015 and March 2020. A total of 315 patients with a diagnosis of NMIBC localized to the lateral wall of the bladder were analyzed at the İzmir Bakırçay University Çiğli Training and Research Hospital Urology Department and Recep Tayyip Erdogan University Urology Department. Patients with a history of previous TUR-BT, diagnosis of non-urothelial carcinoma, coagulopathy, history of allergic reaction to the local anesthetic agent, presence of muscle invasive bladder cancer, history of chemotherapy or radiotherapy before TUR-BT, presence of variant histopathology, use of bipolar energy for the resection of bladder tumor, the presence of concomitant upper urothelial tract urothelial carcinoma, neuromuscular disease, pregnancy, or history of medication affecting the immune system were excluded. Of the initial 315 patients, 209 were excluded from the study, and the remaining 106 patients were included (Figure 1). After local ethical committee permission was received (Recep Tayyip Erdoğan University Non-Invasive Clinical Research Ethics Committee; number: 2020/131, date: 01.07.2020), data from the patients with a diagnosis of NMIBC were recorded retrospectively from the hospital patient record system. Patients' demographic characteristics, localization, largest tumor size, histopathological type of tumor, presence of recurrence and/or progression, time to recurrence from initial TUR-BT, presence of muscle tissue in the surgical specimen, inability to complete resection, death from cancer, and both perioperative and postoperative complications were recorded for further statistical analyses.

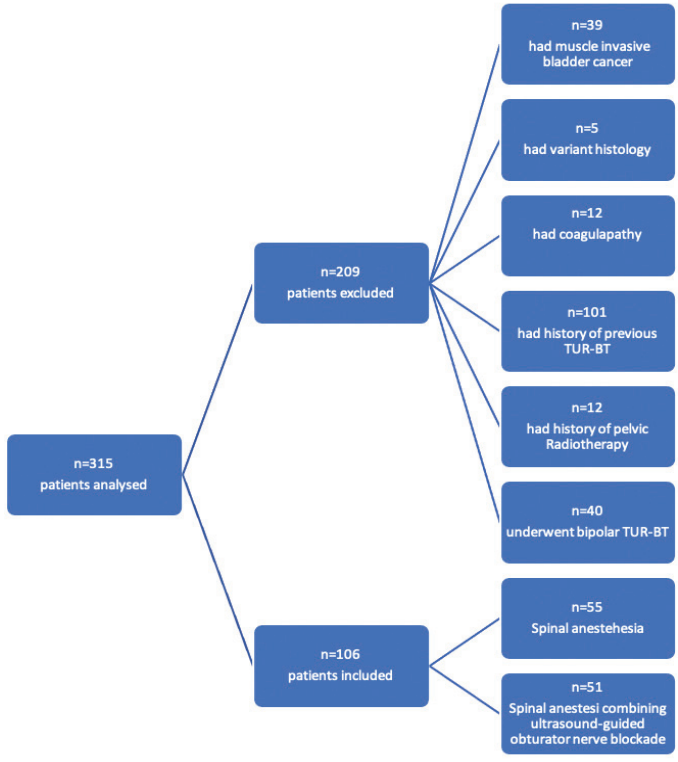

Figure 1. Clinical course of the study

All TUR-BT procedures were performed using monopolar energy for the resection of the tumor with a 26 Fr Karl-Storz resectoscope under 30-degree optical vision with adjustment to 120 joules for cutting and 80 joules for coagulation. Spinal anesthesia was performed in the operating room with the patient in a sitting position. The 25-gauge Quincke needle was inserted at the level of the L3-4 or L4-5 intervertebral space, and 10-15 mg of 2-3 mL 0.5% hyperbaric bupivacaine was administered through the needle into the subarachnoid space before the patient was repositioned to a supine position. After waiting for 10 min, and when sensorial blockade up to the T10 dermatome was observed, a lithotomy position was performed. Additional obturator nerve blockade with ultrasound guidance was performed according to the localization of the tumor. First, the antero-medial side of the femur was demonstrated with a two-dimensional 38 mm, 6-13 MHz ultrasound probe (Mindray, M7, Biomedical Electronics Co., Shenzhen, China). Afterward, a high-frequency probe was placed proximal to the adductor longus muscle to determine the adductor longus, brevis, and magnus muscles. When the obturator nerve was demonstrated between the muscle groups, the position of the nerve was confirmed by setting the current of the stimulator (Braun Stimuplex HNS11, B. Braun, Melsungen, Germany) to 1.5-2 mA and the duration of 0.1 ms. Using ultrasound vision, a 50 mm needle (21-gauge, 50 mm Stimuplex A, B. Braun, Melsungen, Germany) was inserted parallel to the long axis of the probe and guided to the anterior branch of the obturator nerve. After adductor contractions were observed at 0.3-0.5 mA, a maximum of 10 mL 2% lidocaine was injected through the needle. Surgery began 10 min later. During the surgery, patients were monitored using non-invasive blood pressure, pulse, and SpO_2 intraoperative electrocardiography.

Meta-analyses have reported no statistically significant differences between bipolar and monopolar TUR-BT in terms of obturator reflex and bladder perforation rates (10,11). In our study, all patients underwent monopolar TUR-BT due to the presence of controversial results in comparisons of bipolar versus monopolar techniques and current urology guidelines giving strong advice to use monopolar TUR-BT (12). Patients were divided into two groups according to the anesthesia used. While only spinal anesthesia was performed in Group 1, spinal anesthesia was combined with ultrasound-guided obturator nerve blockade according to the localization of the tumor for Group 2. The groups were compared statistically in terms of oncological outcomes. In patients with an incomplete resection, another TUR-BT was performed 4-6 weeks after the first TUR-BT. Intravesical immunotherapy using Bacillus Calmette-Guerin (BCG) was performed based on pathological results and recommendations of the European Urology Guidelines for non-muscle invasive bladder cancer.

The first follow-up was performed with all patients the third month after the initial TUR-BT, and subsequent follow-ups were performed every 3 months up to 2 years, then every 6 months up to 5 years and 1 per year after 5 years. A detailed history, physical examination, cystoscopic examination, and urinary cytology were collected at each follow-up (12).

Statistical Analysis

All statistical analyses were conducted using the SPSS Statistics 26.0 (IBM Inc., Armonk, NY, US) software package. Categorical variables were described with frequencies and percentages; continuous variables were described with means and standard deviations. The Kolmogorov-Smirnov test was used to evaluate the normality of the distributions, and the Mann-Whitney U test was used to compare groups and quantitative independent data. The chi-square test was used for qualitative independent data. Spearman's correlation analysis was applied for correlation, and the Kaplan-Meier test was used to calculate survival statistics. A p-value less than 0.05 was chosen as the criterion for statistical significance.

Results

The mean age of the patients was 64.71±11.70 years. The mean follow-up time was 39.75±14.61 months. There were 85 (80.2%) male patients and 21 (19.8%) females. A total of 40 patients (37.7%) underwent a second TUR-BT after the initial TUR-BT due to incomplete resection or absence of muscle tissue sampling in the surgical specimens. In terms of complications, three patients (2.8%) had bladder perforation, six patients (5.7%) had hematuria and 10 patients (9.4%) had cystitis. All patients who had bladder perforation were extraperitoneal and managed with catheterization. No patient needed open laparotomy for bladder perforation.

In Group 1, 55 patients (51.9%) underwent TUR-BT with only spinal anesthesia, and 51 patients (48.1%) underwent TUR-BT using spinal anesthesia combined with ultrasound-guided obturator nerve blockade (Group 2). In all, the efficacy rate of the obturator nerve blockade was 92.1%. The patients' initial characteristics, which were collected during the first diagnosis, are summarized in Table 1. Recurrent tumor was observed in 25 patients (45.5%) in Group 1 and 11 patients (21.6%) in Group 2. Additionally, tumor progression was observed in eight patients (14.5%) in Group 1 and two patients (3.9%) in Group 2. For all patients, the 1-year overall recurrence-free survival (RFS) was 99.0%, whereas the overall 5-year RFS was 49.3%. In Group 1, the 1-year RFS was 98.0% and the 5-year RFS was 23.5%. In Group 2, the 1-year and 5-year RFSs were 97.4% and 57.2%, respectively (Figure 2).

Single-dose adjuvant chemotherapy was administered to 22 patients (40.0%) in Group 1 and 18 patients (35.3%) in Group 2. Adjuvant intravesical immunotherapy was administered to 20 patients (36.4%) in Group 1 and 21 patients (41.2%) in Group 2.

Table 1. Patients' initial characteristics at diagnosis	
Age, mean ± standard deviation (SD), years	64.71±11.70
Gender, n (%)	
Male	85 (80.2%)
Female	21 (19.8%)
Diabetes mellitus, n (%)	
Present	87 (82.1%)
Absent	19 (17.9%)
Hypertension, n (%)	
Present	66 (62.3%)
Absent	40 (37.7%)
Tumor size, mean ± SD, mm	3.21±1.43
Tumor localization, n (%)	
Left	62 (58.5%)
Right	44 (41.5%)
T stage, n (%)	
Ta	72 (67.9%)
T1	34 (32.1%)
Grade, n (%)	
Low grade	68 (64.2%)
High grade	38 (35.8%)
Recurrence, n (%)	
Present	36 (34.0%)
Absent	70 (66.0%)
Progression, n (%)	
Present	10 (9.4%)
Absent	96 (90.6%)

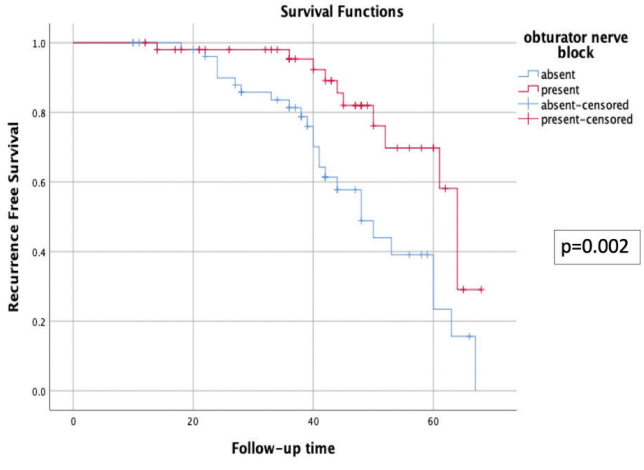

Figure 2. Group Kaplan-Meier curves in terms of recurrence-free survival

Maintenance immunotherapy could be completed in 14 patients (25.5%) in Group 1 and 10 patients (19.6%) in Group 2. 22 (88.8%) patients had a recurrent tumor and 8 (40.3%) had tumor progression, although received intravesical immunotherapy with BCG in group 1. In Group, 11 (4.7%) patients had a recurrent tumor and 2 (9.5%) had tumor progression, although received immunotherapy with BCG ($p<0.001$). While no death due to bladder cancer was observed in our study, one patient died from acute myocardial infarction. The oncological outcomes of the groups are summarized in Table 2. Statistical significance was observed in differences between the groups in terms of tumor size, recurrence rate, adequate muscle tissue sampling, ability to complete resection, and persistent obturator reflex. In the Spearman's correlation analysis, we observed a positive correlation between obturator nerve blockade and tumor size, adequate muscle tissue sampling, and ability to complete the resection. There were also negative correlations of the obturator nerve blockade with tumor recurrence and persistent obturator reflex (Table 3).

Discussion

In this study, we investigated the effects of an obturator nerve blockade on oncological outcomes in patients who underwent TUR-BT. The results revealed that ultrasound-guided obturator nerve blockade combined with spinal anesthesia was associated with lower rates of tumor recurrence and tumor progression and better rates of RFS, tumor size, adequate muscle tissue, and complete resection. The ultrasound-guided obturator nerve blockade combined with spinal anesthesia correlated positively with tumor size, adequate muscle tissue sampling and complete resection rates and a negative correlation with tumor recurrence and persistent obturator reflex.

TUR-BT is the gold standard method for both the initial diagnosis and treatment of patients with NMIBC. The frequency of severe adductor muscle contractions during the transurethral resection of laterally located bladder tumors has been reported to be approximately 20% (13). Major complications, such as bladder perforation and excessive hemorrhage, incomplete resection of tumor and inadequate sampling of muscle tissue in surgical specimens, may occur during resection due to adductor muscle contractions via stimulation of the obturator nerve (14). To prevent this undesirable adductor reflex, obturator nerve blockade with ultrasound guidance was recommended in several studies (5,15,16). First, Labat (17) described an obturator nerve blockade with a nerve stimulator in 1922. Afterwards, Wassef (18) described the inter-adductor approach, Khorammi et al. (2) described the transvesical approach using a nerve stimulator, Choquet et al. (19) studied the inguinal approach to block the obturator nerve, and several studies have compared sonographic

Table 2. Comparison of group oncological outcomes			
	Group 1 n=55	**Group 2 n=51**	**p-value**
Tumor size, mean ± standard deviation (SD), mm	2.90±1.43	3.55±1.37	**0.030**
T stage, n (%)			0.131
Ta	41 (74.5%)	31 (60.8%)	
T1	14 (25.5%)	20 (39.2%)	
Grade, n (%)			0.057
Low grade	40 (72.7%)	28 (54.9%)	
High grade	15 (27.3%)	23 (45.1%)	
Muscle tissue sampling, n (%)			
Absent	15 (27.3%)	4 (7.8%)	**0.010**
Present	40 (70.2%)	47 (92.2%)	
Resection, n (%)			
Incomplete	10 (18.2%)	2 (3.9%)	**0.021**
Complete	45 (81.8%)	49 (96.1%)	
Obturator reflex, n (%)			**0.003**
Absent	38 (69.1%)	47 (92.2%)	
Present	17 (30.9%)	4 (7.8%)	
Recurrence, n (%)			**0.010**
Absent	30 (54.5%)	40 (78.4%)	
Present	25 (45.5%)	11 (21.6%)	
Progression, n (%)			0.106
Absent	47 (85.5%)	49 (96.1%)	
Present	8 (14.5%)	2 (3.9%)	
Time to recurrence mean ± SD, months	4.44±6.02	7.76±15.66	0.097
Complications, n (%)			
Hematuria	5 (9.1%)	1 (2.0%)	0.117
Cystitis	5 (9.1%)	5 (9.8%)	
Bladder perforation	3 (5.5%)	0	

Table 3. Correlation coefficients of study parameters (Spearman's correlation)								
	Obturator nerve blockade	**Presence of muscle tissue**	**Complete resection**	**Tumor size**	**Recurrence**	**Progression**	**Time to recurrence**	**Complication**
Obturator nerve blockade	1							
Presence of muscle tissue	**0.253****	1						
Complete resection	**0.225***	**0.532****	1					
Tumor size	**0.208***	0.089	0.056	1				
Recurrence	**–0.252****	-0.132	-0.058	0.039	1			
Progression	-0.182	-0.102	-0.088	–0.038	**0.382****	1		
Time to recurrence	-0.162	-0.055	-0.015	0.038	**0.955****	**0.393****	1	
Complication	-0.153	0.032	-0.049	0.044	0.179	0.106	0.142	1

Values in bold are statistically significantly different. *p<0.05, **p<0.01

demonstrations of obturator nerve-to-nerve stimulation methods (20). In a recent study, Smith described a combined ultrasound and nerve stimulator approach (21). Despite all of these techniques effectively blocking the obturator nerve, undesirable adductor muscle spasms may still occur during TUR-BT, even when an obturator nerve block is performed correctly, due to variations in the obturator nerve's ramifications (22). The efficacy rate of obturator nerve blockade is between 84% and 96%, according to several studies (23,24). In our study, we performed a combination of ultrasound guidance and nerve stimulator to block the obturator nerve, and our efficacy rate was 92.1%, meaning it was as effective as the rates reported in other studies.

Although an obturator nerve blockade is an intervention that reassures physicians during surgery and reduces the rate of peroperative complications, its contribution to oncological outcomes is not yet clear. Erbay et al. (25) showed that patients with lateral wall-localized NMIBC who underwent spinal anesthesia combined with obturator nerve blockade had longer RFS than patients who received only spinal anesthesia. In addition, rates of complete resection and the presence of muscle tissue in the surgical specimen were higher in patients who received an obturator nerve blockade combined with spinal anesthesia (25). Tekgül et al. (16) reported that patients with a lateral wall-localized bladder tumor and where an obturator nerve blockade was used had a prolonged time to recurrence compared to patients without an obturator nerve blockade. We observed a significantly increased RFS in patients who received an obturator nerve blockade, but we did not find any significant difference in prolonged time to recurrence.

The presence of detrusor muscle tissue in the specimen provides accurate pathologic staging that allows for the determination of an adequate follow-up protocol and potential adjuvant treatment according to tumor grade and invasiveness. Additionally, a complete resection of all tumor tissues significantly reduces the risk of NMIBC recurrence and progression. Understaging of NMIBCs at the first resection due to the lack of detrusor muscle in the resected specimen is reported in up to 49% of patients, compared with 14% for patients with adequate muscle tissue sampling (26,27). In our study, we found lower inadequate muscle tissue sampling and higher detrusor muscle complete resection rates in the obturator nerve blockade group.

The recurrence rate in the first year after an incomplete resection is 15-61% in Ta and T1 tumors (12). The presence of residual tumor tissue after a TUR-BT procedure increases recurrence rates and decreases RFS. One study investigating the presence of residual tumor in the marginal resection after a complete TUR-BT of Ta/T1 transitional urinary bladder cancer reported that 26% of patients had residual tumor tissue after a complete resection of Ta/T1 bladder tumors (28). This possibility increases further with undesirable conditions, such as the obturator reflex during the resection of tumors located in the lateral wall of the bladder. Our results were similar. In our study, RFS was longer in patients who underwent spinal anesthesia combined with obturator nerve blockade, and no patients had tumor progression. Moreover, we observed that patients who received an obturator nerve blockade had a higher pathological T stage according to the TNM classification and decreased recurrence progression rates compared with patients who did not receive an obturator nerve blockade.

Another challenging complication due to adductor spasm from stimulation of the obturator nerve during resection is bladder perforation. Several studies have reported bladder perforation due to the obturator reflex in 0.9% to 5% of cases (29,30). Bladder perforation can lead to extravesical dissemination of the tumor (31). In our study, only three patients (2.8%) had extraperitoneal bladder perforation, and they were treated with only a urinary catheter. Open laparotomy was not required in any patient with bladder perforation, and no pelvic mass was observed at follow-ups due to extravesical tumor dissemination.

Study Limitations

This study has some limitations. First, due to the retrospective design of the study, randomization could not be included. Second, the study population was small, and due to the population size, we could not reach statistical significance in terms of some variables, such as time to recurrence.

Conclusion

This study revealed that patients with NMIBC localized to the lateral wall of the bladder who received an obturator nerve blockade combined with spinal anesthesia had a significantly increased RFS, decreased major peroperative complication rate, increased rate of complete resection, and adequate detrusor muscle sampling. The obturator nerve blockade combined with spinal anesthesia also contributed to the correct staging of patients with lateral wall-localized NMIBC, which plays a critical role in subsequent treatment.

Ethics

Ethics Committee Approval: After local ethical committee permission was received (Recep Tayyip Erdoğan University Non-Invasive Clinical Research Ethics Committee; number: 2020/131, date: 01.07.2020).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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References

1. Seo M, Langabeer Ii JR. Demographic and Survivorship Disparities in Non-muscle-invasive Bladder Cancer in the United States. J Prev Med Public Health 2018;51:242-247.
2. Khorrami MH, Javid A, Saryazdi H, Javid M. Transvesical blockade of the obturator nerve to prevent adductor contraction in transurethral bladder surgery. J Endourol 2010;24:1651-1654.
3. Panagoda PI, Vasdev N, Gowrie-Mohan S. Avoiding the Obturator Jerk during TURBT. Curr Urol 2018;12:1-5.
4. Hızlı F, Argun G, Güney I, Güven O, Arık AI, Başay S, Günaydın H, Başar H, Köşüş A. Obturator nerve block transurethral surgery for bladder cancer: comparison of inguinal and intravesical approaches: prospective randomized trial. Ir J Med Sci 2016;185:555-560.
5. Tatlisen A, Sofikerim M. Obturator nerve block and transurethral surgery for bladder cancer. Minerva Urol Nefrol 2007;59:137-141.
6. Cesur M, Erdem AF, Alici HA, Yapanoglu T, Yuksek MS, Aksoy Y. The role of succinylcholine in the prevention of the obturator nerve reflex during transurethral resection of bladder tumors. Saudi Med J 2008;29:668-671.
7. Alavi CE, Asgari SA, Falahatkar S, Rimaz S, Naghipour M, Khoshrang H, Jafari M, Herfeh N. Effectiveness of spinal anesthesia combined with obturator nerve blockade in preventing adductor muscle contraction during transurethral resection of bladder tumor. Turk J Urol 2017;43:507-511.
8. Brausi M, Collette L, Kurth K, van der Meijden AP, Oosterlinck W, Witjes JA, Newling D, Bouffioux C, Sylvester RJ; EORTC Genito-Urinary Tract Cancer Collaborative Group. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol 2002;41:523-531.
9. Capogrosso P, Capitanio U, Ventimiglia E, Boeri L, Briganti A, Colombo R, Montorsi F, Salonia A. Detrusor Muscle in TUR-Derived Bladder Tumor Specimens: Can We Actually Improve the Surgical Quality? J Endourol 2016;30:400-405.
10. Cui Y, Chen H, Liu L, Chen J, Qi L, Zu X. Comparing the Efficiency and Safety of Bipolar and Monopolar Transurethral Resection for Non-Muscle Invasive Bladder Tumors: A Systematic Review and Meta-Analysis. J Laparoendosc Adv Surg Tech A 2016;26:196-202.
11. Liem EIML, McCormack M, Chan ESY, Matsui Y, Geavlete P, Choi YD, de Reijke TM, Farahat Y, Inman BA, de la Rosette JJMCH, Naito S. Monopolar vs. bipolar transurethral resection for non-muscle invasive bladder carcinoma: A post-hoc analysis from a randomized controlled trial. Urol Oncol 2018;36:338.e1-338.e11.
12. Babjuk M, Böhle A, Burger M, Capoun O, Cohen D, Compérat EM, Hernández V, Kaasinen E, Palou J, Rouprêt M, van Rhijn BWG, Shariat SF, Soukup V, Sylvester RJ, Zigeuner R. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol 2017;71:447-461.
13. Prentiss RJ, Harvey GW, Bethard WF, Boatwright DE, Pennington RD. Massive Adductor Muscle Contraction in Transurethral Surgery: Cause And Prevention; Development Of Electrical Circuitry. J Urol 1965;93:263-271.
14. Mydlo JH, Weinstein R, Shah S, Solliday M, Macchia RJ. Long-term consequences from bladder perforation and/or violation in the presence of transitional cell carcinoma: results of a small series and a review of the literature. J Urol 1999;161:1128-1132.
15. García Rodríguez J, Jalón Monzón A, González Alvarez RC, Ardura Laso C, Fernández Gomez JM, Rodríguez Martinez JJ, Martínez Gómez FJ, Regadera Sejas J, González Huergo F. Tecnica alternativa para prevenir la estimulación del nervio obturador durante la RTU vesical de neoformaciones en cara lateral [An alternative technique to prevent obturator nerve stimulation during lateral bladder tumours transurethral resection]. Actas Urol Esp 2005;29:445-447.
16. Tekgül ZT, Divrik RT, Turan M, Konyalioğlu E, Şimşek E, Gönüllü M. Impact of obturator nerve block on the short-term recurrence of superficial bladder tumors on the lateral wall. Urol J 2014;11:1248-1252.
17. Labat G. Regional Anesthesia: Its Technic and Clinical Application. Philadelphia, PA: WB Saunder; 1923.
18. Wassef MR. Interadductor approach to obturator nerve blockade for spastic conditions of adductor thigh muscles. Reg Anesth 1993;18:13-17.
19. Choquet O, Capdevila X, Bennourine K, Feugeas JL, Bringuier-Branchereau S, Manelli JC. A new inguinal approach for the obturator nerve block: anatomical and randomized clinical studies. Anesthesiology 2005;103:1238-1245.
20. Manassero A, Bossolasco M, Ugues S, Palmisano S, De Bonis U, Coletta G. Ultrasound-guided obturator nerve block: interfascial injection versus a neurostimulation-assisted technique. Reg Anesth Pain Med 2012;37:67-71.
21. Smith HE, Borowski W, Bohm M, et al. Ultrasound-guided selective block of the anterior branch of the obturator nerve for transurethral resection of bladder tumor. J Clin Urol 2016;9:351–355.
22. Yoshida T, Nakamoto T, Kamibayashi T. Ultrasound-Guided Obturator Nerve Block: A Focused Review on Anatomy and Updated Techniques. Biomed Res Int 2017;2017:7023750.
23. Jo YY, Choi E, Kil HK. Comparison of the success rate of inguinal approach with classical pubic approach for obturator nerve block in patients undergoing TURB. Korean J Anesthesiol 2011;61:143-147.
24. Ahmed N, Haider MZ, Ahmed F, Rana SM, Mahmood A, and Alvi MS. Obturator nerve block: transurethral resection of lateral bladder wall tumors (TUR-BT). Professional Med J 2009;16:48–52.
25. Erbay G, Akyol F, Karabakan M, Celebi B, Keskin E, Hirik E. Effect of obturator nerve block during transurethral resection of lateral bladder wall tumors on the presence of detrusor muscle in tumor specimens and recurrence of the disease. Kaohsiung J Med Sci 2017;33:86-90.
26. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol 2001;165:808-810.
27. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999;162:74-6.
28. Jancke G, Rosell J, Jahnson S. Residual tumour in the marginal resection after a complete transurethral resection is associated with local recurrence in Ta/T1 urinary bladder cancer. Scand J Urol Nephrol 2012;46:343-347.
29. Ploeg M, Aben KK, Kiemeney LA. The present and future burden of urinary bladder cancer in the world. World J Urol 2009;27:289-293.
30. Dick A, Barnes R, Hadley H, Bergman RT, Ninan CA. Complications of transurethral resection of bladder tumors: prevention, recognition and treatment. J Urol 1980;124:810-811.
31. Collado A, Chéchile GE, Salvador J, Vicente J. Early complications of endoscopic treatment for superficial bladder tumors. J Urol 2000;164:1529-1532.

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The Effect of Targeted Antibiotic Prophylaxis on Lower Urinary Tract Symptoms Following Prostate Biopsy: A Prospective Randomized Trial

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What's known on the subject? and What does the study add?

Prostate biopsy is the most common diagnostic procedure in urology practice. It is generally an easily applicable and well-tolerated method, but lower urinary tract symptoms (LUTS) has an important place among the increasing complication rates recently. There is no consensus in the literature regarding risk factors and prophylactic measures for biopsy-associated LUTS. Targeted antibiotic prophylaxis is recommended by recent studies and guidelines, especially for patients at risk. In our study, it was seen that targeted prophylaxis had a significant effect on biopsy-associated LUTS, and it could be an important method in preventing LUTS complaints.

Abstract

Objective: Targeted antibiotic prophylaxis in prostate biopsy is recommended for patients at risk due to increased complication rates seen in recent years. Lower urinary tract symptoms (LUTS) is currently one of the most prevalent complications with a rate of more than 40%. The study examined the effects of targeted antibiotic prophylaxis on biopsy-related LUTS and to compare the results with standard prophylaxis.

Materials and Methods: A total of 240 patients were included in the study, 120 of whom had been administered targeted antibiotic prophylaxis and 120 of whom had received ciprofloxacin treatment between January 2021-Januray 2023. Patients' results before the procedure, on the 7th day, and in the first month were prospectively recorded and compared.

Results: While Qmax mean values were measured as 18.3±5.1 mL/s in the targeted prophylaxis group and 17.4±4.6 mL/s in the control group (p=0.157) before the procedure, these values were found to be 14.6±3.3 mL/s and 11.7±4.1 mL/s (p<0.001) on the 7th day and 16.8 16.8±4.3 mL/s and 14.9±3.5 mL/s (p=0.013) in first month, respectively. IPSS mean scores of the groups were calculated as 16.8±4.3 mL/s and 14.9±3.5 mL/s (p=0.013) before the procedure, respectively, while these scores were found to be 18.12±6.1 and 22.97±7.4 (p<0.001) on the 7th day and 17.5±5.5 and 22.8±7.5 (p<0.001) in the first month, respectively.

Conclusion: In this study, we found that targeted antibiotic prophylaxis had a significant effect on preventing biopsy-related LUTS. We believe that routine application of targeted antibiotic prophylaxis can be effective in reducing the rates of biopsy-related LUTS.

Keywords: Prostate biopsy, prostate cancer, targeted prophylactic antibiotherapy, lower urinary tract symptoms

Introduction

Prostate cancer is the most prevalent solid organ cancer observed in males, and it is the second most prevalent type of cancer that leads to malignancy-related mortality worldwide (1). The prevalence of prostate cancer increases by 2-3% every year in Europe and the USA (2). Among the reasons for this increase are the widespread use of prostate-specific antigen (PSA) screening tests and the increasing role of multiparametric magnetic resonance imaging applied in the pre-biopsy period (3). Hence, prostate biopsy is the most frequently used diagnostic procedure in urology, and its application number in Europe and the USA is more than two million (4). Most of these applications are performed with a transrectal approach, and although there are new techniques developing today, the most frequently used

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method is still transrectal ultrasound (TRUS) guided biopsy, which is also the standard procedure for pathological sampling in the diagnosis of prostate cancer (5).

TRUS guided prostate biopsy is a method that is easily applied and well tolerated. However, a significant increase in biopsy-related complications has recently been reported (6). One of the current debates over this issue is related to antibiotic prophylaxis to be applied before the procedure. In studies conducted and American Urological Association guidelines, it has been stated that targeted antibiotic prophylaxis applied because of culture obtained through rectal swab is more successful compared to standard fluoroquinolones prophylaxis or augmented prophylaxis, and that a decrease by 84% in complication rates has been achieved (7).

Lower urinary tract symptoms (LUTS) that develop following prostate biopsy are among the more frequently observed complications compared to infectious complications such as fever and sepsis (8). These complaints usually develop because of a biopsy procedure and causes related to the application procedure such as trauma, edema, inflammation, and infection. The probability of LUTS development following TRUS-guided prostate biopsy is reported to be 40% (9). In the literature, there are studies that were conducted in order to determine risk factors for urination complaints that may develop after TRUS-guided prostate biopsy and in which medical agents that could be applied prophylactically for LUTS were used; however, there is no clear procedure related to this issue (10).

In relevant guidelines, targeted antibiotic prophylaxis is recommended especially in risky patients due to its effect on post-biopsy complications (11). However, the number of prospective randomized trials that examined the effects of this procedure on LUTS is rather limited. Therefore, it was aimed in the present study to examine whether targeted antibiotic prophylaxis has a more significant effect on LUTS compared to fluoroquinolone prophylaxis and to discuss the results obtained considering the literature.

Materials and Methods

In the study, the data of 240 patients who underwent prostate biopsy between January 2021 and January 2023 and were followed up by prospectively recording their information were analyzed. Using GPower 3.1 software, it was calculated that the sample size should be at least n=220 (110+110) for a statistical power of 0.95 at alpha=0.05 level. The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the local ethics committee of Ordu University, Turkiye (approval no: 2021/208, date: 23.09.2021). Written informed consent of the patients included in the study was obtained before the procedure.

TRUS - guided 12-quadrant prostate biopsy was applied to patients who presented to the urology outpatient clinic and who had serum PSA levels of 4 ng/mL and abnormal digital rectal examination findings. The patients were divided into two groups according to pre-planned randomization. While routine ciprofloxacin prophylaxis was applied to one group of patients, the other group was administered antibiotic prophylaxis in line with the antibiogram obtained from the rectal sample, which was previously taken through the rectal swab method. Antibiotic prophylaxis was applied as 1-day prophylaxis, once 2 h prior to the procedure and once at the 12th hour post-procedure 12th hour.

The patients' age, body mass index (BMI), comorbidities, biochemical parameters, serum PSA values, medical treatment for BPO, antibiogram results of the targeted antibiotic prophylaxis group and antibiotic agents used in prophylaxis, number of nocturia, maximum urinary flow rate (Qmax) values, prostate volumes (P.V.), and international prostate symptom scores and detailed points were analyzed.

The International Prostate Symptom Score (IPSS) is a validated and current 7-item questionnaire that inquires about patients' lower urinary tract complaints. It examines incomplete emptying (urinary retention), need to urinate again in less than 2 h (frequency), intermittent urination (intermittency), inability to hold urination (urgency), decrease in urinary flow rate (weak stream), difficulty in starting urination (straining), and number of nocturia. Also, it is a commonly used questionnaire in diagnosis and follow-up of patients with the addition of quality of life to urinary symptoms.

Patients who were below the age of 40 years, who had life expectancy of less than 10 years, who had undergone rectal or pelvic surgery, who had active urinary system infection, who received pelvic radiotherapy, who were suspected to have neurogenic urination symptoms, whose postvoiding residue amount was more than 150 mL, whose Qmax value was below 15 mL/s and who needed additional treatment for BPO, and who had rectal anomaly or a disease that might affect rectal flora were excluded from the study.

Statistical Analysis

In the analysis of the data obtained because of the study, SPSS 21.0 package software was used. Kolmogorov-Smirnov test was employed in determining whether the data were normally distributed. Nonparametric tests of Mann-Whitney U, Wilcoxon Signed-Ranks test, and mixed pattern ANOVA were used in the analysis of the data. Statistical significance level was set as $p<0.05$.

Results

In the group that was administered targeted antibiotic prophylaxis, the mean age was found to be 65.6±7.2 years (n=120), while it was determined to be 65.3 65.3±6.4 years (n=120) in the control group. BMI values were calculated as 28.7±3.7 kg/m^2 and 29.3±4.2 kg/m^2, respectively (p=0.858). No significant difference was found between the groups in terms of systemic diseases and prevalence rates (Table 1). The mean serum PSA value measured before the procedure was found to be 24.45±6.66 ng/mL in the targeted antibiotic phylaxis group, while it was determined to be 25.41±6.53 ng/mL in the control group, with no significant difference between them (p=0.958). No significant difference was observed between the groups before the procedure in terms of inflammatory parameters of C-reactive protein (p=0.919), sedimentation (p=0.501), fibrinogen (p=0.444) values, blood count results, and biochemical parameters (Table 2).

According to the antibiogram results of the group from which rectal swab was taken, the most frequently growing agents were *Escherichia coli* in 74 patients (62%), enterobacterial in 22 patients (18%), klebsiella in 14 patients (12%), and pseudomonas in 10 patients (8%). In line with the antibiogram results, antibiotic agents administered the most were ceftriaxone in 44 patients (36.7%), gentamicin in 30 patients (25%), amikacin in 22 patients (18.3%), ceftazidime in 14 patients (11.7%), and ciprofloxacin in 10 patients (8.3%) (Figure 1).

When LUTS prevalence was questioned as yes/no after the biopsy was applied to the patients, 36 patients (30%) in the targeted antibiotic prophylaxis group responded as yes, while 70 patients (58.3%) responded as yes (p=0.002). The number of urinations during the daytime was 4.8±2.1 in the prophylactic group and 4.7±2.3 (p=0.775) in the control group before the procedure, while it was found to be 5.6±2.7 and 7.7±3.5 (p=0.03) respectively on the post-procedure 7th day and 5.5±2.8 and 6.8±3.7 (p=0.044) respectively in the post-procedure 1st month.

In the pre-procedure period, while the Qmax value was determined as 18.3±5.1 mL/s in the prophylaxis group, it was measured as 17.4±4.6 mL/s in the control group (p=0.157). The Qmax value was measured as 14.6±3.3 mL/s and 11.7±4.1 mL/s on the post-procedure 7th day (p<0.001), and it was calculated to be 16.8±4.3 mL/s and 14.9±3,5 mL/s (p=0.013) respectively in the post-procedure 1st month. The mean P.V. value before the procedure was 50.77±25 mL in the targeted prophylaxis group and 46.47±27 mL in the control group (p=0.511).

Table 1. Systemic diseases and their distribution in the groups

Comorbidities	Targeted prophylaxis n (%)	Control n (%)	p
Diabetes Mellitus	30 (25.0%)	36 (30.0%)	0.580
Hypertension	32 (26.6%)	33 (27.5%)	0.856
Cardiac	32 (26.6%)	28 (23.3%)	0.676
COPD, asthma	14 (11.7%)	8 (6.7%)	0.347
Neurological	6 (5.0%)	12 (10.0%)	0.315
Psychological	6 (5.0%)	18 (15.0%)	0.74

COPD: Chronic obstructive pulmonary disease

Table 2. Distribution of serum parameters in the groups

Groups	Targeted prophylaxis	Control	p
PSA (ng/dL)	24.45±95.9	25.41±87.35	0.985
Creatinine	0.94±0.21	1.02±0.30	0.108
CRP	0.58±1.28	0.61±1.03	0.919
Sedimentation	13.4±9.2	15.0±14.9	0.501
Fibrinogen	363.6±89.1	375.21±83.5	0.444
LDH	198.48±54.0	191.22±46.47	0.474
Calcium	9.38±0.4	9.53±0.7	0.184
Hemoglobin (g/dL)	14.76±1.28	14.57±1.57	0.503
WBC	7.07±1.5	7.6±2.1	0.133

CPR: C-reactive protein, LDH: Lactate dehydrogenase, PSA: Prostate specific antigen, WBC: White blood cell

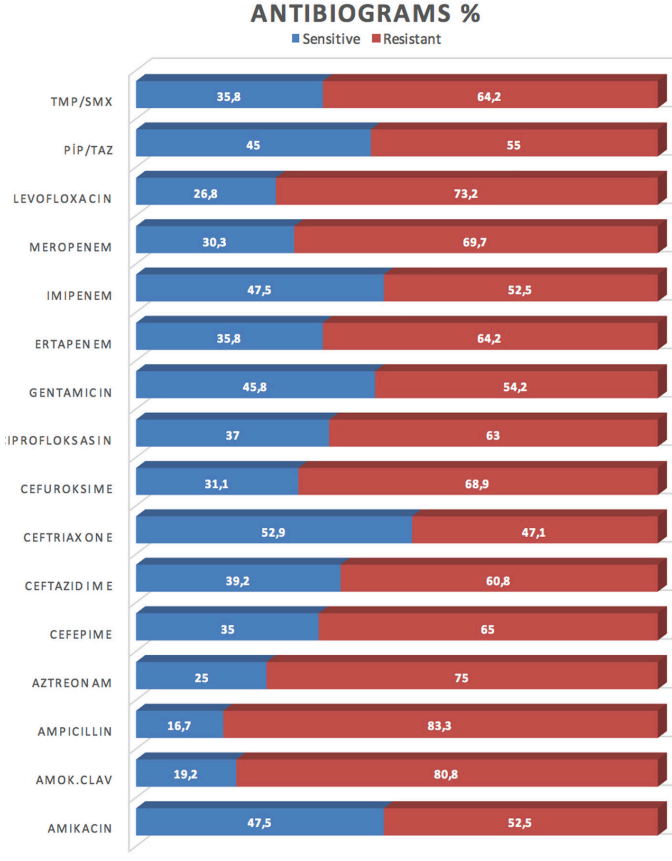

Figure 1. Antibiogram profiles obtained by rectal swab

In the evaluations made over the patients' IPSS questionnaire items and their total scores, the feeling of residue after urination before the procedure was found to be 2.08±1.0 in the prophylaxis group and 2.32±1.1 (p=0.055) in the control group, while these values were 2.37±1.3 and 3.10± 1.6 (p=0.009), respectively, on the post-procedure 7th day and 2.22±1.2 and 2.95±1.5 (p=0.006) respectively in the post-procedure 1st month. The patients' need for urination in less than 2 h was determined as 1.78±0.7 in the prophylaxis group and 2.25±0.9 (p=0.004) in the control group, while it was 2.08±0.9 and 2.86±1.3 (p<0.001) respectively on the post-procedure 7th day and 2.07±0.9 and 2.98±1.7 (p<0.001) respectively in the post-procedure 1st month. The patients' intermittent urination complaints before the procedure were found to be 1.88 1.88±0.7 in the prophylactic group and 2.05±0.9 (p=0.69) in the control group, while they were 2.93±1.1 and 3.57±1.5 (p<0.001) respectively on the post-procedure 7th day and 2.53±1.1 and 3.52±1.5 (p<0.001) respectively in the post-procedure 1st month. The patients' complaints regarding difficulty in holding urination before the procedure were found to be 1.82 1.82±0.7 in the prophylaxis group and 2.28±1.1 (p=0.007) in the control group, while they were 2.43±1.2 and 3.13±1.5 (p=0.006) respectively on the post-procedure 7th day and 2.35±1.1 and 3.08±1.4 (p=0.003) respectively in the post-procedure 1st month. Decreases in urinary flow rate before the procedure were found to be 1.95 1.95±0.8 and 2.22±1.2 (p=0.139) in the prophylaxis group and the control group, respectively, while they were 2.83 2.83±1.3 and 3.18±1.5 (p=0.175) respectively on the post-procedure 7th day and 2.73±1.2 and 3.25±1.4 (p=0.039) respectively in the post-procedure 1st month. Difficulty in starting urination before the procedure was found to be 1.68±0.8 and 2.37±1.1 (p<0.001) in the two groups, respectively, while it was 2.43±1.1 and 3.15±1.4 (p=0.003) on the post-procedure 7th day and 2.37±1.0 and 3.17±1.4 (p=0.001) in the post-procedure 1st month. Finally, nocturia complaint before the procedure was found as 3.03±1.5 and 3.08±1.4 (p=0.859) in the groups, respectively, while this value was 3.33±1.5 and 3.85±1.4 (p=0.063) on the post-procedure 7th day and 3.23±1.5 and 3.88±1.4 (p=0.02) in the post-procedure 1st month (Table 3).

While the patients' quality of life (QoL) score before the procedure was 2.4±1.0 in the targeted prophylaxis antibiotic group and 2.7±1.3 (p=0.057) in the control group, it was determined to be 2.8±1.3 and 3.6±.1.6 (p=0.004) respectively on the post-procedure 7th day and 2.6±1.1 and 3.5±1.6 (p=0.002) respectively in the post-procedure 1st month.

Discussion

In this study, it was determined that the application of targeted antibiotic prophylaxis before prostate biopsy was significantly effective on LUTS with respect to standard prophylaxis. When IPSS total scores of the patients who underwent prostate biopsy were examined, it was seen that this value was 13.93±4.1 in the prophylaxis group and 16.67±5.6 before the procedure (p=0.03), while their scores were calculated as 18.1±6.1 and 22.9±7.4 respectively on the post-procedure 7th day, which was a statistically significant difference (p<0.001). The patients' total scores were calculated as 17.5±5.5 and 22.8±7.5 respectively in the post-procedure 1st month (p<0.001) (Table 3). When the effective factors on the values in both patient groups were analyzed, it was seen that the increase in the scores of the prophylaxis group determined in the measurements performed at different times was statistically significantly lower according to the mixed pattern ANOVA test compared to the control group (p<0.001). It was determined that targeted antibiotic prophylaxis had a positive effect in terms of preventing LUTS that might develop after prostate biopsy compared to the control group (p=0.001) (Figure 2).

LUTS is among the leading complications that are frequently seen the most following prostate biopsy with rates reaching up

Table 3. Comparison of IPSS questions before the procedure, on the 7th day and in the1st month

	Before			7th day			1st month		
IPSS	Targeted Prophylaxis	Control	p	Targeted Prophylaxis	Control	p	Targeted Prophylaxis	Control	p
Q1	2.08±1.0	2.32±1.1	0.055	2.37±1.3	3.10±1.6	0.009	2.22±1.2	2.95±1.5	0.006
Q2	1.78±0.7	2.25±0.9	0.004	2.08±0.9	2.86±1.3	<0.001	2.07±0.9	2.98±1.7	<0.001
Q3	1.88±0.7	2.05±0.9	0.69	2.93±1.1	3.57±1.5	<0.001	2.53±1.1	3.52±1.5	<0.001
Q4	1.82±0.7	2.28±1.1	0.007	2.43±1.2	3.13±1.5	0.006	2.35±1.1	3.08±1.4	0.003
Q5	1.95±0.8	2.22±1.2	0.139	2.83±1.3	3.18±1.5	0.175	2.73±1.2	3.25±1.4	0.039
Q6	1.68±0.8	2.37±1.1	<0.001	2.43±1.1	3.15±1.4	0.003	2.37±1.0	3.17±1.4	0.001
Q7	3.03±1.5	3.08±1.4	0.859	3.33±1.5	3.85±1.4	0.063	3.23±1.5	3.88±1.4	0.02
Total	13.9±4.1	16.6±5.6	0.03	18.1±6.1	22.9±7.4	<0.001	17.5±5.5	22.8±7.5	<0.001
QoL	2.4±1.0	2.7±1.3	0.057	2.8±1.3	3.6±1.6	0.004	2.6±1.1	3.5±1.6	0.002

IPSS: International prostate symptom score, Q: Question, QoL: Quality of Life

to 40% (12). There are various causes of LUTS development after prostate biopsy. Prostatic edema that may develop because of inflammation after the procedure and trauma caused by the biopsy procedure are especially the first ones that come to mind. periprostatic blockage applied during the procedure is effective in the development of LUTS (13). In addition to the inflammation developing in the prostatic tissue, expansion of intestinal microbiota due to transrectal application and gradual spreading of bacteria resistant to prophylactic agents administered routinely in intestinal microbiota today are becoming a serious problem (14). It is thought that other than the septic complications caused by resistant strains, localized infections and inflammatory problems occupy a significant place in biopsy-related urination disorders, and LUTS complaints occur because of bladder outflow resistance along with all these causes (15). For this reason, there are studies in the literature in which various agents such as fluoroquinolones and additionally fosfomycin, cephalosporins, aminoglycosides, ertapenem, trimethoprim, and metronidazole are used alone or in combination. Currently, fluoroquinolones can be used frequently in current randomized controlled trials and were routinely applied to patients in the control group in our study. It has been stated that patients' complaints regarding LUTS generally continue for one month after transrectal prostate biopsy (16). When the risk factors that could create a sensitivity towards LUTS in patients before the procedure are examined, it has been stated in the literature that prostate volume does not affect post-procedure urination symptoms, that postvoiding residue amount has no effect on IPSS score after the procedure, that the number of cores sampled during the procedure and symptoms do not correlate, and that procedures applied to the transitional zone do not create an additional risk factor for urination symptoms (17,18). It has also been indicated that the presence of LUTS before the procedure is not exacerbate existing symptoms (19). The presence of LUTS is usually considered a factor that causes patients to present to a doctor in early periods. In some studies, it was attempted to use a PSA value between 4 and 10 ng/mL as a predictive value for determining the presence of LUTS. However, it was stated that the presence of LUTS did not have any effect on biopsy results and post-biopsy complications (20). Nevertheless, it has been stated in some studies that biopsy-related LUTS should be considered especially in patient groups with IPSS score above 20 (21). In this study, pre-procedure IPSS scores were determined as 13.9±4.1 in the targeted antibiotic prophylaxis group and 16.6±5.6 in the control group. A higher IPSS score in the control group before the procedure is not considered as an additional risk factor in the literature. When the increases in IPSS scores in both groups are compared, it is seen that the increase in the prophylaxis group was lower compared to the control group, that their biopsy-related LUTS rate was lower, and that targeted biopsy had significant effects on LUTS (p<0.001) (Figure 3).

When IPSS questions are examined in detail in both groups, it is seen that the difference between the two groups resulted especially from the need to urinate in less than two hours and urgency and storage symptoms such as difficulty in holding urination. Although there is no significant difference between the groups in terms of the presence of additional diseases such as diabetes, long-term changes related to chronic diseases can be effective in reducing the differences in scores (22,23). Patients' awareness levels about changes occurring in the long term also affect the responses given. Regarding the symptoms inquired through the 7 questions in the IPSS questionnaire as yes/no before the procedure in the present study, incomplete emptying was found in 38 patients (31.7%) in the prophylaxis group and in 52 patients (43.3%) in the control group (p=0.190);

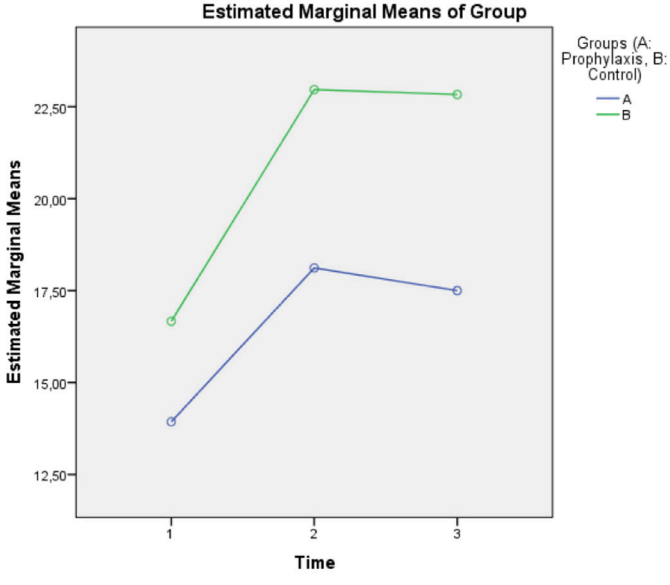

Figure 2. According to the mixed pattern ANOVA test, targeted prophylaxis is significantly effective in preventing biopsy-related LUTS (p=0.001)

LUTS: Lower urinary tract symptoms

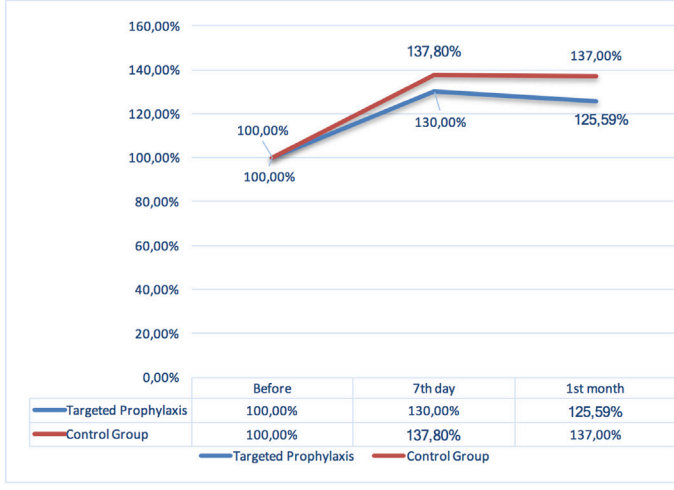

Figure 3. Percentage comparison of the total scores of the groups

need to urinate again in less than two hours was determined in 20 patients (16.7%) in the prophylaxis group and in 38 patients (31.7%) in the control group; intermittent urination was found in 58 patients (48.3%) and 74 patients (%61.7), respectively (p=0.145); inability to hold urination and urgency was determined in 38 patients (31.7%) and in 46 patients (38.3%), respectively (p=0.448); decrease in urinary flow rate was found in 70 patients (58.3%) and in 72 patients (60%), respectively (p=0.854); difficulty in starting urination was identified in 47 patients (39.2%) and in 63 patients (52.5%), respectively (p=0.75); and nocturia complaint was determined in 45 patients (37.5%) and in 39 patients (32.5%), respectively (p=0.236). When they were asked verbally, no significant difference was observed between the groups in terms of complaints. In addition, lack of a significant difference between the groups in terms of Qmax values before the procedure and IPSS scores being lower than 20 in both groups before the procedure are important in terms of evaluating the study results. Therefore, when the increases in IPSS scores after the procedure are compared, the significantly higher increase in the IPSS score of the control group shows that targeted antibiotic prophylaxis application could be an effective method in terms of preventing biopsy-related LUTS. Because of infectious complications developing after transrectal prostate biopsy, the frequency of prostate biopsy applications through transperineal methods is increasing. However, LUTS complaints and retention problems are more frequently witnessed in transperineal applications as well (24, 25). When both infection and LUTS-related problems involved in applications through transrectal method and increased LUTS risk in the transperineal method, need for anesthesia, difficulty in performing the procedure, and increased costs thereof are considered, it is thought that targeted antibiotic prophylaxis is increasingly becoming a more effective and significant method (26).

Study Limitations

The study being conducted at a single center and the absence of urodynamic studies regarding LUTS complaints are the limitations of this study. There is a need for multicenter studies with larger samples to evaluate the effects of targeted antibiotic prophylaxis on LUTS complaints.

Conclusion

Although there still exist different opinions on prophylactic antibiotic regimens before prostate biopsy, targeted antibiotic prophylaxis has been recommended by studies and guidelines in recent years. Because of the present study, it was determined that targeted antibiotic prophylaxis had a significant effect on LUTS, which is a common problem frequently seen after prostate biopsy. We believe that applying targeted antibiotic prophylaxis as a routine treatment would be a significant method for preventing LUTS complaints and infectious complications.

Ethics

Ethics Committee Approval: The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the local ethics committee of Ordu University, Turkiye (approval no: 2021/208, date: 23.09.2021).

Informed Consent: Written informed consent of the patients included in the study was obtained before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y., E.B., A.Ç., İ.N., Concept: A.Y., E.B., A.Ç., İ.N., Design: A.Y., E.B., İ.N., Data Collection or Processing: A.Y., A.Ç., M.K., N.K., Analysis or Interpretation: E.B., A.Ç., M.K., N.K., Literature Search: A.Y., M.K., N.K., Writing: A.Y.

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

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References

1. Boehm BE, York ME, Petrovics G, Kohaar I, Chesnut GT. Biomarkers of Aggressive Prostate Cancer at Diagnosis. Int J Mol Sci 2023;24:2185.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
3. O'Connor LP, Lebastchi AH, Horuz R, Rastinehad AR, Siddiqui MM, Grummet J, Kastner C, Ahmed HU, Pinto PA, Turkbey B. Role of multiparametric prostate MRI in the management of prostate cancer. World J Urol 2021;39:651-659.
4. Pradere B, Veeratterapillay R, Dimitropoulos K, Yuan Y, Omar MI, MacLennan S, Cai T, Bruyère F, Bartoletti R, Köves B, Wagenlehner F, Bonkat G, Pilatz A. Nonantibiotic Strategies for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta-Analysis. J Urol 2021;205:653-663.
5. Jhan JH, Huang SP, Li WM, Li CC, Huang TY, Ke HL, Huang CN, Chou YH, Wen SC. Outcomes and complications after transrectal ultrasound-guided prostate biopsy: A single-center study involving 425 consecutive patients. Urol Sci 2018;29:129-133.
6. Sosenko A, Owens RG, Yang AL, Alzubaidi A, Guzzo T, Trabulsi E, Danella J, Diorio G, Reese A, Tomaszewski J, Ginzburg S, Smaldone M, Fonshell C, Syed K, Jacobs B, Singer EA, Raman JD. Non-infectious complications following transrectal prostate needle biopsy - Outcomes from over 8000 procedures. Prostate Int 2022;10:158-161.
7. Glick L, Vincent SA, Squadron D, Han TM, Syed K, Danella JF, Ginzburg S, Guzzo TJ, Lanchoney T, Raman JD, Smaldone M, Uzzo RG, Tomaszweski JJ, Reese A, Singer EA, Jacobs B, Trabulsi EJ, Gomella LG, Mann MJ. Preventing Prostate Biopsy Complications: to Augment or to Swab? Urology 2021;155:12-19.
8. Efesoy O, Bozlu M, Çayan S, Akbay E. Complications of transrectal ultrasound-guided 12-core prostate biopsy: a single center experience with 2049 patients. Turk J Urol 2013;39:6-11.

9. Kölükçü E, Beyhan M, Atılgan D. Factors affecting complications of transrectal ultrasound-guided prostate biopsy: A cohort study with 403 patients in a single center. J Surg Med 2019;3:183-186.
10. Chung SJ, Jung SI, Ryu JW, Hwang EC, Kwon DD, Park K, Kim JW. The preventive effect of tamsulosin on voiding dysfunction after prostate biopsy: a prospective, open-label, observational study. Int Urol Nephrol 2015;47:711-715.
11. Rothe K, Querbach C, Busch DH, Gschwend JE, Hauner K. Antibiotic prophylaxis for transrectal prostate biopsy : In the context of restricted indications for fluoroquinolones and antibiotic stewardship. Urologe A 2022;61:160-166.
12. Wadhwa K, Carmona-Echeveria L, Kuru T, Gaziev G, Serrao E, Parashar D, Frey J, Dimov I, Seidenader J, Acher P, Muir G, Doble A, Gnanapragasam V, Hadaschik B, Kastner C. Transperineal prostate biopsies for diagnosis of prostate cancer are well tolerated: a prospective study using patient-reported outcome measures. Asian J Androl 2017;19:62-66.
13. Glaser AP, Novakovic K, Helfand BT. The impact of prostate biopsy on urinary symptoms, erectile function, and anxiety. Curr Urol Rep 2012;13:447-454.
14. Piekarska K, Zacharczuk K, Wołkowicz T, Mokrzyś M, Wolaniuk N, Nowakowska M, Szemplиński S, Dobruch J, Gierczyński R. The molecular mechanisms of fluoroquinolone resistance found in rectal swab isolates of Enterobacterales from men undergoing a transrectal prostate biopsy: the rationale for targeted prophylaxis. Ann Clin Microbiol Antimicrob 2021;20:81.
15. Temi AP, Gbenga OJ. Prevalence of voiding dysfunction after finger-guided prostate needle biopsy in Nigerian men. Med Sur Urol 2017;6:1-4.
16. Klein T, Palisaar RJ, Holz A, Brock M, Noldus J, Hinkel A. The impact of prostate biopsy and periprostatic nerve block on erectile and voiding function: a prospective study. J Urol 2010;184:1447-1452.
17. Aktas BK, Bulut S, Gokkaya CS, Ozden C, Salar R, Aslan Y, Baykam MM, Memis A. Association of prostate volume with voiding impairment and deterioration in quality of life after prostate biopsy. Urology 2014;83:617-621.
18. Başer A, Baykam MM, Çağlayan MS, Aydın C, Yaytokgil M, Ekici M. Voiding Dysfunctions and Prevention after Prostate Biopsy. Prospective Observational Study. Black Sea Journal of Health Science 2021;4:114-119.
19. Weight CJ, Kim SP, Jacobson DJ, McGree ME, Boorjian SA, Thompson RH, Leibovich BC, Karnes RJ, St Sauver J. The effect of benign lower urinary tract symptoms on subsequent prostate cancer testing and diagnosis. Eur Urol 2013;63:1021-1027.
20. Dobruch J, Modzelewska E, Tyloch J, Misterek B, Czapkowicz E, Bres-Niewada E, Borówka A. Lower urinary tract symptoms and their severity in men subjected to prostate biopsy. Cent European J Urol 2014;67:177-181.
21. Zisman A, Leibovici D, Kleinmann J, Cooper A, Siegel Y, Lindner A. The impact of prostate biopsy on patient well-being: a prospective study of voiding impairment. J Urol 2001;166:2242-2246.
22. Bedir S, Kilciler M. Transrektal Ultrasonografi Eşliğinde Yapılan Prostat Biyopsisinin Komplikasyonları. Turk Urol Sem 2011;2:218-222.
23. Pop-Busui R, Braffett BH, Wessells H, Herman WH, Martin CL, Jacobson AM, Sarma AV. Diabetic Peripheral Neuropathy and Urological Complications in Type 1 Diabetes: Findings From the Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2022;45:119-126.
24. Thomson A, Li M, Grummet J, Sengupta S. Transperineal prostate biopsy: a review of technique. Transl Androl Urol 2020;9:3009-3017.
25. LR, Zhang CG, Lu LX, Ruan L, Lan JH, Feng SQ, Luo JD. Comparison of ultrasound-guided transrectal and transperineal prostate biopsies in clinical application. Zhonghua Nan Ke Xue. 2014;20:1004-1007.
26. Akgüneş E, Aydın M, Görgün S, Günal Ö, Bitkin A, Keleş M, Atilla MK, Irkilata L. The Evaluation of Goal-Directed Antibiotics Prophylaxis Applied Via Rectal Swab Before Transrectal Ultrasound-Guided Prostate Biopsy. Bull Urooncol 2022:21;52-57.

ORIGINAL RESEARCH
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Nocturnal Vaginal pH Monitoring: A Possible New Assessment Method for Female Sexual Function

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What's known on the subject? and What does the study add?

Male sexual arousal response is penile erection due to vasocongestion. There is also a phenomenon that men have 4 or more penile erection phases lasting at least 30 min during night sleep. In females, sexual arousal responses are clitoral engorgement and vaginal lubrication. These responses are also seen due to vasocongestion. It is unknown whether females have similar nocturnal vasocongestion episodes. This study investigated whether women have nocturnal vasocongestion episodes like men and whether nocturnal vaginal pH monitoring can be used for female sexual function assessment such as nocturnal penile tumescence and rigidity test in men.

Abstract

Objective: The aim of this preliminary study was to investigate whether women have nocturnal vasocongestion episodes like men and whether nocturnal vaginal pH (NVpH) monitoring can be used for female sexual function assessment-like nocturnal penile tumescence and rigidity (NPTR) test in men.

Materials and Methods: Twelve premenopausal volunteers were included in the study. All women were within sexually active age and had normal hormonal profiles. NVpH was performed in an ambulatory manner on the same day and phase of the menstrual cycle. Female sexual function index (FSFI) scores, lubrication scores, and clitoral artery peak systolic velocity (PSV) were recorded. The volunteers were grouped according to the number of elevated pH episodes (EPE).

Results: Four women had four or more EPEs and constituted group 1. Eight women had 3 or less EPEs and constituted group 2. Group 2 had statistically significantly lower FSFI scores and clitoral artery PSV (p=0.001 and p=0.014, respectively). However, there was no statistically significant difference between the groups for lubrication scores and age.

Conclusion: The results of this preliminary study suggested that women and men has the same nocturnal vasocongestion episodes and NVpH measurement in women might be considered as analogous to NPTR in men.

Keywords: Femal, hydrogen-ion concentration, physiologica, sexual function, the vagina

Introduction

Sexual complaints are reported by approximately 40% of women worldwide (1,2). The most reported types of dysfunction are low sexual desire (26 to 43%) and inability to reach orgasm (18 to 41%) (1). Self-reports by women often do not distinguish between desire and arousal (3). Arousal may be either subjective (thoughts, feelings) or objective (genital vasocongestion or lubrication) (3). The management of difficulty with arousal must be tailored to whether the problem is subjective, objective, or combined.

Male sexual arousal response is penile erection due to vasocongestion. There is also a phenomenon that men have 4 or more penile erection phases lasting at least 30 min during night sleep, and analogous phenomena are present in women (4,5).

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In females, sexual arousal responses are clitoral engorgement and vaginal lubrication (6). These responses are also seen due to vasocongestion (7). It is unknown whether females have similar nocturnal vasocongestion episodes.

The female sexual response cycle includes four phases: desire (libido), arousal (excitement), orgasm and resolution. The arousal phase entails a subjective sense of sexual pleasure accompanied by physiologic changes, including genital vasocongestion and increase in heart rate, blood pressure, and respiratory rate (8). Within the sexually aroused vagina, the capillaries of the microcirculation are filled with blood, causing an increase in hydrostatic pressure inside them that forces out a plasma transudate (ultrafiltrate) into the interstitial space around the blood vessels (9). This increases the resting vaginal pH. The normal value of vaginal pH for premenopausal women is ≤4.5 (10,11).

The sexual physiology of males and females are similar. The sexual dysfunction in women and men can be due to organic or psychological factors. Male sexual dysfunction can be diagnosed with several quantitative tests such as the (NPTR) test, penile colored Doppler ultrasonography, and others, whereas the quantitative assessments of female sexual dysfunction are limited. In the past, many studies were performed to understand the female sexual function (FSF) using different methods including genital blood flow measurement, vaginal photoplethysmography (VP), vaginal and labial thermistors, thermography, clitoral and labial photoplethysmography, duplex Doppler ultrasonography and laser Doppler perfusion imaging of the female genitalia, dynamic contrast and non-contrast magnetic resonance imaging, laser oximetry, clitoral intracavernosal pressure, pudendal arteriogram and vaginal pH measurement (12). However, most of these methods are considered experimental except VP. Additionally, the common feature of these methods is that they require clinical and technical experience.

Knowledge and experience of the male sexual dysfunction are more settled; therefore, application of this knowledge to female sexual dysfunction might lower the workload needed to design diagnostic tests for FSD. The aim of this preliminary study was to investigate whether women have nocturnal vasocongestion episodes like men and whether nocturnal vaginal pH monitoring can be used for female sexual function assessment the NPTR test in men.

Materials and Methods

The study protocol was approved by the Institutional Review Board and Ethics Committee of Başkent University (project no: KA06/143, date: 07.06.2006).

Volunteers

Healthy sexually active premenopausal unpregnant women whom defining themselves as sexually normal and healthy were included in the study. Women with a history of vaginal/pelvic surgery, radiotherapy, or infection, and those taking any medications, including oral contraceptives were excluded. All volunteers were evaluated with validated Female Sexual Function Index (FSFI) scores, genital examination, and hormonal profile, including serum thyroid-stimulating hormone, follicle stimulating hormone, luteinizing hormone, prolactin, testosterone, and estradiol (13,14). Twelve women were enrolled in the study. All volunteers' hormonal profiles were within normal limits. The vaginal cultures did not indicate infection before pH monitoring. Informed consent was obtained from all individual participants included in the study. All volunteers' menstrual cycle lengths were recorded. Before every pH measurement, procedure volunteers were evaluated with vaginal culture and β-human chorionic gonadotropin serum level to prove the absence of vaginal infection and pregnancy, which may affect vaginal pH, respectively. All volunteers' lubrication scores were calculated according to FSFI questionaries' questions 7, 8, 9, and 10.

Ambulatory pH Monitoring

Nocturnal pH monitoring was performed in an ambulatory manner using an Orion II™ recording device [Medical Measurements Systems (MMS), Enschede, The Netherlands USA] and single crystal antimony pH catheters (Synectics Medical, Sweden) (Figure 1). This device is commonly used for diagnosis of gastroesophageal reflux. All measurements were done at the volunteers' home. The catheters were calibrated with solutions having pH 1 and 7 before each recording. All volunteers were educated for the placement and fixation of the catheter and for the operating procedures of Orion II. The pH catheters were marked with a water-resistant marker from 7 cm of the tip. The volunteers placed the pH catheters inside their vagina till to marker on the catheter just before night sleep. The mark on the pH catheters guaranteed as the active point of the catheter

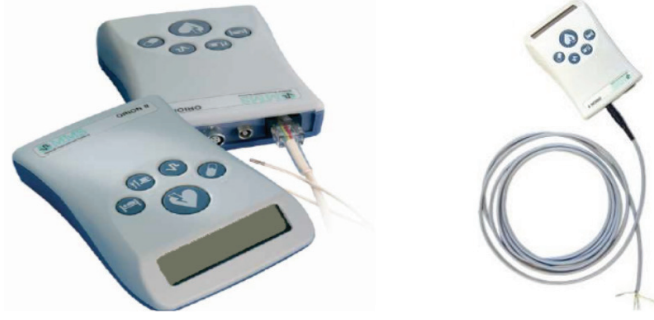

Figure 1. Orion II™ ambulatory pH recorder (Medical Measurements System, Enschede The Netherlands)

would be approximately 5 cm from the introitus. The catheters were fixed to the labium magus with a medical plaster to keep them in place during one-night sleep. The catheter is also fixed by three medical plaster locations to the leg. The volunteers kept the Orion II device at the top of the chiffonier beside the bed to be undisturbed due to the device. To minimize the hormonal effects, all volunteers were asked to use the device 10 days before menstruation. All measurements were done at least twice. The repeating measurements were performed in the following menstrual cycle. The recorded data were evaluated for mis-recordings such as dislocation of the catheter, halting of recording due to finished battery, or gross movements (such as walk to urination, awakening etc.). In the case of mis-recording, the procedure was repeated in the following menstrual cycle.

Clitoral Artery Peak Systolic Velocity Measurements

Clitoral colored Doppler ultrasonography was performed with a 7.5 MHz linear transducer (Acuson, Siemens, Germany). The ultrasound probe was applied sagittally proximal to the clitoris root, as described in previous reports (15,16). Bilateral clitoral cavernosal artery diameter and peak systolic velocity (PSV) parameters were recorded. A clitoral artery PSV ≥10 cm/s was accepted as normal (15).

Data Evaluation

A chart of the nocturnal vaginal pH values was plotted using the recording device's computer-based software (MMS, The Netherlands). All recordings were evaluated for mis-recordings. The mis-recordings were detected seen in the pH charts as unexpected pH changes as seen in before sleep part of the Figure 1A. The last successful set of recordings were evaluated. A pH elevation greater than 6, lasting for more than 30 minutes, was considered an elevated pH episode (EPE) that was an indicator of vasocongestion episode. Four or more EPEs were accepted as an indicator of normal FSF. Three or less EPEs were considered an indicator of inadequate FSF. The volunteers were divided into 2 groups according to sexual function based on the number of EPEs; group 1 consisted of the volunteers with 4 or more EPEs, and group 2 consisted of the volunteers with 3 or less EPEs.

Statistical Analysis

Statistical analyses were performed using the statistical package SPSS (Version 23.0; IBM SPSS Inc., Chicago, IL, USA). For each continuous variable, normality was checked by the Kolmogorov-Smirnov's test, Shapiro-Wilk's test, and histograms. Welch's t-test was used for the comparison between groups and $p<0.05$ was considered as statistically significant (17). A post-hoc power analysis for t-test is performed.

Results

The mean age of the volunteers was 32.4±4.9 (range; 25-41) years. None of the recorded pH values was below 4, and the maximum-recorded value was 6.2. The FSFI scores of the volunteers ranged between 7.8 and 28.6 (median; 16.55), and the lubrication scores ranged between 0.9 and 6 (median; 3.9). The clitoral artery PSV ranged between 4 to 15 cm/s (median; 10 cm/s). The recorded EPEs were ranged between 0 and 5 (median; 2). The FSFI and lubrication scores of the volunteers according to age and clitoral PSV values and min/max NVpH levels are summarized in Table 1.

Four women had 4 or more nocturnal EPEs, and 8 women had 3 or less nocturnal EPEs. Group 1 consisted of 4 women and group 2 consisted of 8 women. Group 2 had significantly lower FSFI scores and clitoral artery PSV (p=0.001 and p=0.014,

Table 1. The Female Sexual Function index, lubrication scores, clitoral artery peak systolic velocity values, and number of elevated pH episodes of the volunteers

Volunteer number	Age (years)	FSFI[a]	Lubrication score	Clitoral PSV[b] (cm/s)	Number of EPE[c]	Min-max pH
1	25	15.40	3.3	6.00	1	4.48-6.02
2	26	7.80	0.9	9.00	0	5.36-5.66
3	28	21.30	5.1	14.00	4	4.27-6.20
4	30	26.90	4.8	15.00	4	4.01-6.15
5	31	28.60	5.1	11.00	5	4.49-6.19
6	32	11.50	3.0	4.00	0	5.36-5.68
7	32	25.90	2.1	12.00	4	4.89-6.11
8	33	9.40	0.9	10.00	0	4.21-5.76
9	35	21.80	6.0	8.00	3	4.68-6.07
10	36	13.10	5.7	10.00	0	4.10-5.17
11	40	17.70	4.2	15.00	2	5.01-6.08
12	41	14.10	3.6	6.00	2	4.51-6.06

[a]FSFI: Female Sexual Function index, [b]Lubrication score: Calculated with questions 7, 8, 9, and 10 of the FSFI Questionnaire, PSV: Peak systolic velocity of the clitoral artery, [c]EPE: Elevated pH episode

respectively) (Table 2). There was no statistically significant difference in lubrication scores and age between both groups (Table 2). The post-hoc power analysis of the study was 0.998.

The nocturnal pH charts of the volunteers with FSFI scores 26.9 and 9.4 are shown and compared with the nocturnal penile tumescence charts in Figure 2.

Discussion

Female sexual dysfunction is a multi-causal and multidimensional medical problem that has both biological and psychosocial components (18). The multidimensional nature of FSD mandates an understanding of the normal physiology of FSF. One of the easiest methods for the assessment of FSF is scoring questionnaires (13,14). FSFI is widely accepted and used for assessing FSF. An FSFI score ≤26.55 is associated with FSD (19). However, FSD can be diagnosed according to the current Diagnostic and Statistical Manual of Mental Disorders (8). Assesses 6 subheadings such as desire, arousal, lubrication, orgasm, satisfaction, and pain; therefore, the score does not identify the underlying pathology as organic or psychological. In this study, we used the FSFI scores to identify the volunteers' sexual function status and the volunteers' FSFI scores ranged between 7.8 and 28.6. Only 2 of the volunteers' FSFI scores were

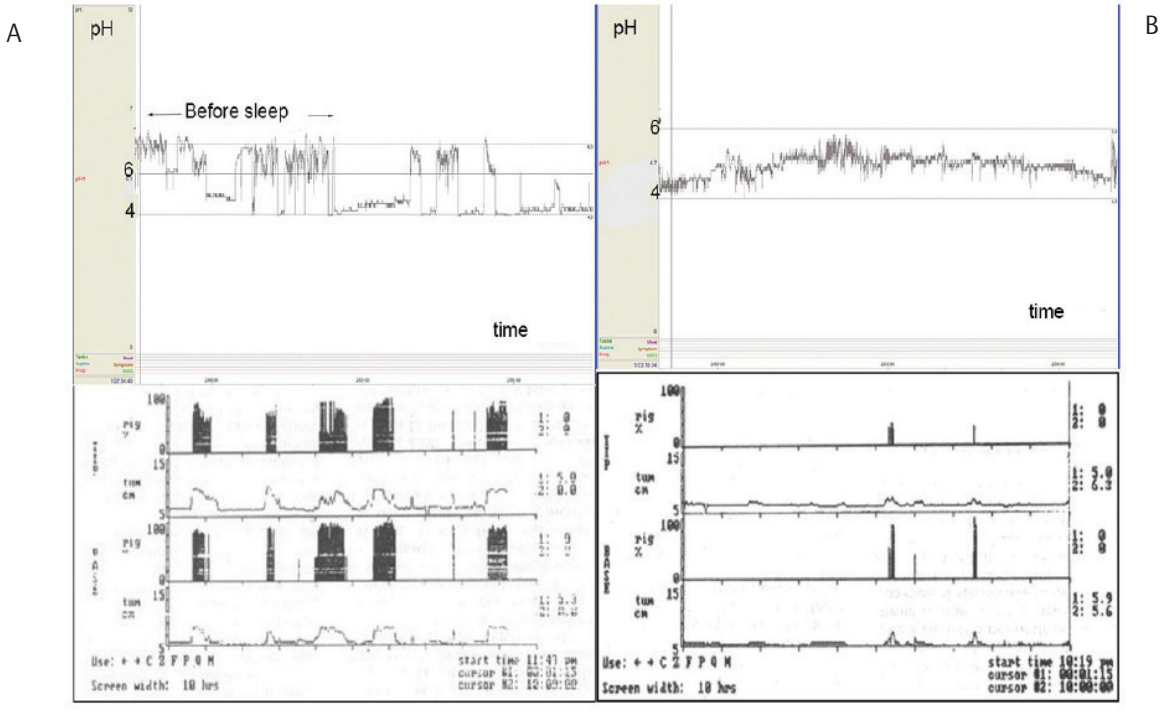

Figure 2. Comparison of nocturnal pH monitoring charts with nocturnal penile tumescence and rigidity (NPTR) charts

A. Nocturnal pH chart of a 30-year-old female volunteer with a FSFI score 26.90. Her chart was compared with a non-pathologic NPTR chart. On the right section of the chart, 3 of 4 elevated pH episodes can be seen. Each episode lasted more than 30 min. The pH fluctuations before sleep were caused due to gross movements

B. Nocturnal pH chart of a 33-year-old female volunteer with a FSFI score 9.40. Her chart is compared with a non-erected NPTR. There was no increased vaginal pH episodes during nocturnal monitoring

FSFI: Female Sexual Function index, NPTR: Nocturnal penile tumescence and rigidity

Table 2. Comparison between the two groups

	Group 1 (number of EPE ≥4) (n=4) Median (min-max)	Group 2 (number of EPE<4) (n=8) Median (min-max)	p-value
Age	30.5 (28-32)	34 (25-41)	0.179
FSFI[a]	26.4 (21.3-28.6)	13.6 (7.8-21.8)	0.001
LS[b]	4.95 (2.1-5.1)	3.45 (0.9-6)	0.430
PSV[c]	13 (11-15)	8.5 (4-15)	0.014

[a]FSFI: Female Sexual Function index, [b]LS: Lubrication score, calculated with questions 7, 8, 9, and 10 of the FSFI Questionnaire, [c]PSV: Peak systolic velocity of the clitoral artery ,EPE: Elevated pH episode

above 26.55. This was an unexpectedly high rate of low FSFI scores in the absence of organic or psychological problems. This might be explained by volunteer bias.

In 1968, Shapiro et al. (20) performed the first studies to assess vaginal acidity. They could not show the alteration of pH with the technology available at that time. With the improvement in the pH measurement technology, Masters and Johnson reported that vaginal pH increased slightly with sexual arousal. However, continuous measurement of vaginal pH with radiotelemetry during sexual intercourse revealed that vaginal lubrication did not appreciably change the pH (12). Nevertheless, this report was based on the results from two couples only. Wagner and Levin investigated the surface pH of the vagina before and after sexual arousal by self-stimulation and found that clitoral self-stimulation to orgasm generally results in a small increase in pH by up to 1 unit (12). Berman et al. (21) used a digital pH-meter inserted into the vagina and found an increase in pH post self-stimulation and with sildenafil, and they also reported an increase in baseline mean vaginal pH measurements to 6 following sexual stimulation. In our study, the nocturnal vaginal pH of the volunteers ranged between 4 and 6.2, and elevated pH over 6 lasting more than 30 min was considered an indicator of vasocongestion episode. The pH elevations over the threshold, 6, can be considered as ignorable. However, pH is calculated as $-\log[H^+]$; thus, the hydrogen ion concentration change for every pH unit is not equal.

All NVpH measurements were performed 10 days before the menstruation. This day was decided using three parameters. The menstrual cycle has four phases such as follicular, ovulation, luteal and menstruation. The sexual arousal of women changes within these phases (22). It has been shown that sexual arousal peaks with ovulation and remains high till the mid-luteal phase (22). The mid-luteal phase starts one week after the ovulation. The vaginal pH, salivary pH, and body temperature are changed during ovulation (23). To the best of our knowledge, there is no confirmed vaginal pH-level changes in the luteal phase. The luteal phase duration is almost the same in healthy women therefore it is easy to calculate the mid-luteal phase (24). The day, which NVpH measurements were done has the beneficial effects such as high sexual arousal and avoiding pH-level changes in ovulation.

The glandulae vestibulares majores (larger vestibular or Bartholin glands) actively secretes clear, viscid, and stringy mucoid substance with an alkaline pH during sexual activity (11). Vaginal lubrication can be considered to be the keystone of pH alteration during sexual arousal. Thus, in this study, the lubrication scores were separately evaluated, but there was no statistically significant difference in the lubrication scores between both groups. There was an interesting finding in the pH charts. The pH elevation during EPEs can be explained with the alkaline secretions, but the pH sharply decreased to basal levels at the end of the EPEs. The pH catheter used in this study has only one active point. The alkaline secretions are moving toward the labium magnus; thus, when the alkaline fluid passed the active point of the catheter, it measures the acidic vaginal mucosa pH (25).

Vaginal photoplethysmography has been the most widely used physiological measurement of vaginal vasocongestion, demonstrating adequate validity and reliability in psychophysiological studies of healthy and sexually dysfunctional women. Several other physiological measurement approaches have been proposed and are in development, including measurements of clitoral and labial temperature and oxygenation, vaginal and clitoral Doppler, and blood flow measurements and vaginometry. Despite the obvious interest and appeal of these alternatives, none has been adequately validated or standardized in patients or healthy controls (26). Vaginal pulse amplitude (VPA) and vaginal blood volume can be calculated using VP (27). Vaginal photoplethysmography requires special equipment that can cost more than $10,000; thus, it is a relatively expensive technique (27). In summary, the measurement of VPA with VP are laboratory-based methods to provide specific information about the impact of various conditions on vaginal blood flow. Although VP is considered to be the most reliable method for assessing vaginal blood flow, it has limitations such as potential bias and high cost (27). Nocturnal vaginal pH monitoring can be done at home; it is cheaper than VP and might reduce the potential bias.

Men and women have similar sexual physiology with different promoters. Therefore, the implementation of the concepts behind male sexual dysfunction diagnostic techniques to women might be possible with experience and after standardization. Clitoral artery PSV measurement is equivalent to penile cavernosal artery PSV measurement. The normal values of basal clitoral artery PSV are not yet been standardized, therefore in our study, clitoral PSV was not used as the primary diagnostic criterion for FSD. However, duplex Doppler ultrasound studies in women with sexual dysfunction were useful in a diagnostic and therapeutic contexts (28). In this study, clitoral artery PSV ≥10 cm/s was accepted as normal, according to previous reports (15,16). However, group 2 had significantly lower clitoral artery PSV than group 1, which also supported the feasibility of nocturnal vaginal pH monitoring on evaluation of FSF.

The NPTR monitoring reflects the integrity of the efferent arm of the erectile reflex, indirectly testing the neural, vascular, and hormonal influences on erectile function. Many clinicians use NPTR testing as the noninvasive reference standard for the differentiation between organic and psychogenic causes of erectile dysfunction (29). In men, sleep-related erections are present throughout life with only a slight decline in older

healthy people, and analogous phenomena are present in women (5). The recommended criteria for normal NPTR include 4-5 erectile episodes per night with a mean duration longer than 30 min, and an increase in the circumference of more than 3 cm at the base and more than 2 cm at the tip, with a maximal rigidity above 70% at both the base and tip (30). In males, both sexual arousal response and nocturnal penile erection are due to vasocongestion (4,31). In females, the sexual arousal response is clitoral erection and lubrication due to vasocongestion (6). In males, if 4 or more nocturnal vasocongestion episodes, which represent as penile erection, are normal, females might have the same physiology. Therefore, in this study, we considered 4 or more EPEs as an indicator of normal female sexual function. Four women with an FSFI score ≥21.8 had 4 or more EPEs. However, 4 women with an FSFI score <13.1 did not have EPE. Four women with an FSFI scores between 14.1 and 21.8 had between 1 and 3 EPEs. In our study, nocturnal vaginal pH peaks in women with FSFI score ≥21.8 revealed similar characteristics as NPTR as seen in Figure 1. In Figure 1, the woman with an FSFI score 26.9 had 4 EPEs (3 of 4 are shown in the Figure), and the chart of these pH episodes was very similar to the model NPTR chart. In our study, all women-except that one with FSFI score ≥21.8-had ≥4 EPEs. A volunteer with an FSFI score of 25.9 had 3 EPEs.

Study Limitations

There were 3 limitations of this study. The main limitation was the number of women involved in the study. Therefore, the data were analyzed with the Welch's t-test because the sample size was small (less than 10) and unequal (17). Despite the use of post hoc power analysis controversial, we have performed post hoc power analysis to define the interpretability of our data, and the result of the analysis was 0.998. Although the number of volunteers was limited, the data obtained from this study revealed important results.

Second, the electrodes used in this study were made of antimony. Antimony electrodes are affected by the oxygen tension of the fluids (32). This might have altered the vaginal pH measurements. However, the electrode was calibrated before all the measurements. Finally, this was a volunteer-based study; therefore, volunteer bias is expected.

Our data must be confirmed with studies including healthy and sexually dysfunctional women and men. These studies should evaluate sleep cycles with electroencephalography and evaluate vaginal blood flow with photoplethysmography and assess sexual function with different questionnaires in women.

Conclusion

Women and men might have the same nocturnal vasocongestion episodes, and NVpH measurement in women might be considered as analogous to NPTR in men. More studies on larger populations, including healthy subjects and patients with FSD, are required to define this technique and to make a better comment on the results.

Ethics

Ethics Committee Approval: The study protocol was approved by The Başkent University's Institutional Review Board and Ethics Committee (project no: KA06/143, date: 07.06.2006).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Concept: M.R.G, İ.O., Design: M.R.G, C.Ö., Data Collection of Processing: M.R.G, İ.O., Analysis or Interpretation: M.R.G, C.Ö., İ.O., Literature Search: M.R.G., Writing: M.R.G., C.Ö.

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References

1. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E, Wang T; GSSAB Investigators' Group. Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. Int J Impot Res 2005;17:39-57.
2. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. Obstet Gynecol 2008;112:970-978.
3. Basson R. Women's sexual function and dysfunction: current uncertainties, future directions. Int J Impot Res 2008;20:466-478.
4. Mann PDDK, Sohn M. Spontaneous nocturnal erections—Physiology and clinical applications. Somnologie - Schlafforschung und Schlafmedizin 2005;9:119-126.
5. Hirshkowitz M, Moore CA. Sleep-related erectile activity. Neurol Clin 1996;14:721-737.
6. Basson R, Wierman ME, van Lankveld J, Brotto L. Summary of the recommendations on sexual dysfunctions in women. J Sex Med 2010;7:314-326.
7. Hatch JP. Vaginal photoplethysmography: methodological considerations. Arch Sex Behav 1979;8:357-374.
8. American-Psychiatric-Association. Sexual Dysfunctions. Diagnostic and statistical manual of mental disorders: DSM-5 5th ed. Washington, DC, the American Psychiatric Association, 2013, pp 423-450.
9. Salonia A, Giraldi A, Chivers ML, Georgiadis JR, Levin R, Maravilla KR, McCarthy MM. Physiology of women's sexual function: basic knowledge and new findings. J Sex Med 2010;7:2637-2660.
10. Danielsson D, Teigen PK, Moi H. The genital econiche: focus on microbiota and bacterial vaginosis. Ann N Y Acad Sci 2011;1230:48-58.

11. Nathan L, DeCherney A, Goodwin TM, Laufer N, Roman A. CURRENT Diagnosis & Treatment Obstetrics & Gynecology, 2012.
12. Woodard TL, Diamond MP. Physiologic measures of sexual function in women: a review. Fertil Steril 2009;92:19-34.
13. Aygin A, Aslan FE. The Turkish Adaptation of The Female Sexual Function Index. Turkiye Klinikleri Journal of Medical Sciences 2005;25:393-399.
14. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191-208.
15. Bechara A, Bertolino MV, Casabé A, Munarriz R, Goldstein I, Morin A, Secin F, Literat B, Pesaresi M, Fredotovich N. Duplex Doppler ultrasound assessment of clitoral hemodynamics after topical administration of alprostadil in women with arousal and orgasmic disorders. J Sex Marital Ther 2003;29 Suppl 1:1-10.
16. Dirim A, Goren MR, Peskircioglu L. The effect of topical synthetic prostaglandin E1 (misoprostol) on clitoral hemodynamics. J Sex Med 2011;8:800-805.
17. McDonald JH. Handbook of biological statistics. Baltimore, Sparky House Publishing, 2009.
18. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA 1999;281:537-544.
19. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1-20.
20. Shapiro A, Cohen HD, Di Bianco P, Rosen G. Vaginal blood flow changed during sleep and sexual arousal. Psychophysiology 1968;4:394.
21. Berman JR, Berman LA, Lin H, Flaherty E, Lahey N, Goldstein I, Cantey-Kiser J. Effect of sildenafil on subjective and physiologic parameters of the female sexual response in women with sexual arousal disorder. J Sex Marital Ther 2001;27:411-420.
22. Salonia A, Nappi RE, Pontillo M, Daverio R, Smeraldi A, Briganti A, Fabbri F, Zanni G, Rigatti P, Montorsi F. Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. Horm Behav 2005;47:164-169.
23. Deans A. Your new pregnancy bible. London, Carroll & Brown, 2013.
24. Lenton EA, Landgren BM, Sexton L. Normal variation in the length of the luteal phase of the menstrual cycle: identification of the short luteal phase. Br J Obstet Gynaecol 1984;91:685-689.
25. Levin RJ. The ins and outs of vaginal lubrication. Sex Relation Ther 2003;18:509-513.
26. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, Goldstein I, Graziottin A, Heiman J, Laan E, Leiblum S, Padma-Nathan H, Rosen R, Segraves K, Segraves RT, Shabsigh R, Sipski M, Wagner G, Whipple B. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. J Urol 2000;163:888-893.
27. Alexander MS, Biering-Sørensen F, Elliott S, Kreuter M, Sønksen J. International spinal cord injury female sexual and reproductive function basic data set. Spinal Cord 2011;49:787-790.
28. Nader SG, Maitland SR, Munarriz R, Goldstein I. Blood flow: duplex Doppler ultrasound. In: Goldstein I, Meston CM, Davis SR, Traish AM. Women's sexual function and dysfunction : study, diagnosis, and treatment. London; New York, Taylor & Francis 2006, pp 383-390.
29. Kaneko S, Bradley WE. Evaluation of erectile dysfunction with continuous monitoring of penile rigidity. J Urol 1986;136:1026-1029.
30. Cilurzo P, Canale D, Turchi P, Giorgi PM, Menchini Fabris GF. Il Rigiscan system nella diagnostica dell'impotenza sessuale maschile [The Rigiscan system in the diagnosis of male sexual impotence]. Arch Ital Urol Nefrol Androl 1992;64 Suppl 2:81-85.
31. Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. Endocr Rev 2001;22:342-388.
32. Levin RJ. Measuring female genital functions—a research essential but still clinical luxury? Sex Relation Ther 2004;19:191-200.

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Relationship Between the Visceral Adiposity Index and Peyronie's Disease

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What's known on the subject? and What does the study add?

Peyronie's disease (PD) is an acquired benign localized connective tissue disease. Abnormal healing pattern and excessive fibrosis development in the tunica albuginea secondary to penile microtrauma is the most accepted mechanism. Clinical conditions, including hypertension, hyperlipidemia, and abnormal glucose metabolism, can increase PD by creating a hypoxic microenvironment in erectile tissues. The visceral adiposity index (VAI), defined as a marker of adipose tissue dysfunction, is a beneficial mathematical model based on anthropometric and functional parameters. This study is the first one ever to define VAI as a new independent risk factor for PD. We think that considering VAI in the follow-up and treatment protocols of PD will offer important innovations in clinical practice.

Abstract

Objective: We aimed to investigate the relationship between Peyronie's disease (PD) and the visceral adiposity index (VAI), which is thought to predict visceral obesity homogeneously.

Materials and Methods: We included 102 healthy volunteers (Group 1) and 89 patients with PD (Group 2) in this retrospective study. We recorded demographic, anthropometric, and clinical data, including age, comorbidity, International Index of Erectile Function (IIEF) score, waist circumference (WC), body mass index (BMI), visceral adiposity index testosterone (VAI), serum fasting glucose, high-density lipoprotein (HDL), and triglyceride (TG). For Group 2 participants, plaque size, duration of symptoms, and degree of penile curvature were recorded.

Results: The mean ages of Group 1 and Group 2 were 55.12±9.51 years and 54.79±9.99 years, respectively ($p>0.05$). The mean BMI, WC, VAI, fasting glucose, and TG values were significantly higher in Group 2 ($p<0.001$, $p=0.004$, $p=0.001$, $p=0.001$, and $p=0.003$, respectively). The mean HDL values between the groups were similar ($p>0.05$). The mean IIEF score was lower in Group 2 than in Group 1 ($p=0.008$). An increase of 1 unit in the VAI value increases the probability of having PD 1.2 times ($p=0.001$). Each VAI integer increase decreased 1.25 points in the IIEF score, a 1 mm increase in plaque size, and a 1.98-degree increase in curvature.

Conclusion: Our study has shown that VAI can be used as a reliable, independent risk factor for plaque size and penile curvature in patients with patients with PD.

Keywords: Peyronie's disease, visceral adiposity index, men, penile curvature

Introduction

Peyronie's disease (PD) is an acquired benign localized connective tissue disease characterized by fibrous collagen plaque formation in the tunica albuginea of the penile corpus cavernosum (1,2). Penile plaques can be palpated when the penis is flaccid. PD can cause impotence, painful erection, and penile deformities such as narrowing, contraction, and shortening (3). As PD progressed, severe sexual dysfunction may occur (1,4). The incidence of PD

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is reported to be 26 per 100.000 with a prevalence of 389 per 100.000, and it varies between geographies (3). PD is a clinical condition whose pathophysiology has not been sufficiently elucidated to date. Abnormal healing pattern and excessive fibrosis development in the tunica albuginea secondary to penile microtrauma are the most accepted mechanism. Clinical conditions, including hypertension, hyperlipidemia, and abnormal glucose metabolism, can increase PD by creating a hypoxic microenvironment in erectile tissues (1).

With an increasing prevalence, obesity and obesity-related health problems have become a threatening global problem. Epidemiological studies have shown that the number of overweight people in the world will increase to 1.35 billion in 2030 and the number of obese people to 573 million (5). Obesity may lead to endothelial dysfunction by increasing susceptibility to hypertension and metabolic syndrome. Obesity also causes significant changes in hormonal function (6). Body mass index (BMI) and waist circumference (WC) are commonly used anthropometric measures to assess obesity. However, BMI is not a reliable indicator for estimating body fat distribution due to such factors as age, gender, race, high muscle mass, and fluid intake habits. Similarly, WC also fails to show visceral adipose tissue because it measures the subcutaneous adipose tissue (6,7). It plays an essential role in the physiopathology of disorders secondary to obesity (8).

Visceral adiposity is closely related to increased adipocytokine production, increased proinflammatory activity, atherosclerosis, hypertension, insulin resistance, glucose, and lipid profile disorders (9). Different medical equipment, such as bioelectrical impedance, magnetic resonance imaging, and dual-energy X-ray absorptiometry are needed to reveal the visceral adipose tissue distribution directly. Since these techniques require specific technological infrastructure and are costly, it is almost impossible to apply them in our daily clinical practice (10). This situation has led researchers to look for easy and practical methods. In this context, the visceral adiposity index (VAI), defined as a marker of adipose tissue dysfunction, has attracted great interest. VAI is a beneficial mathematical model based on anthropometric and functional parameters. Ever since Amato et al. (10) first described the concept of VAI in 2010, numerous studies have been conducted for many conditions such as neurologic, cardiovascular, and metabolic disorders (11). However, as a predictor of adipose tissue function, in Andrology, the VAI has been considered only recently, and few studies have been published (12).

We conducted out this study to show whether the VAI can affect the plaque size and severity of penile curvature in Peyronie's disease. To the best of our knowledge, this is the first study in the English literature that analyzed VAI in patients with PD patients.

Materials and Methods

Patients

Of the 191 participants, 102 were assigned to the control group (Group 1), and 82 patients with PD were to Group 2. We retrospectively analyzed the data of the patients who applied to our clinics between April 2010 and March 2021, and we obtained detailed informed consent from the participants. Patients with PD were defined as Group 1. The patients who applied for routine checks and had no uropathology was determined as Group 2. We recorded their demographic data, comorbidities, clinical complaints, duration of symptoms, physical examination findings, and any history of trauma, pelvic radiotherapy, and genital surgery. The diagnosis of PD was established based on the characteristic symptoms and palpable penile plaque on physical examination.

Plaque size was determined by physical examination. Curvature degree was calculated by reviewing the images taken after intracavernosal injection (1,2). Additionally, the weight, height, and WC of the patients were measured. The erectile function was calculated using the International Index of Erectile Function (IIEF) (6). Fasting morning blood samples were taken between 8:30 and 10:00 in the morning for total testosterone, fasting blood glucose, HDL, and TG.

This study was conducted according to the Declaration of Helsinki Principles. The local ethics committee (Clinical Studies Ethics Committee decision no: 21-KAEK-132, date: 20.05.2021) approved this study.

Measurements of BMI, WC, and VAI

BMI was determined as weight/height^2 (kg/m^2). WC was calculated by measuring the circle's circumference passing through the midpoint of the lines perpendicular to the 10th rib on both sides and the spina iliaca anterior superior. The units for BMI and WC were kg/m^2 and cm, respectively (9). The VAI was calculated according to the male gender-specific formula [WC/39.68 + (1.88xBMI)] [TG/1.03] [1.31/HDL] (10).

Inclusion and Exclusion Criteria

Only the participants with complete data were included in our study. Cases with a history of penile trauma, pelvic surgery, and radiotherapy were excluded.

Statistical Analysis

Statistical analysis of the data was carried out using the SPSS (Version 22, SPSS Inc., Chicago, IL, USA) package Inc..

The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics of continuous variables were presented using mean ± standard deviation or median ± interquartile range (IQR), depending on the data distribution. Categorical variables were presented as number (n) and percentage (%). Student's t-test and the Mann-Whitney U test were used to compare the numerical variables between two independent groups for normally and non-normally distributed data, respectively. Proportion comparisons between categorical variables were performed using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) analysis was used to determine whether the AVI scores could be a prognostic indicator for disease prediction. ROC curves and area under the curve (AUC) and 95% confidence intervals (CIs) were also calculated. The AUC values obtained in the analyses were interpreted as 0.9-1: excellent, 0.8-0.9: good, 0.7-0.8: fair, 0.6-0.7: poor, and 0.5-0,6: unsuccessful. The Youden index (maximum sensitivity and specificity) was used to determine the best cut-off point in the ROC analysis. The success of the cut-off points was evaluated using the values of accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and positive likelihood ratio. Pearson correlation coefficients and Univariate linear regression analysis were used to make the correlation analysis between the VAI score and the IIEF score, plaque size, and degree of curvature. Binary logistic regression analysis was used to show the effect of VAI on PD, and the odds ratios were calculated. Statistical significance level was accepted as p<0.05.

Results

The mean ages were 55.12±9.51 years and 54.79±9.99 years in Groups 1 and 2, respectively (p>0.05). The mean symptom duration of the patients in Group 2 was 17.1±4.1 months. The mean penile curvature degree and plaque size of the patients in this group were 47.83±12.79° and 16.1±4.9 mm. Patients with PD had a higher rate of Dupuytren's contracture, hyperlipidemia, and smoking than Group 1 (p<0.05). Both groups had similar rates of coronary artery disease (p=0.074) (Table 1).

Group 2 patients had higher BMI and WC than Group 1 (p<0.001 and p=0.004). When blood biochemical analyses were examined, the mean fasting glucose and TG levels in Group 2 were found to be 100±30 mg/dL and 155±84 mg/dL, respectively. These values were significantly higher than Group 1 (p=0.001 and p=0.003, respectively). Conversely, total testosterone levels were significantly lower in Group 2 than in Group 1 (p=0.002). HDL values were similar in Groups 1 and 2 (p>0.05). Mean VAI values in Groups 1 and 2 were recorded as 3.83±1.79 and 5.72±4.62, respectively. These values were significantly higher in Group 2 (p=0.001). While erectile dysfunction was observed in only 20 (19.6%) cases in Group 1, it was detected in 44 (49.4%) patients in Group 2 (p<0.001), and the IEFF score in Group 2 was recorded to be significantly lower than Group 1 (p=0.008) (Table 2). The distribution of VAI and IIEF scores among the groups is documented in Figure 1.

The results of the linear regression analysis showed that each integer increase in VAI increased the probability of having PD 1.2 times (CI: 1.07-1.35), decreased the IIEF score by 1.25 points (CI: 1.03-1.47) (R2=0.4, p<0.001), increased plaque diameter by

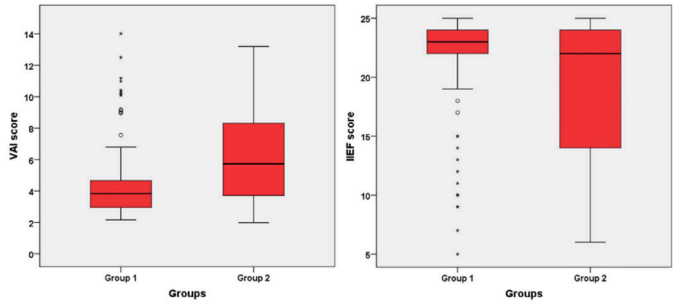

Figure 1. Boxplot of the distribution of VAI and IIEF scores among the research groups

VAI: Visceral adiposity index, IIEF: International Index of Erectile Function

Table 1. Distribution of the study population by comorbidity

Comorbidity	Group 1 (n=102)	Group 2 (n=89)	p-values
Diabetes mellitus	9 (8.8%)	17 (19.1%)	**0.039**[a]
Hypertension	6 (5.9%)	13 (14.6%)	**0.044**[a]
Hyperlipidemia	15 (14.7%)	32 (36%)	**0.001**[a]
Coronary artery disease	3 (2.9%)	8 (9%)	0.074[a]
Smoking	34 (33.3%)	46 (51.7%)	**0.010**[a]
Dupuytren's contracture	2 (2%)	8 (9%)	**0.047**[b]

[a]Chi-square test, [b]Fisher exact test

Table 2. General characteristics of Groups 1 and 2

Characteristics	Group 1 (n=102)	Group 2 (n=89)	p-values
Age (years)	55.12±9.51	54.79±9.99	**0.816**[b]
WC (cm)	95.6±12.3	101.8±16.3	**0.004**[a]
BMI (kg/m^2)	26.23±3.65	28.50±4.61	**<0.001**[a]
TG (mg/dL)	142.5±65.75	155±84	**0.003**[b]
HDL (mg/dL)	50±13.25	45±26	0.185[b]
Testosterone (ng/dL)	456±33	308±300	**0.002**[b]
Glucose (mg/dL)	95±19.25	100±30	**0.001**[b]
VAI	3.83±1.79	5.72±4.62	**0.001**[b]
IIEF score	23±2	22±10	**0.008**[b]

[a]Student's t-test with mean ± standard deviation
[b]Mann-Whitney U test with median ± interquartile range (IQR), WC: Waist circumference, BMI: Body mass index, TG: Triglyceride, HDL: High-density lipoprotein, VAI: Visceral adiposity index, IIEF: International Index of Erectile Function

1 mm (CI: 0.07-0.13) (R2=0.31, p<0.001), and penile curvature by 1.98 degrees (CI: 1.14-2.82) (R2=0.2, p<0.001) (Figure 2) (Table 3).

ROC analysis was performed to determine the success of VAI scores in predicting PD. AUC values, accuracy, sensitivity, selectivity, positive-negative predictive values, and likelihood ratio (+) values together with the 95% confidence intervals calculated because of the ROC analysis are shown in Table 4. The ROC curve is documented in Figure 3. ROC analysis showed a statistically significant difference between the VAI scores of Groups 1 and 2 [AUC=0.640 (0.559-0.721); p=0.001]. In terms of the AUC value, the discrimination power of VAI was weak. The cut-off point for the VAI score was found to be 5.43. For this cut-off point, classification success was determined as: 55.1% sensitivity and 80.4% selectivity.

Table 4. ROC analysis results and sensitivity, specificity, PPV, NPV, and likelihood ratio (+) values of VAI score in disease prediction

	VAI
AUC (95% CI)	0.640 (0.559-0.721)
P values	0.001
Cut-off	≤1.43
Accuracy	68.6% (131/191)
Sensitivity (95% CI)	55.1% (44.1-65.5) (49/89)
Specificity (95% CI)	80.4% (71.1-87.3) (82/102)
PPV (95% CI)	71% (58.7-81) (49/69)
NPV (95% CI)	67.2% (58-75.3) (82/122)
LR+ (95% CI)	2.81 (1.82-4.34)

ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval, VAI: Visceral adiposity index, LR: Likelihood ratio

Discussion

To the best of our knowledge, this study is first ever to define VAI as a new independent risk factor for PD. Each integer increase in the VAI value increases the probability of having Peyronie's disease 1.2 (1.07-1.35) times. Each VAI integer increase decreased 1.25 (CI: 1.03-1.47) points in the IIEF score, an increase of 1 mm (CI: 0.7-1.3) in plaque diameter, and an increase of 1.98 degrees (CI: 1.14-2.82) in curvature.

Table 3. Correlation analysis results between the VAI score and IIEF score, plaque size, and curvature degree in Group 2

		IIEF score	Plaque size (mm)	Curvature degree
VAI	r	-0.610*	0.557*	0.449*
	P values	<0.001	<0.001	<0.001
	N	89	89	89

*Pearson correlation coefficient (statistically significant p<0.001), VAI: Visceral adiposity index, IIEF: Index of Erectile Function

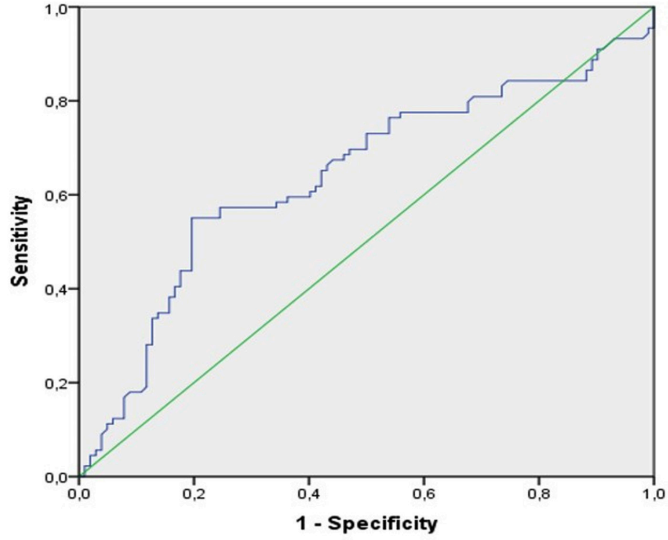

Figure 3. ROC curves for VAI scores in disease prediction

VAI: Visceral adiposity index, ROC: Receiver operating characteristic

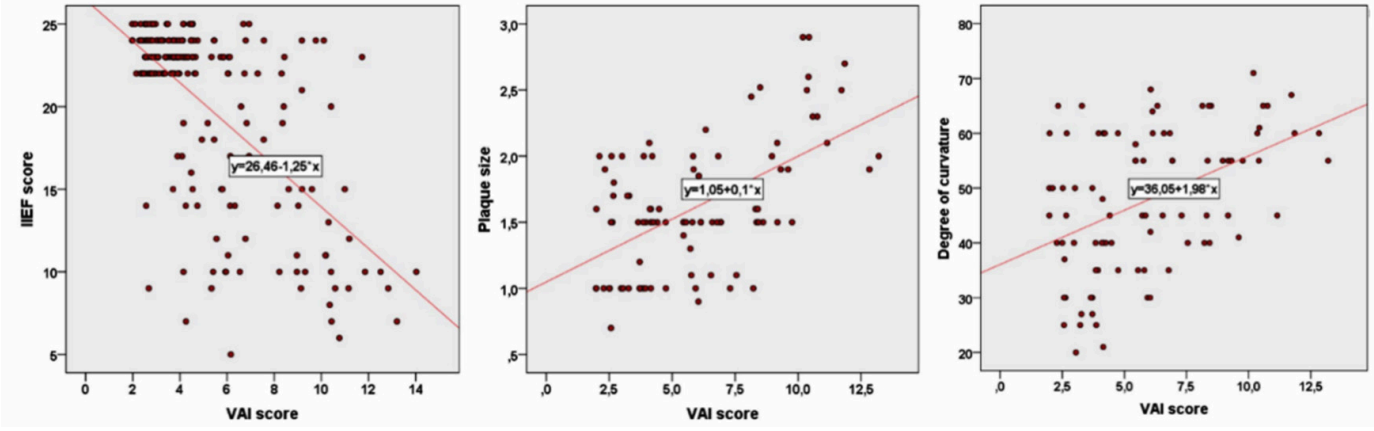

Figure 2. Scatterplots with regression curve for the correlation between VAI score and IIEF score, plaque size, and degree of curvature in the case group

VAI: Visceral adiposity index, IIEF: International Index of Erectile Function

Penile curvature is a common finding of PD. According to the most widely accepted theory, repetitive penile microtraumas stimulate subsequent scar formation in the penile tunica albuginea. Some conditions that accelerate the atherosclerotic process by decreasing tissue oxygenation, such as diabetes mellitus, hyperlipidemia, hypertension, and ischemic heart disease, may play a role in the etiopathogenesis of PD (10,13). One study reported 4.15 times reduced erectile response to combined injection and penile stimulation in patients with PD with type 2 diabetes mellitus (1). Excessive fibrin production and inhibition of fibrinolytic activity at the site of inflammation cause excessive fibrin deposition (14). Neutrophils, macrophages, and mast cells, which have a strong chemotactic effect, increase the production of proinflammatory cytokines such as transforming growth factor beta (TGF-β1) (15,16). The increase in TGF-β1 has a pleiotropic effect on fibroblast functions by increasing the synthesis of tissue collagenase inhibitors, which prevents connective tissue destruction (17). Fibroblasts have the same phenotype as smooth muscle cells and differentiate into myofibroblasts, mesenchymal cells capable of contraction and collagen synthesis (18). Myofibroblasts are the common cell types of all fibrotic diseases (19). Under normal conditions, collagen synthesis increases with the differentiation of fibroblasts to myofibroblasts in wounds, the damage is repaired, and re-epithelialization occurs with the formation of granulation tissue. In the later stages of healing, collagen synthesis is inhibited by apoptosis of myofibroblasts, the fibrinolytic system degrades fibrin, and matrix metalloproteinases remodel collagen fibers. In PD, unlike normal wound healing, myofibroblast production continues, and excess collagen causes tissue contraction, ultimately leading to fibrosis and plaque formation (20). One study reported that 67.5% of patients with PD had at least one risk factor (1). Another study reported that patients with diabetes with PD had much more severe penile deformity (21). Similarly, the rate of diabetes mellitus in this study was two times higher among patients with PD than in the control group.

Some studies have reported that plaque diameter was associated with decreased serum testosterone levels in patients with PD patients, whereas some showed only mild hypoandrogenemia and failed to show a relationship between increased plaque diameter and serum testosterone level (20-25). Based on testosterone levels, our results showed that androgen levels were within normal ranges, but the PD group had a slightly lower testosterone level. Testosterone is an endogenous anabolic hormone and is central to wound healing. Testosterone deficiency results in impaired wound healing and subsequent keloid formation by suppressing the overexpression of TGF-β1 (20,21).

A reason for decreased testosterone levels is the increased BMI (5). Adipose tissue dysfunction reduces adiponectin production decrease and increases proatherogenic, proinflammatory, and prediabetic adipocytokines (26). It is widely accepted that adipose tissue dysfunction is a critical process in the pathophysiology of obesity-related disorders by negatively affecting oxygenation (27). Adipose tissue, also known as fuel storage, supports the internal organs, which play an essential role in maintaining homeostasis via many bioactive mediators such as leptin, estrogen, resistin, and tumor necrosis factor-alpha (26). The distribution of adipose tissue may show individual heterogeneity. The adipose tissue is mainly localized in the superficial subcutaneous region and deep areas surrounding the internal organs. These components have different metabolic properties depending on tissue-specific gene expression, vascularization, and anatomical location. Visceral adiposity content is the most effective component of the pathophysiologic process (28).

Previous studies have showed obesity-associated decreases in testosterone levels secondary to decreased sex hormone-binding globulin, increased insulin resistance, and suppression of the hypothalamic-pituitary-testicular axis (5). Wang et al. (29) reported that obesity is closely related to hypogonadism. That study reported a high VAI level with high FSH and LH levels in response to hypogonadism.

Erectile dysfunction is a prevalent clinical condition in patients with PD. Erectile dysfunction in patients with PD is closely related to penile deformity, vascular dysfunction, or psychological reasons (30). Previous studies have reported the prevalence of erectile dysfunction in patients with PD patients ranging between 20% and 54.4% (31). Increased penile deformity may mechanically challenge the movement of the penis within the vagina, resulting in unsuccessful sexual intercourse. Patients may suffer from impaired body perception, leading to performance anxiety (32). Tunica albuginea is an essential part of penile erection where the veno-occlusive mechanism is provided. Irreversible structural changes within the penile tunica albuginea may potentialize the underlying ED (30,32). Indeed, previous reports showed that 30-86% of patients with PD had veno-occlusive dysfunction, and 44-52% had arterial insufficiency (30). We found that VAI increase was related to erectile dysfunction (1.25 odds ratio, CI: 1.03-1.47). Recent studies have showed similar odds ratios for erectile dysfunction ranging between 1.21 and 3.0 (33,34). The vascular endothelium is a sensitive part of the vascular system which can be negatively affected by inflammatory products including cytokines, adipokines, and fatty acids, in obese and dyslipidemic individuals (23). A subsequent decrease in nitric oxide release resulted in erectile dysfunction.

These factors are the potential contributing risk factors causing hypooxygenation at the level of the penile microenvironment (35). In addition, patients with PD younger than 40 years had a two-fold higher incidence of hypertension and hyperlipidemia

than those in the control group (36). Contrary to these reports, conflicting reports exist that show no relationship between PD and these comorbidities (31,37). Our results also showed no relationship between PD and ischemic heart disease.

In their study evaluating 1,833 cases, 319 of which were patients with PD, Habous et al. (38) found no relationship between PD and metabolic syndrome. They did report, however, that the incidence of PD increased in cases with uncontrolled diabetes (38). We examined the physiopathology of PD from a broad perspective in our study by analyzing VAI, which is closely related to a wide range of pathologies such as ischemic heart disease, hypertension, insulin resistance, pre-diabetes, diabetes mellitus, dyslipidemia, and hormonal disorders.

Study Limitations

The main limitation of our study is that it was conducted retrospectively with a limited number of cases. The lack of a quantitative analysis investigation of the abovementioned cytokines that are involved in the inflammatory process is another limitation.

Conclusion

This study has shown that as a predictor of visceral adipose dysfunction, VAI can be used as a reliable, independent risk factor for plaque size and penile curvature in patients with patients with PD. That being said, further evidence-based, comprehensive studies are needed to support our data.

Ethics

Ethics Committee Approval: This retrospective study involving human participants was in accordance with the ethical standards of the Institutional and National Research Committee; and with 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Gaziosmanpasa University Clinical Studies Ethics Committee approved this study (decision 21-KAEK-132, date: 20.05.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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References

1. Kadioglu A, Tefekli A, Erol B, Oktar T, Tunc M, Tellaloglu S. A retrospective review of 307 men with Peyronie's disease. J Urol 2002;168:1075-1079.
2. Culha M, Alici B, Acar O, Mutlu N, Gökalp A. The relationship between diabetes mellitus, impotence and veno-occlusive dysfunction in Peyronie's disease patients. Urol Int 1998;60:101-104.
3. Levine LA, Estrada CR, Storm DW, Matkov TG. Peyronie disease in younger men: characteristics and treatment results. J Androl 2003;24:27-32.
4. Ateş E, Gökçe A. The pathophysiology of peyronie's disease. Androl Bul 2019;21:161-169.
5. Fui MN, Dupuis P, Grossmann M. Lowered testosterone in male obesity: mechanisms, morbidity and management. Asian J Androl 2014;16:223-231.
6. Bolat MS, Kocamanoglu F, Ozbek ML, Buyukalpelli R, Asci R. Can High Visceral Adiposity Index Be a Risk Factor for Sexual Dysfunction in Sexually Active Men? J Sex Med 2020;17:1926-1933.
7. Nusrianto R, Tahapary DL, Soewondo P. Visceral adiposity index as a predictor for type 2 diabetes mellitus in Asian population: A systematic review. Diabetes Metab Syndr 2019;13:1231-1235.
8. Eren H, Horsanlı MO, Dil E, Özbek E. Visceral Adiposity Index and Overactive Bladder in Postmenopausal Woman: A Novel Predictive Risk Factor. Kocaeli Med J 2019;8:84-89.
9. Karabay E, Karsiyakali N, Kayar K, Verim L, Tosun C, Yucebas OE. Evaluation of the relationship between visceral adiposity index and overactive bladder symptoms in females. Endourol Bull 2020;12:150-156.
10. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A; AlkaMeSy Study Group. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care 2010;33:920-922.
11. Li R, Li Q, Cui M, Ying Z, Li L, Zhong T, Huo Y, Xie P. Visceral adiposity index, lipid accumulation product and intracranial atherosclerotic stenosis in middle-aged and elderly Chinese. Sci Rep 2017;7:7951.
12. Bolat MS, Ozbek ML, Şahin B, Yılmaz M, Kocamanoglu F, Buyukalpelli R, Sunter AT, Asci R. Impact of high visceral adiposity index associated with metabolic syndrome on erectile function in sexually active men: Results of a cross-sectional study. Int J Clin Pract 2021;75:e14111.
13. Pryor J, Akkus E, Alter G, Jordan G, Lebret T, Levine L, Mulhall J, Perovic S, Ralph D, Stackl W. Peyronie's disease. J Sex Med 2004;1:110-115.
14. El-Sakka AI, Salabas E, Dinçer M, Kadioglu A. The pathophysiology of Peyronie's disease. Arab J Urol 2013;11:272-277.
15. Garaffa G, Trost LW, Serefoglu EC, Ralph D, Hellstrom WJ. Understanding the course of Peyronie's disease. Int J Clin Pract 2013;67:781-788.
16. Wynn TA, Vannella KM. Macrophages in Tissue Repair, Regeneration, and Fibrosis. Immunity 2016;44:450-462.
17. Diegelmann RF. Cellular and biochemical aspects of normal and abnormal wound healing: an overview. J Urol 1997;157:298-302.
18. Ryu JK, Kim WJ, Choi MJ, Park JM, Song KM, Kwon MH, Das ND, Kwon KD, Batbold D, Yin GN, Suh JK. Inhibition of histone deacetylase 2 mitigates profibrotic TGF-β1 responses in fibroblasts derived from Peyronie's plaque. Asian J Androl 2013;15:640-645.
19. Cannito S, Novo E, Parola M. Therapeutic pro-fibrogenic signaling pathways in fibroblasts. Adv Drug Deliv Rev 2017;121:57-84.
20. Ilg MM, Mateus M, Stebbeds WJ, Milenkovic U, Christopher N, Muneer A, Albersen M, Ralph DJ, Cellek S. Antifibrotic Synergy Between

Phosphodiesterase Type 5 Inhibitors and Selective Oestrogen Receptor Modulators in Peyronie's Disease Models. Eur Urol 2019;75:329-340.

21. Tefekli A, Kandirali E, Erol B, Tunc M, Kadioglu A. Peyronie's disease: a silent consequence of diabetes mellitus. Asian J Androl 2006;8:75-79.
22. Cavallini G, Biagiotti G, Lo Giudice C. Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. J Androl 2012;33:381-388.
23. Nam HJ, Park HJ, Park NC. Does testosterone deficiency exaggerate the clinical symptoms of Peyronie's disease? Int J Urol 2011;18:796-800.
24. Moreno SA, Morgentaler A. Testosterone deficiency and Peyronie's disease: pilot data suggesting a significant relationship. J Sex Med 2009;6:1729-1735.
25. Kirby EW, Verges D, Matthews J, Carson CC, Coward RM. Low testosterone has a similar prevalence among men with sexual dysfunction due to either Peyronie's disease or erectile dysfunction and does not correlate with Peyronie's disease severity. J Sex Med 2015;12:690-696.
26. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J 2008;29:2959-2971.
27. Goossens GH, Blaak EE. Adipose tissue dysfunction and impaired metabolic health in human obesity: a matter of oxygen? Front Endocrinol (Lausanne) 2015;6:55.
28. Mittal B. Subcutaneous adipose tissue & visceral adipose tissue. Indian J Med Res 2019;149:571-573.
29. Wang N, Zhai H, Han B, Li Q, Chen Y, Chen Y, Xia F, Lin D, Lu Y. Visceral fat dysfunction is positively associated with hypogonadism in Chinese men. Sci Rep 2016;6:19844.
30. Carson C. Peyronie's disease: new paradigm for the treatment of a unique cause of erectile dysfunction. Postgrad Med 2020;132(sup4):4-8.
31. Usta MF, Bivalacqua TJ, Jabren GW, Myers L, Sanabria J, Sikka SC, Hellstrom WJ. Relationship between the severity of penile curvature and the presence of comorbidities in men with Peyronie's disease. J Urol 2004;171:775-779.
32. Gholami SS, Gonzalez-Cadavid NF, Lin CS, Rajfer J, Lue TF. Peyronie's disease: a review. J Urol 2003;169:1234-1241.
33. Akdemir AO, Karabakan M, Aktas BK, Bozkurt A, Ozgur EG, Akdogan N, Yarıs M. Visceral adiposity index is useful for evaluating obesity effect on erectile dysfunction. Andrologia 2019;51:e13282.
34. Dursun M, Besiroglu H, Cakir SS, Otunctemur A, Ozbek E. Increased visceral adiposity index associated with sexual dysfunction in men. Aging Male 2018;21:187-192.
35. Kadioglu A, Dincer M, Salabas E, Culha MG, Akdere H, Cilesiz NC. A Population-Based Study of Peyronie's Disease in Turkey: Prevalence and Related Comorbidities. Sex Med 2020;8:679-685.
36. Tefekli A, Kandirali E, Erol H, Alp T, Köksal T, Kadioğlu A. Peyronie's disease in men under age 40: characteristics and outcome. Int J Impot Res 2001;13:18-23.
37. Casabé A, Bechara A, Cheliz G, De Bonis W, Rey H. Risk factors of Peyronie's disease. What does our clinical experience show? J Sex Med 2011;8:518-523.
38. Habous M, Malkawi I, Han E, Farag M, Muir G, Abdelwahab O, Nassar M, Mahmoud S, Santucci R, Binsaleh S. Peyronie's Disease is common in poorly controlled diabetics but is not associated with the Metabolic Syndrome. Urol Ann 2019;11:252-256.

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Prevalence of Poor Sleep Quality and Its Determinants Among Men Suffering from Erectile Dysfunction

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What's known on the subject? and What does the study add?

Erectile dysfunction is frequent among men with sleep disorders. Men with current sleep disturbances have also increased the risk for erectile difficulty in their future life. The correlation between sleep quality and erectile function and determinants of poor sleep quality among men who suffer from erectile dysfunction are still obscure. Near half of the men with erectile dysfunction are poor sleepers. Quality of sleep correlates with erectile function. Lean body mass, younger age, and severe depression are the main predictors of poor sleep quality.

Abstract

Objective: Recent findings implicate a higher prevalence of erectile dysfunction (ED) among men with sleep disorders. We investigated sleep quality among men with ED.

Materials and Methods: A prospective study was conducted at 12 different andrology outpatient clinics among men with complaints of insufficient erections. The subjective quality of sleep was measured using the Pittsburgh Sleep Quality Inventory. Erectile function and its dimensions were measured using the International Index of Erectile Function (IIEF) questionnaire. The age-adjusted Charlson comorbidity index and Beck Depression Inventory were used to evaluate interrelations with comorbid disease severity and depression of the subjects consecutively in the study.

Results: Among 431 eligible men, the median age of the participants and their erectile function scores in the IIEF were 51 [interquartile range (IQR)=43-59] and 16 (IQR=11-19), respectively. Poor sleep was observed in 192 of 431 (44.5%) subjects. Multivariable analysis revealed that younger age [odds ratio (OR)=0.95, p=0.01], lower body mass (OR=0.86, p=0.01), lower serum high-density lipoprotein cholesterol (OR=0.95, p=0.02), and higher severity of depression (OR=2.1, p=0.0001) were predictors of poor sleep quality among men with ED.

Conclusion: Nearly half of the men with ED also suffer from poor sleep. Younger age, lean body mass, and severe depression were the main predictors of poor sleep quality among ED sufferers.

Keywords: Erectile dysfunction, sexual satisfaction, sleep quality

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Introduction

As an important pillar of good health, such as diet and exercise, sleep quality is hypothesized to be closely related to erectile function (1). Recent data obtained from large population-based surveys reveal the prevalence of poor sleep quality about 8.3% which is also associated with advanced age, female gender, smoking, the presence of cardiovascular diseases, respiratory diseases, anxiety, and depression (2-5). Sleep disorders and their association with erectile dysfunction (ED) are increasing topics of interest in recent studies (1,6-13). Data obtained from several studies with few human subjects who suffered from sleep dysfunction demonstrated that ED is frequent among men with sleep disorders (6-13). Furthermore, recent longitudinal studies have emphasized increased odds of ED in the future life of men with current sleep disturbances (3). In this manner, several conditions were proved to be associated with sleep dysfunction such as higher body mass index (BMI), advanced age, comorbid diseases such as diabetes, depression and, anxiety among men accompanied with ED (1,6-13).

Although there are several studies indicating the higher prevalence of ED or worse outcomes by the means of erectile function among men who have sleep dysfunction, reverse association still needs to be clarified. In other words, "How much attention should be given to sleep quality in men complaining of ED?". Does the quality of sleep correlate with erectile function in patients with ED? Furthermore, determinants of the sleep quality among men complaining of ED are awaiting validation.

In this study, investigation of subjective sleep quality, the prevalence of poor sleeping, and the role of associated factors like BMI, age, and comorbid diseases among men who were admitted with ED complaints to andrology clinics were aimed.

Materials and Methods

Subjects

We conducted a cross-sectional study among men who were admitted to andrology outpatient clinics with complaints of ED. Patients who had a stable heterosexual relationship in the last six months and who gave informed consent to participate in this questionnaire-based study were eligible. Subjects who had proven neurological disease or used psychotropic medications (antidepressants, sedatives, anxiolytics, and so on) were excluded from the study. The study design was approved by Ethical Review Board of the Niğde Ömer Halisdemir University (no: 2019/33, date: 01.11.2019) and permission of the provincial health management office (2019-11/02). The study was conducted between November 2019 and November 2020 following institutional review board recommendations from 12 different training hospitals. Informed consent was obtained from all participants, and survey administration was conducted face-to-face by researchers in all participating centers.

Outcome Measures

Erectile function severity was measured by the International Index of Erectile Function (IIEF) and degree of sleep quality was measured using the Pittsburgh Sleep Quality Inventory (PSQI). The presence and degree of depression measured by the Beck Depression Inventory (BDI) were the main outcome measures of the current study. Validated versions of the three questionnaires were used (14-16).

Data Management

Demographic characteristics, BMI and waist circumference measurements, summary of the age-adjusted Charlson comorbidity index (AACCI) ratings, and serum measurements of fasting blood glucose (FBG), cholesterol total, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and serum testosterone levels (as nanogram per dL) obtained from routine baseline initial evaluations were recorded (17). All recorded data were submitted by each participating author to a web-based data management program. The presence of ED was attributed to the subjects' ratings in the erectile function domain of the IIEF (below 21 points indicated ED). Scores in the BDI were interpreted as follows: 0-9, minimal level; 10-16, mild level; 17-29, moderate level; and 30-63, severe level of depression. The PSQI consists of 19 items (15 rated 0-3 and 4 open ended) that generate seven components of sleep as follows: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of medications for sleep, and daytime disturbance (14). The global PSQI score is calculated by the sum of all of the above components (14). We used the original version of this questionnaire, with 5 points or greater used as the global score cut-off for which to define poor sleep quality (14,18).

Statistical Analysis

We anticipated to enroll at least 270 subjects in the study due on the sample size estimation summary obtained from a G*Power analysis with a power value of 80% and an alpha error probability of 5.0%. The latest version of PASW (IBM, Armonk, NY, USA) was used for statistical analysis. A reliability analysis of the PSQI scores of our cohort was performed. We used the chi-square test and non-parametric tests. Binomial logistic regression for dichotomous outcomes and stepwise hierarchical linear regression for the measured variables. P-values of 0.05 or lower were considered significant, while p-values of 0.01 indicated strong correlations in the correlation analysis.

Results

Among the 431 eligible subjects, the median age was 51 [interquartile range (IQR)=43-59]. The demographic characteristics of the subjects are depicted in Table 1. During the initial physical examination, palpable Peyronie's plaque and benign scrotal pathologies were noted in 5 (1.0%) and 8 (1.8%) patients, respectively. Sixty-two (14.6%) patients had taken a previous medication for ED in the last 6 months, which included tadalafil, sildenafil, and intra-cavernous injection therapy (10.7%, 3.0%, and 0.5%, respectively).

Among participants, the mean IIEF erectile function score was 14.3±6.5. The distribution of subjects according to categories of erectile function in IIEF was as follows: 108 (26%) with severe ED, 142 (33%) with moderate ED, 139 (32%) with mild-to-moderate ED, 34 (7.0%) with mild ED, and no ED in 8 (2.0%). The mean BDI score of the subjects was 13.9±8.1. We noticed a moderate to severe degree of depression in 147 (34%) subjects in our cohort. The distribution of the depression categories was as follows: 32%, minimal; 34%, mild; 30%, moderate; and 4.0%, severe. The mean global PSQI score in our cohort was 4.7±2.9. Reliability analysis among the seven components of the PSQI questionnaire revealed a high level of consistency (Cronbach's alpha=0.66). We observed that 192 of 431 (44.5%) responders in our cohort were poor sleepers. The distribution of variables between the good and poor sleepers is shown in Table 2.

Table 1. Demographic characteristics of the participants

Age	**<40**	**40-49**	**50-59**	**60-69**	**>70**	
	13%	30%	34%	18%	5%	
Graduation	Primary School	High School	University	Master, PhD etc.		
	28%	43%	28%	1%		
Count of children	0	1	2	3	4	>5
	10%	13%	34%	%24	9%	10%
Smoking status	No	Yes				
	56%	44%				
Alcohol consumption	No	Yes				
	88%	12%				
AACCI	0	1	2	3	4	>5
	33%	27%	20%	10%	6%	4%
Main co-morbid diseases	DM	CAD	PVD	COPD	CTD	Peptic Ulcer
	25%	8%	3%	3%	2%	1%

Table 2. Differences between good and poor sleepers

	Good sleepers n=233	**Poor sleepers n=192**	**p-value**
Age	52.9±11.6	48.6±10.8	0.0001
BMI (kg/m²)	28.3±3.9	27,5±4.0	0.04
WC (cm)	92.4±11.3	94.4±13.9	0.18
AACCI score	1.5±1.6	1.3±1.5	0.10
FBG level	117.7±57.3	118.6±63.7	0.87
Total-Cholesterol level	199.2±42.3	195.6±48.1	0.42
LDL-C level	127.4±82.5	118.7±48.2	0.22
HDL-C level	47.6±15.1	44.2±12.7	0.01
Triglycerides	165.1±99.4	193.4±147.4	0.02
Serum Testosterone level (ng/dL)	301.0±224.5	307.2±233.4	0.78
Erectile function (IIEF)	15.3±6.1	13.1±6.7	0.001
Orgasmic function (IIEF)	5.4±2.7	5.3±3.1	0.59
Sexual desire (IIEF)	5.6±1.9	5.5±2.1	0.70
Sexual satisfaction (IIEF)	6.5±3.2	5.8±3.4	0.02
Overall satisfaction (IIEF)	5.0±2.0	4.5±2.0	0.01
Depression score (BDI)	11.2±6.2	17.1±8.8	0.0001

Correlation Analysis

We noticed correlations between the EF scores of the subjects and their AACCI scores (Spearman's Rho=-0.20), FBG (Spearman's Rho=-0.15), BDI scores (Spearman's Rho=-0.19), and PSQI scores (Spearman's Rho=-0.14). The means of the sexual satisfaction IIEF domain and the overall satisfaction scores of our cohort were correlated with the global PSQI scores (Spearman's Rho=-0.11 and Spearman's Rho=-0.11). Additionally, the global PSQI scores of the patients were correlated with their BDI scores (Spearman's Rho=0.42), age (Spearman's Rho=-0.17), degree of graduation (Spearman's Rho=0.19), consumption of alcohol (Spearman's Rho=0.20), and serum HDL levels (Spearman's Rho=-0.14). Finally, the BDI scores of the patients were correlated with age (Spearman's Rho=-0.13). We noticed a higher estimate of coincidence between the presence of poor sleep quality (global PSQI score ≥5) and moderate to severe depression (according to their BDI scores) in our cohort [odds ratio (OR)=3.4 (95% confidence interval (CI) 2.2-5.3), p=0.0001].

Multivariable analysis: In our multinomial logistic regression analysis, the BMI of the subjects significantly predicted the presence of ED (OR=1.2, p=0.03). Poor sleep quality was predicted by age (OR=0.95, p=0.01), waist circumference (OR=1.04, p=0.03), BMI (OR=0.86, p=0.01), serum HDL level (OR=0.95, p=0.02), BDI (OR=2.1, p=0.0001), and IIEF score (OR=0.89, p=0.03). The level of serum testosterone (OR=1.002, p=0.01) and global PSQI score (OR=1.45, p=0.0001) of the enrolled subjects were predictors for the presence of depression.

Finally, a path analysis using hierarchical linear regression was applied. Our results with path analysis using the erectile function score of the subjects as the dependent outcome variable, are depicted in Figure 1. Our model demonstrates that the erectile function of subjects is predicted by a score of comorbidity index and depression level, while sleep quality and depression level of the subjects are in relation with bidirectional way.

Discussion

We evaluated the prevalence and contribution of poor sleep quality in men with ED in a hospital setting. Poor sleep according to questionnaire-based evaluations has been observed in nearly half of the men having ED. Poor sleepers were younger, had lower BMI values, had more severe ED and had poor satisfaction with intercourse and more depression compared with men who had good sleep quality. However, erectile function predicted by sleep quality in the unadjusted model along with depression levels and BMI values of the ED sufferers were the predictors of sleep quality in our final model.

Subjective sleep quality in the current study was measured using a self-reported questionnaire (PSQI), which is accepted as the most useful tool in both clinical and non-clinical settings (18). The results of the internal consistency level of the questionnaire were in accordance with the previously reported results and support the higher internal reliability of the questionnaire components (18-20). The prevalence of poor sleep quality among our study subjects was higher than that reported in the general population (2-5,21-23). The mean global score of our study subjects was also higher than that previously reported in the general population of Shanghai (5). The prevalence of sleep quality measured by the same tool among ED sufferers has been evaluated previously in a Chinese study, and they found slightly higher prevalence rates (24). We noticed that in our study, the cut-off level to define poor sleep quality in the PSQI was lower and the mean age of the participating ED sufferers was higher than that in the Chinese study, which might have contributed to the difference. Furthermore, previous surveys demonstrated a higher prevalence of ED among sleep disorders, and a higher incidence of ED in longitudinal studies among patients with poor sleep quality (2-7,13,25-27). Our study results contribute to the literature by describing the presence of a reverse association.

Our study clarifies that sleep quality is predicted by erectile function, and poor sleep quality is related to lower BMI, lower serum HDL level, younger age, higher WC, and severe depression. The adjusted hierarchical model in our study emphasizes the severity of depression and lean body mass among men with ED as the main predictors of sleep quality. Previous surveys conducted in the general population have demonstrated that sleep disturbance is predicted by older age, smoking, lower educational level, more comorbid diseases, higher anxiety,

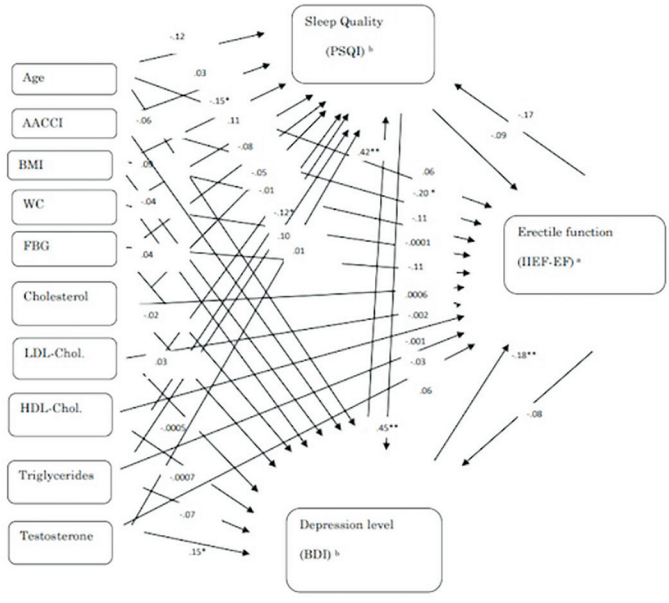

Figure 1. Results of path analysis

*p-value of <0.05, **p-value <0.01, [a]Higher score indicates better outcome, [b]Higher score indicates worse outcome

and depression (2,4,5). Cross-sectional studies investigating interactions between erectile functions and sleep disorders revealed an association between sleep disturbances and ED, perceived stress, and depression (2,7,26,28). To understand the type of interrelation, our study revealed consistent findings with the study by Seehuus and Pigeon (3) that concluded an association between sleep disturbance and ED. We found a depression-dependent relationship between sleep quality and erectile function, which was independent of a previous survey. In a previous study, Seehuus and Pigeon (3) demonstrated a relationship between erectile function and insomnia severity, rather than sleep quality. In this regard, we conclude that the tools used to evaluate sleep disturbance (sleep quality vs. insomnia severity) and the differences in the populations studied may play roles in this issue.

Our study findings regarding the correlation between ED and age were concordant with those of Cheng et al.'s (24) study; however, our findings were in contrast to the findings of Martin et al. (27). In the study by Martin et al. (27), the independent interrelation of sleep disturbance with erectile function was demonstrated only in older men (ages >65 years old) (27). However, in the latter study, obstructive sleep problems were evaluated methodologically, which is different from our study (27). Our findings support a depression-dependent relationship between ED and subjective sleep quality in relatively younger patients. In this context, we conclude that the knot untier of this complex interrelation appears to be age. Age-dependent mediators, such as depression, exist in younger populations with poor sleep quality, as well as endothelial risk factors that manifest as obstructive sleep problems and insomnia in relatively older men with ED.

In our study subjects, ED predicted only the BMI of men in the multivariate model. The quality of erectile function was hierarchically related to sleep quality, depression, and the quantity of comorbid diseases after regression analysis. Current knowledge in the literature about the possible role of sleep disorders in the etiopathogenesis of ED is limited. A clinical study performed in a small population demonstrated lower serum melatonin levels in patients with ED than in those without non-ED patients, as well as an association with ED severity (29). The preventive role of melatonin on the morphological changes in erectile tissue induced by diabetes and chronic ischemia has also been clarified in a few preclinical studies (30,31). There are also clinical studies reporting improvements in erectile function with the treatment of accompanying obstructive sleep disorders alone (9-12,32). With the current findings, we are still far from making a precise conclusion. However, our study clarifies that comorbid diseases and accompanying depression should be considered when considering sleep disorders as a risk factors for ED.

Study Limitations

Ongoing concerns about the use of the PSQI as a diagnostic tool to differentiate between good and poor sleepers and the lack of objective sleep measurements via methods such as polysomnography are limitations of the current study. The lack of health- and sex-related quality of life measurements in our study subjects is another limitation. The recruitment period of the study overlapped with the first wave of the COVID-19 pandemic. As we had already established our study protocol prospectively, we had not performed any of the COVID-19 tests. However, subjects the study had no proven COVID-19 infection while they could admit us for their erectile difficulty. However, we cannot ignore either the effects of asymptomatic COVID-19 infection or the acute traumatic effects of a pandemic on the psychological health of the study subjects, which might be rendered as a limitation theoretically.

Conclusion

We revealed the frequency of poor sleep and determinants of sleep quality among patients with ED. A considerable number of subjects were poor sleepers within the representative sample of men with ED. The quality of sleep correlated with erectile function among patients with ED. Poor sleep quality was more frequent in younger men, and lean body mass among ED sufferers, and was associated with worse satisfaction, erectile function, and depression. Depression is central to the interrelation between sleep dysfunction and ED. Longitudinal and multidisciplinary studies are required on this topic.

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Ethics

Ethics Committee Approval: The study design was approved by ethical review board of the Niğde Ömer Halisdemir University (no: 2019/33, date: 01.11.2019) and permission of the provincial health management office (2019-11/02).

Informed Consent: Informed consent was obtained from all participants.

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Authorship Contributions

Surgical and Medical Practices: A.C., Concept: A.C., İ.O.K., K.E.A., Design: A.C., İ.O.K., K.E.A., Data Collection or Processing: A.C., İ.O.K., M.B.D., Ö.Y., A.B., Ü.G., E.H., Y.K., T.T., H.İ.Ç., B.Ş., Analysis or Interpretation: A.C., B.Ş., Literature Search: A.C., Writing: A.C.

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References

1. Cho JW, Duffy JF. Sleep, Sleep Disorders, and Sexual Dysfunction. World J Mens Health 2019;37:261-275.
2. Zheng W, Luo XN, Li HY, Ke XY, Dai Q, Zhang CJ, Cassidy RM, Zhang XY, Ning YP. Gender differences in the prevalence and clinical correlates of sleep disturbance in general hospital outpatients. Psychiatry Res 2018;269:134-139.
3. Seehuus M, Pigeon W. The sleep and sex survey: Relationships between sexual function and sleep. J Psychosom Res 2018;112:59-65.
4. Li N, Xu G, Chen G, Zheng X. Sleep quality among Chinese elderly people: A population-based study. Arch Gerontol Geriatr 2020;87:103968.
5. Wu W, Jiang Y, Wang N, Zhu M, Liu X, Jiang F, Zhao G, Zhao Q. Sleep quality of Shanghai residents: population-based cross-sectional study. Qual Life Res 2020;29:1055-1064.
6. Steinke E, Palm Johansen P, Fridlund B, Broström A. Determinants of sexual dysfunction and interventions for patients with obstructive sleep apnoea: a systematic review. Int J Clin Pract 2016;70:5-19.
7. Chen KF, Liang SJ, Lin CL, Liao WC, Kao CH. Sleep disorders increase risk of subsequent erectile dysfunction in individuals without sleep apnea: a nationwide population-base cohort study. Sleep Med 2016;17:64-68.
8. Jara SM, Hopp ML, Weaver EM. Association of Continuous Positive Airway Pressure Treatment With Sexual Quality of Life in Patients With Sleep Apnea: Follow-up Study of a Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg 2018;144:587-593.
9. İrer B, Çelikhisar A, Çelikhisar H, Bozkurt O, Demir Ö. Evaluation of Sexual Dysfunction, Lower Urinary Tract Symptoms and Quality of Life in Men With Obstructive Sleep Apnea Syndrome and the Efficacy of Continuous Positive Airway Pressure Therapy. Urology 2018;121:86-92.
10. Pascual M, de Batlle J, Barbé F, Castro-Grattoni AL, Auguet JM, Pascual L, Vilà M, Cortijo A, Sánchez-de-la-Torre M. Erectile dysfunction in obstructive sleep apnea patients: A randomized trial on the effects of Continuous Positive Airway Pressure (CPAP). PLoS One 2018;13:e0201930.
11. Barbosa FT, Silva MP, Fontes LES, Pachito DV, Melnik T, Riera R. Non-invasive positive airway pressure therapy for improving erectile dysfunction in men with obstructive sleep apnoea. Cochrane Database Syst Rev 2021;9:CD013169.
12. Yang Z, Du G, Ma L, Lv Y, Zhao Y, Yau TO. Continuous positive airway pressure therapy in obstructive sleep apnoea patients with erectile dysfunction-A meta-analysis. Clin Respir J 2021;15:163-168.
13. Mostafa RM, Kamel NM, Elsayed EM, Saad HM. Assessment of sexual functions in male patients with obstructive sleep apnea. Am J Otolaryngol 2021;42:102899.
14. Buysse DJ, Hall ML, Strollo PJ, Kamarck TW, Owens J, Lee L, Reis SE, Matthews KA. Relationships between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and clinical/polysomnographic measures in a community sample. J Clin Sleep Med 2008;4:563-571.
15. Beck AT, Steer RA BG. Beck Depression Inventory. 2nd ed. Manual. San Antonio, TX: Psychol Corp 1996;40.
16. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822-830.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
18. Fabbri M, Beracci A, Martoni M, Meneo D, Tonetti L, Natale V. Measuring Subjective Sleep Quality: A Review. Int J Environ Res Public Health 2021;18:1082.
19. Salahuddin M, Maru TT, Kumalo A, Pandi-Perumal SR, Bahammam AS, Manzar MD. Validation of the Pittsburgh sleep quality index in community dwelling Ethiopian adults. Health Qual Life Outcomes 2017;15:58.
20. Becker NB, de Neves Jesus S. Adaptation of a 3-factor model for the Pittsburgh Sleep Quality Index in Portuguese older adults. Psychiatry Res 2017;251:298-303.
21. Morin CM, LeBlanc M, Daley M, Gregoire JP, Mérette C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. Sleep Med 2006;7:123-130.
22. Ohayon MM, Reynolds CF 3rd. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Med 2009;10:952-960.
23. Cho YW, Shin WC, Yun CH, Hong SB, Kim J, Earley CJ. Epidemiology of insomnia in korean adults: prevalence and associated factors. J Clin Neurol 2009;5:20-23.
24. Cheng QS, Liu T, Huang HB, Peng YF, Jiang SC, Mei XB. Association between personal basic information, sleep quality, mental disorders and erectile function: a cross-sectional study among 334 Chinese outpatients. Andrologia 2017;49.
25. Lin HH, Ho FM, Chen YF, Tseng CM, Ho CC, Chung WS. Increased risk of erectile dysfunction among patients with sleep disorders: a nationwide population-based cohort study. Int J Clin Pract 2015;69:846-852.
26. Soterio-Pires JH, Hirotsu C, Kim LJ, Bittencourt L, Tufik S, Andersen ML. The interaction between erectile dysfunction complaints and depression in men: a cross-sectional study about sleep, hormones and quality of life. Int J Impot Res 2017;29:70-75.
27. Martin SA, Appleton SL, Adams RJ, Taylor AW, Vincent A, Brook NR, Catcheside PG, Vakulin A, McEvoy RD, Antic NA, Wittert GA. Erectile dysfunction is independently associated with apnea-hypopnea index and oxygen desaturation index in elderly, but not younger, community-dwelling men. Sleep Health 2017;3:250-256.
28. Kellesarian SV, Malignaggi VR, Feng C, Javed F. Association between obstructive sleep apnea and erectile dysfunction: a systematic review and meta-analysis. Int J Impot Res 2018;30:129-140.
29. Bozkurt A, Karabakan M, Aktas BK, Gunay M, Keskin E, Hirik E. Low serum melatonin levels are associated with erectile dysfunction. Int Braz J Urol 2018:794-799.
30. Sawada N, Nomiya M, Zarifpour M, Mitsui T, Takeda M, Andersson KE. Melatonin Improves Erectile Function in Rats With Chronic Lower Body Ischemia. J Sex Med 2016;13:179-186.
31. Zhang JL, Hui Y, Zhou F, Hou JQ. Neuroprotective effects of melatonin on erectile dysfunction in streptozotocin-induced diabetic rats. Int Urol Nephrol 2018;50:1981-1988.
32. Schulz R, Bischof F, Galetke W, Gall H, Heitmann J, Hetzenecker A, Laudenburg M, Magnus TJ, Nilius G, Priegnitz C, Randerath W, Schröder M, Treml M, Arzt M; German Sleep Apnea Research Network (GERSAN). CPAP therapy improves erectile function in patients with severe obstructive sleep apnea. Sleep Med 2019;53:189-194.

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Evaluation of the Genetic Analysis Results in Infertile Patients with Non-Obstructive Azoospermia

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What's known on the subject? and What does the study add?

Genetic factors are important among the causes of non-obstructive azoospermia (NOA). Genetic tests can provide information about the possibility of sperm retrieval before microscopic testicular sperm extraction (micro-TESE) is applied to NOA patient. Age, testis volume, serum FSH and testosterone levels, and the presence of Klinefelter syndrome (KS) were found to affect the sperm retrieval rates (SRR) in micro-TESE. Moreover, sperm retrieval rate (SRR) of patients with KS and Y chromosome microdeletion was lower than the literature.

Abstract

Objective: To evaluate the genetic analysis results of patients who referred to our clinic infertility and whom semen analysis revealed non-obstructive azoospermia (NOA).

Materials and Methods: Among 994 patients who underwent a microscopic testicular sperm extraction (micro-TESE) operation for NOA, 497 patients who were tested for karyotype analysis and 450 patients who were tested for chromosome Y microdeletion were included in our study. The rates of Klinefelter syndrome (KS) and Y chromosome microdeletion, sperm retrieval rates (SRR) in these genetic anomalies and the factors affecting them were investigated. Additionally, the association between the age, duration of infertility, testicular size, serum follicle stimulant hormone (FSH) and testosterone levels of patients and sperm extraction rates of micro-TESE operations were also evaluated.

Results: The overall SRR of NOA patients who underwent micro-TESE was 47.5%. Among 104 patients with KS, sperm was successfully found after micro-TESE in 22 (21.2%). Fourteen patients were diagnosed with the Y chromosome microdeletion and sperm was successfully found in 4 (28.6%) of them; while the duration of infertility did not affect the SRR after micro-TESE ($p=0.712$); age, testicular volume serum FSH and testosterone levels had a significant effect on the SRR ($p<0.005$).

Conclusion: In this study, the SRR of patients who have chromosome Y microdeletion or KS, was found to be lower than other studies in the literature. This difference could be derived from the genetically tested population's structure, variance in the gene areas used for scanning and different demographic characteristics of different regions.

Keywords: Genetic analysis, Klinefelter syndrome, micro-TESE, non-obstructive azoospermia, Y microdeletion

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Introduction

Infertility is defined as the failure to achieve pregnancy after a year or more of regular and unprotected sexual intercourse (1). When all married couples are considered, the worldwide prevalence of infertility is thought to be 15%. In studies consisting of normal healthy couples having unprotected sex, it has been shown that pregnancy can be achieved within 6 months in 60-75%, and within 1 year in 90% of them (2).

Azoospermia is defined as the absence of sperm in the ejaculate, and has been determined in 1% of all males and 10-15% of infertile males (3). Non-obstructive azoospermia (NOA) is defined as the absence of spermatozoa in the ejaculate due to minimal or inability to produce mature sperm in the testicles. Genetic factors are important among the causes of NOA. Genetic tests can provide information about the possibility of sperm retrieval before microscopic testicular sperm extraction (micro-TESE) is applied to patients with NOA.

Micro-TESE is a surgical method in which spermatogenesis is shown to continue in the testes in small foci under a microscope and mature sperm cells are obtained from those foci. In patients who present because of infertility, Y-chromosome microdeletion genetic analysis should be applied to patients with a sperm count of <5 million, and karyotype analysis to patients with sperm count of <10 million, as well as to those with azoospermia (4,5). While chromosome anomalies are seen in 0.5% of the normal population, this rate increases up to 5.8% in infertile males (6). Therefore, it is recommended screening for genetic anomalies in infertile males before intracytoplasmic sperm injection (ICSI). These genetic analyses should include genetic tests related to sex chromosome anomalies [Klinefelter syndrome (KS), XYY syndrome, XX male syndrome, mixed gonadal dysgenesis, Y chromosome microdeletion, other Y chromosome structural anomalies, reciprocal translocation between sex chromosomes], anomalies in autosomal chromosomes (reciprocal translocations, Robertsonian translocations, chromosomal segmental inversion, other autosomal chromosome anomalies) and genetic abnormalities in reproductive cells.

In daily practice, patients with KS and Y chromosome microdeletion are the most frequently encountered of the infertile patients. This study aimed to evaluate the genetic analysis results of patients who presented because of infertility, were diagnosed with NOA and underwent a micro-TESE operation.

Materials and Methods

Data of 1076 patients who presented to our clinic with the inability to achieve pregnancy and were found to have NOA were retrospectively analyzed. Males older than 18 years who had not received any prior treatment for infertility, undergone any assisted reproductive technique and undergone a urological operation; NOA patients who tested for genetic analysis and underwent micro-TESE operation in our clinic were included in the study. The exclusion criteria were as follows: Patients who were lost to follow-up or whose retrospective information was not available from the hospital database, obstructive azoospermia patients and patients who had chemotherapy and radiotherapy.

A clinical examination included secondary sexual characteristics, testicular size and consistency, epididymal distension, the presence of the vas deferens and varicocele. Patient's age, the duration of infertility, the volume of the testes, serum follicle stimulant hormone (FSH) and testosterone levels were recorded. Patients with KS and Y chromosome microdeletion according to the results of genetic analysis and those without genetic anomaly were compared separately in terms of the probability of finding sperm in the micro-TESE operation. No medical treatment was administered to the patients before micro-TESE. Approval for the study was granted by the Local Ethics Committee (project no: KA14/277, date: 24.09.2014 - Baskent University Ethics Committee for Non-Interventional Clinical Trials).

Statistical Analysis

Data were analyzed statistically using SPSS v.22 Software (Statistical Package for Social Sciences). Independent Samples t-test was used for evaluation of the parameters. The chi-square test was applied to determine the relationship between micro-TESE result and KS or Y chromosome microdeletion. Logistic regression analysis was performed by forming a model with variables determined in One-Way analysis to affect the micro-TESE result, and the factors affecting the micro-TESE result were determined. A value of $p<0.05$ was set as statistically significant in all analyses.

Results

The total number of patients included in the study with NOA who underwent micro-TESE operation in our clinic was 994. While sperm were detected in 472 (47.5%) of these patients, no sperm could be found in 522 (52.5%) of them.

The number of patients who underwent karyotype analysis and underwent micro-TESE was 497. KS was determined in 104 (20.9%) of these patients, of which non-mosaic KS (47, XXY) was present in 101 (97.1%). In micro-TESE, while sperm was detected in 22 (21.2%) of the 104 patients determined by KS, sperm was found in 176 (44.7%) of 393 patients with normal chromosome analysis. The sperm detection rate in micro-TESE was found to be significantly lower in patients with KS compared to patients with normal karyotype analysis. The rates of sperm detection

and the distribution of age, testis volume, FSH and testosterone levels of the 497 patients subjected to karyotype analysis are shown in Table 1.

In the 450 patients examined for Y chromosome microdeletion and subjected to micro-TESE operation, Y chromosome microdeletion was present in only 14 (3.1%). In 12 (85%) patients there was *AZFc* deletion, and in 2 (15%) *AZFb* deletion. Sperm was found in micro-TESE in 4 (28.6%) of the 14 patients. Sperm was found only in *AZFc* deletion patients. The rates of sperm detection and the distribution of age, testis volume, FSH and testosterone levels of these two groups are shown in Table 2.

Age, testis volume, serum FSH and testosterone levels, and the presence of KS were determined to affect the sperm retrieval rate (SRR) in micro-TESE (p<0.05). The duration of infertility and the presence of Y chromosome microdeletion were not determined to affect the rate of SRR in micro-TESE (p>0.05). The factors affecting sperm detection in micro-TESE in patients NOA are shown in Table 3.

Discussion

Genetic analysis results of patients diagnosed with NOA who underwent micro-TESE were evaluated and some important findings emerged in this study. To the best of our knowledge, this study is a study that included the largest patient series examining both KS and Y chromosome microdeletion with SRR. The overall SRR of NOA patients was similar to the literature. However, SRR of patients with KS and Y chromosome microdeletion was lower. Age, testis volume, serum FSH and

Table 1. Descriptive information of patients examined karyotype analysis

	KS (-) (average ± SD)	KS (+) (average ± SD)	p-value
Age (year)	33.78±6.06	32.74±5.55	0.115*
Testis volume (mL)	12.24±6.59	5.19±3.37	<0.001*
FSH (mIU/mL)	15.55±11.57	30.99±13.57	<0.001*
Testosterone (ng/mL)	4.31±1.96	3.29±2.61	<0.001*
Sperm retrieval rate (n, %)	176/393 (45%)	22/104 (21.2%)	<0.001**

FSH: Follicle stimulant hormone, KS: Klinefelter syndrome, *Independent groups t-test, **chi-square test

Table 2. Descriptive information of patients examined Y-microdeletion test

	Y-microdeletion (-) (average ± SD)	Y-microdeletion (+) (average ± SD)	p-value
Age (year)	33.36±5.64	31.86±5.80	0.329*
Testis volume (mL)	11.56±6.77	15.93±5.56	0.012*
FSH (mIU/mL)	18.27±13.63	14.26±8.69	0.276*
Testosterone (ng/mL)	4.13±1.82	4.13±1.82	0.284*
Sperm retrieval rate (n, %)	170/436 (39%)	4/14 (28.6%)	0.580**

FSH: Follicle stimulant hormone, *Independent groups t-test, **chi-square test

Table 3. Factors affecting the presence of sperm in micro-TESE in nonobstructive azoospermic patients

		TESE results		p-value
		Sperm (-)	Sperm (+)	
Klinefelter syndrome	Yes (n=104)	78.8%	21.2%	<0.001*
	No (n=393)	55%	45%	
Y-microdeletion	Yes (n=14)	71.4%	28.6%	0.580*
	No (n=436)	61%	39%	
Age (year)		33.82±6.01	34.99±6.55	0.004**
Infertility duration (year)		6.92±5.12	6.80±4.97	0.712**
Testis volume (mL)		11.21±6.55	14.18±6.32	<0.001**
FSH (mIU/mL)		19.67±13.60	14.75±12.50	<0.001**
Testosterone (ng/mL)		4.13±2.08	4.53±1.98	<0.001**

FSH: Follicle stimulant hormone, *chi-square test **Independent groups t-test

testosterone levels, and the presence of KS were found to affect the SRR in micro-TESE.

The fertility management of patients with NOA relies on surgical sperm retrieval techniques. Micro-TESE is one of the most frequent used techniques in this regard. In a review including 116 studies and 4.895 patients, similar to this study, SRR of patients with NOA was found to be 46.6% (7). Unlike these studies, a recent study, which included 85 patients with clinical NOA from Australia, showed an overall SRR of 61.2%, which was found to be higher than that literature (8). The difference in surgical experience, histological pattern, etiology, geographical and genetic differences may cause these variable results.

KS is the most common genetic abnormality causing infertility and approximately 90% of patients with KS have NOA. The most frequently seen karyotype of KS is non-mosaic 47, XXY (80-85%). The mosaic form (46, XY/47, XXY) is seen less often (9). In this study, similar to other studies in the literature, the non-mosaic form was seen more common. However, the rate of KS non-mosaic form was higher than that in other studies, with 97.1%. In a multicenter study from Turkiye, non-mosaic karyotype of KS was found to be 84.4%, and mosaic karyotype was 15.6% (10). There are many studies in the literature that have investigated the sperm detection rates of in patients with KS. In a study by Sabbaghian et al. (11) comprising of 134 patients, SRR was found to be 28.4% in micro-TESE operations in patients with KS. In a recent study, which included 142 patients with KS, SRR was found to be 57.7% (10). Schiff et al. (12) found the highest rate of SRR in micro-TESE operations in patients with KS (70.4%). In this study, SRR was found to be 21.2% of the patients with KS. This rate is lower than in other studies in literature, which could be due to different demographic characteristics in different geographical regions, the inexperience of the surgeon, differences in rates of mosaic and non-mosaic forms of KS, or lack of technical facilities.

Y chromosome microdeletion is seen in 10-15% of azoospermic males and 7-10% of severe oligospermic males. The most frequent deletion type in the literature is the AZFc deletion. While sperm can be obtained from 50% of patients with *AZFc* deletions and partial *AZFb* deletion, there is almost no chance of detecting mature spermatozoa in complete *AZFb* and *AZFa* deletions. In a study that included 374 patients with primary infertility, the incidence of Y chromosome microdeletion was shown as 1.07% (13). The frequency of Y chromosome microdeletion was reported as 1.3% in a Turkish population by Balkan et al. (14), 3.3% by Sargın et al. (15), 3.93% by Akin et al. (16), and 22.64% by Müslümanoglu et al. (17). In this study, Y chromosome microdeletion frequency was found to be 3.1%.

In a study by Oates et al. (18) on 42 infertile males with *AZFc* microdeletions, the SRR was reported as 42%. Of the 42 males examined in that study, 38% were severely oligospermic and 62% were azoospermic. In a study by Simoni et al. (19), a rate of 60% sperm detection with micro-TESE was reported in azoospermic infertile males determined by *AZFc* microdeletions. Mulhall et al. (20) reported 50% sperm detection in cases with deletions affecting the *AZFc* region. In this study, the SRR was found to be 28.6% in patients with Y chromosome microdeletion, which is a lower than that reported in the literature. The reason for this low rate was 2 patients with *AZFb* deletion, for which there is almost no possibility of sperm detection, and sperm was not detected in those patients in micro-TESE. Of the 12 patients in this study with *AZFc* deletion, sperm was detected in 4 (33%) of them and this rate was also lower than findings in the literature. The small number of patients with Y chromosome microdeletion who underwent micro TESE could be the reason for the low rate of sperm detection.

There are very few studies in literature that include both KS and Y chromosome microdeletions. In a study by Altintas et al. (21) consist of 165 patients, sperm was found in micro-TESE in 37.5% of all patients, in 27.2% of 10 patients with *AZFc* deletion, and no sperm was found in 7 patients with KS. Balkan et al. (14) studied 80 infertile males in Turkiye, 71 of them were found to have a normal karyotype, KS was determined in 7 patients and autosomal chromosomal disorder in 2. Apart from these studies, although there are insignificant series of studies evaluating both genetic disorders together in the literature, there is no study evaluating sperm detection rates together in micro-TESE operations in NOA patients, as in this study.

Some variables affecting SRR in micro-TESE operations and some different results are shown. In this context, in the Australian study mentioned above, no correlation was found between SRR and age, serum LH, FSH and testosterone levels (8). However, in another study examining only patients with KS, SRR was associated with patient age and serum testosterone level, but not with serum FSH and LH (10). Also, there are conflicting results on the relationship between testicular volume and SRR (22,23). In this study; age, testis volume, serum FSH and testosterone levels, and the presence of KS were found to affect the SRR in micro-TESE and the duration of infertility and the presence of Y chromosome microdeletion were not determined to affect the SRR in micro-TESE.

Study Limitations

Although karyotype analysis and Y chromosome deletion analysis are recommended for azoospermic patients in the latest guidelines, the lack of genetic analysis of approximately half of the patients undergoing micro-TESE can be considered a limitation of this study. Reasons for this may include increased costs, the long waiting time for genetic test results and that surgery was not preferred or recommended. Another limitation

of this study is its retrospective design. Moreover, the outcome measure utilized, SRR, does not encompass the final goal, which is live birth. The pregnancy rates of the couples were not evaluated as well. Furthermore, some variables, which have relevant albeit controversial predictive values, such as inhibin B, Johnsen score, smoking, and lifestyle, were not recorded.

Conclusion

In this study, the SRR of patients who have chromosome Y microdeletion or KS, was found to be lower than other studies in the literature. This difference could be derived from the genetically tested population's structure, variance in the gene areas used for scanning and different demographic characteristics of different regions.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Local Ethics Committee (project no: KA14/277, date: 24.09.2014 - Baskent University Ethics Committee for Non-Interventional Clinical Trials).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ş., F.İ.Ş., Concept: E.Ş., T.T., F.İ.Ş., Design: E.Ş., T.T., F.İ.Ş., Data Collection or Processing: E.Ş., T.T., F.İ.Ş., Analysis or Interpretation: E.Ş., T.T., Literature Search: E.Ş., Y.K., M.B.D., Writing: E.Ş., Y.K., M.B.D., T.T., H.Ö.

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References

1. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem 2018;62:2-10.
2. Spira A. Epidemiology of human reproduction. Hum Reprod 1986;1:111-115.
3. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol 1989;142:62-65.
4. Dul EC, Groen H, van Ravenswaaij-Arts CM, Dijkhuizen T, van Echten-Arends J, Land JA. The prevalence of chromosomal abnormalities in subgroups of infertile men. Hum Reprod 2012;27:36-43.
5. Kohn TP, Kohn JR, Owen RC, Coward RM. The Prevalence of Y-chromosome Microdeletions in Oligozoospermic Men: A Systematic Review and Meta-analysis of European and North American Studies. Eur Urol 2019;76:626-636.
6. Shah K, Sivapalan G, Gibbons N, Tempest H, Griffin DK. The genetic basis of infertility. Reproduction 2003;126:13-25.
7. Achermann APP, Pereira TA, Esteves SC. Microdissection testicular sperm extraction (micro-TESE) in men with infertility due to nonobstructive azoospermia: summary of current literature. Int Urol Nephrol 2021;53:2193-2210.
8. Lantsberg D, Mizrachi Y, Katz DJ. Micro-testicular sperm extraction outcomes for non-obstructive azoospermia in a single large clinic in Victoria. Aust N Z J Obstet Gynaecol 2022;62:300-305.
9. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet 2004;364:273-283.
10. Kızılay F, Altay B, Aşçı R, Çayan S, Ekmekçioğlu O, Yaman Ö, Kadıoğlu A. Retrospective analysis of factors affecting sperm retrieval with microscopic testicular sperm extraction in infertile men with Klinefelter syndrome: A multicentre study. Andrologia 2022;54:e14379.
11. Sabbaghian M, Modarresi T, Hosseinifar H, Hosseini J, Farrahi F, Dadkhah F, Chehrazi M, Khalili G, Sadighi Gilani MA. Comparison of sperm retrieval and intracytoplasmic sperm injection outcome in patients with and without Klinefelter syndrome. Urology 2014;83:107-110.
12. Schiff JD, Palermo GD, Takeuchi T, Liotta D, Rosenwaks Z, Schlegel PN. Success of TESE-ICSI in men with non-mosaic Klinefelter syndrome. Fertility and Sterility 2002;78:S248.
13. Oz O. Evaluation of Y chromosome microdeletions and chromosomal anomalies in infertile men. Horm Mol Biol Clin Investig 2021;42:279-283.
14. Balkan M, Tekes S, Gedik A. Cytogenetic and Y chromosome microdeletion screening studies in infertile males with Oligozoospermia and Azoospermia in Southeast Turkey. J Assist Reprod Genet 2008;25:559-565.
15. Sargın CF, Berker-Karaüzüm S, Manguoğlu E, Erdoğru T, Karaveli Ş, Gülkesen KH, Baykara M, Lüleci G. AZF microdeletions on the Y chromosome of infertile men from Turkey. Annales de genetique: Elsevier; 2004.
16. Akin H, Onay H, Turker E, Ozkinay F. Primary male infertility in Izmir/Turkey: a cytogenetic and molecular study of 187 infertile Turkish patients. J Assist Reprod Genet 2011;28:419-423.
17. Müslümanoglu MH, Turgut M, Cilingir O, Can C, Ozyürek Y, Artan S. Role of the AZFd locus in spermatogenesis. Fertil Steril 2005;84:519-522.
18. Oates RD, Silber S, Brown LG, Page DC. Clinical characterization of 42 oligospermic or azoospermic men with microdeletion of the AZFc region of the Y chromosome, and of 18 children conceived via ICSI. Hum Reprod 2002;17:2813-2824.
19. Simoni M, Tüttelmann F, Gromoll J, Nieschlag E. Clinical consequences of microdeletions of the Y chromosome: the extended Münster experience. Reprod Biomed Online 2008;16:289-303.
20. Mulhall JP, Reijo R, Alagappan R, Brown L, Page D, Carson R, Oates RD. Azoospermic men with deletion of the DAZ gene cluster are capable of completing spermatogenesis: fertilization, normal embryonic development and pregnancy occur when retrieved testicular spermatozoa are used for intracytoplasmic sperm injection. Hum Reprod 1997;12:503-508.
21. Altintas R, Durmaz AA, Karamazak S, Tavmergen E, Onay H, Altay AB. Relationship between testicular sperm extraction results and AZF gene mutations./Testikuler sperm ekstraksiyonu sonuclarinin AZF gen mutasyonlari ile iliskisi. Turkish Journal of Urol 2011;37:229-235.
22. Corona G, Minhas S, Giwercman A, Bettocchi C, Dinkelman-Smit M, Dohle G, Fusco F, Kadioglou A, Kliesch S, Kopa Z, Krausz C, Pelliccione F, Pizzocaro A, Rassweiler J, Verze P, Vignozzi L, Weidner W, Maggi M, Sofikitis N. Sperm recovery and ICSI outcomes in men with non-obstructive azoospermia: a systematic review and meta-analysis. Hum Reprod Update 2019;25:733-757.
23. Bryson CF, Ramasamy R, Sheehan M, Palermo GD, Rosenwaks Z, Schlegel PN. Severe testicular atrophy does not affect the success of microdissection testicular sperm extraction. J Urol 2014;191:175-178.

ORIGINAL RESEARCH
Endourology

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A Randomized Trial on Surgical Outcomes of Open and Laparoscopic Pyeloplasty in Pelviureteric Junction Obstruction in Pediatric Patients: Is It Time to Conclude the Debate?

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What's known on the subject? and What does the study add?

Some previously conducted studies have shown that laparoscopic pyeloplasty (LP) is the treatment of choice for pelviureteric junction (PUJ) obstruction in adults in centers with advanced laparoscopic expertise. However, evidence is limited to prove the same in the pediatric age group. In our study, we did not find one procedure to be superior to others in the management of pediatric PUJ obstruction. Hence, the decision between the two procedures should be left to the surgical team and the parents/caregivers according to the merit of each case.

Abstract

Objective: Pyeloplasty involves the surgical reconstruction of the pelviureteric junction (PUJ) to drain the urine. We compared the surgical outcomes of open and laparoscopic pyeloplasty (LP) in PUJ obstruction in pediatric patients.

Materials and Methods: A simple randomized, prospective, comparative trial was conducted at two tertiary care centers in North India, from Jan 2015 to Dec 2019, with a follow-up to Dec 2020. A total of 110 patients were included in the study, out of which 52 underwent LP, and 58 were offered open pyeloplasty (OP).

Results: The mean operative time in the OP and LP groups was 100 min (80-140 min) and 170 min (120-240 min), respectively. The mean blood loss in the OP and LP groups was 15 mL and 10 mL. In the OP group, pre-operative mean split renal function was 33.5% (19-40%), which increased to 40.5% (27-46%) postoperatively. In the LP group, pre-operative mean split renal function was 35% (23-39%), which increased to 45.5% (30-48%) post-operatively after one year at the first follow-up scan. The mean number of analgesic doses administered was 12 (range 9-15 doses) in the OP group and 9 (range 7-12 doses) in the LP group.

Conclusion: LP and OP showed no significant differences except for operative time. The analgesic requirement was higher in the OP group without being statistically significant. Both techniques were equally effective, and any procedure being superior to others in all respects is ill-founded and must be viewed with an unbiased approach.

Keywords: Pelviureteric junction obstruction, laparoscopic pyeloplasty, open pyeloplasty, PUJ obstruction

Introduction

Pelviureteric junction (PUJ) obstruction (PUJO) is defined as inadequate drainage of urine from the renal pelvis to the ureter through PUJ, resulting in the dilatation of the pelvicalyceal system [hydronephrosis (HDN)]. It may lead to progressive deterioration of renal function. Mild antenatal fetal HDN is seen in 1 in 100 pregnancies, whereas significant antenatal fetal HDN occurs in 1 in 600 pregnancies. PUJ obstruction accounts for approximately 35% of these significant HDN; hence, the overall incidence is 1 in 1.000-2.000 live births (1). PUJ obstruction is more common in boys than girls (2:1), and 67% of cases are

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seen on the left side; however, it occurs bilaterally in 5-10% of patients (2).

Antenatally detected PUJ obstruction is generally asymptomatic at birth. However, children may present with loin pain, urinary tract infection, hematuria, and stone formation with the growing age (3). The clinical decision-making for managing PUJ obstruction must be guided by the interpretation of the results of different complementary tests like renal ultrasound (USG) and renal dynamic scan (RDS). The functional assessment is based on RDS, which gives DRF and the characteristics drainage curve described by O'Reilly (4). Magnetic resonance urography is also increasingly used. However, it is relatively expensive and requires sedation or general anesthesia in children (5).

Pyeloplasty is the treatment of choice in PUJ obstruction. The two surgical procedures described are dismembered (Anderson Hyne's pyeloplasty) and dismembered (flap techniques such as Foley's Y-V plasty, Culp-deweerd spiral flap, and Scardino and Prince vertical flap) techniques. Pyeloplasty can be performed either by open approach, laparoscopic approach (transperitoneal or retroperitoneal approach), or robotic techniques (6).

Some previously conducted studies have shown that laparoscopic pyeloplasty (LP) is the treatment of choice for PUJ obstruction in adults in centers with advanced laparoscopic expertise (7). However, evidence is limited to prove the same in the pediatric age group. A metanalysis by Huang et al. showed that the success rates of open pyeloplasty (OP) and LP are similar to a longer operating time in LP.

Hence, we planned our study to compare the advantages and disadvantages of OP and LP concerning operative time, intraoperative blood loss, analgesic requirement, the duration of the abdominal drain, the duration of the placement of Foley's catheter, the duration of the hospital stay, Double J (DJ) stent duration, immediate and delayed surgical complications, improvement in renal function, improvement in AP diameter of the renal pelvis on USG and overall parental satisfaction.

Materials and Methods

This simple, randomized, prospective, comparative study was conducted at the Departments of pediatric surgery, at two tertiary care centers in North India, from Jan 2015 to Dec 2019. The present study was approved by the Command Hospital Chandigarh Research Ethics Committee (REC) with reference number 2014/IEC/surg/10, date: 09.12.2014. After obtaining informed consent from the parents, 110 patients aged between 3 and 12 years were included in the study. The patients were assigned to LP and OP groups by a simple randomization method. However, the parents/caregivers of three patients later decided to undergo OP because of personal preference. Hence, 58 cases underwent OP (53%), and 52 patients underwent LP (47%). Of the 58 cases in the OP group, 41 had left-sided PUJO, 14 had right-sided PUJO, and three had bilateral PUJO. In contrast, in the LP group, 39 had left-sided PUJO, 11 had right-sided PUJO, and 2 had bilateral PUJO. The patients with bilateral PUJO were operated only upon one side (symptomatic or with more severity) during the study. All patients were operated upon by two pediatric surgeons with more than ten years of experience. The flow chart of the study is shown in Figure 1.

The relevant steps of the two modalities of surgical options are as follows:

1. Open Anderson Hyne's Dismembered Pyeloplasty (OP)

With the patient in a supine position with an ipsilateral flank elevation of 30-45^{o}, surgical exposure was performed via subcostal, anterolateral muscle cutting retroperitoneal incision, and the PUJ was identified. The pelvis was cleared off all the peri-pelvic fat and mobilized all around. The PUJ was taped with vascular tape using 5-0 round body silk. Variable lengths of the diseased (stenotic) segment of the upper ureter were excised. The normal segment below the stenotic segment was spatulated laterally, and reduction pyeloplasty was done. A watertight, dependent, funnel-shaped anastomosis was created over an appropriate size DJ stent using size (4/0 or 5/0) polyglactin, and a tube drain was placed in the retroperitoneum. The key surgical steps are shown in Figure 2.

2. Laparoscopic AH Dismembered Pyeloplasty (LP)

A total of three 5 mm size ports were placed. pneumoperitoneum was created by a closed technique using a Veress needle, and intra-abdominal pressure was kept at 8-12 cm H_2O.

For left-sided PUJ obstruction, a trans-mesenteric approach was adopted. After the dissection of the pelvis, peripelvic fat was mobilized. A trans-abdominal, 3-0 silk hitching suture was taken onto the pelvis, which acted as a traction suture for identifying the PUJ and assisting in subsequent dissection and anastomosis. The complete dissection was performed right up to the upper pole followed by reduction pyeloplasty. The rest of the steps were similar to the open technique. The anastomosis was performed over the replaced DJ stent using a 5-0/4-0 polyglactin suture depending upon the tissue's condition and the patient's age. Finally, a tube drain was placed using the 5 mm port (2nd port) entry site. The key surgical steps are shown in Figure 3.

For right-sided PUJ obstruction, an extra mesenteric approach was applied, and hepatic flexure was completely mobilized (rest all steps same as explained above).

Post-operative Care: All the patients were managed by a team led by a pediatric surgeon. Oral fluid and feeding were initiated

at the onset of peristaltic bowel sounds (usually 24 h after the surgery). The drain was removed when the output was nil. The catheter was removed sequentially after removing the drain, and the mean time of removal of the DJ stent was on the 23rd post-op day (21 to 28 days post-op). Two additional doses of injectable antibiotics were given, followed by oral antibiotics for five days and oral uro-prophylaxis till further review in the outpatient department.

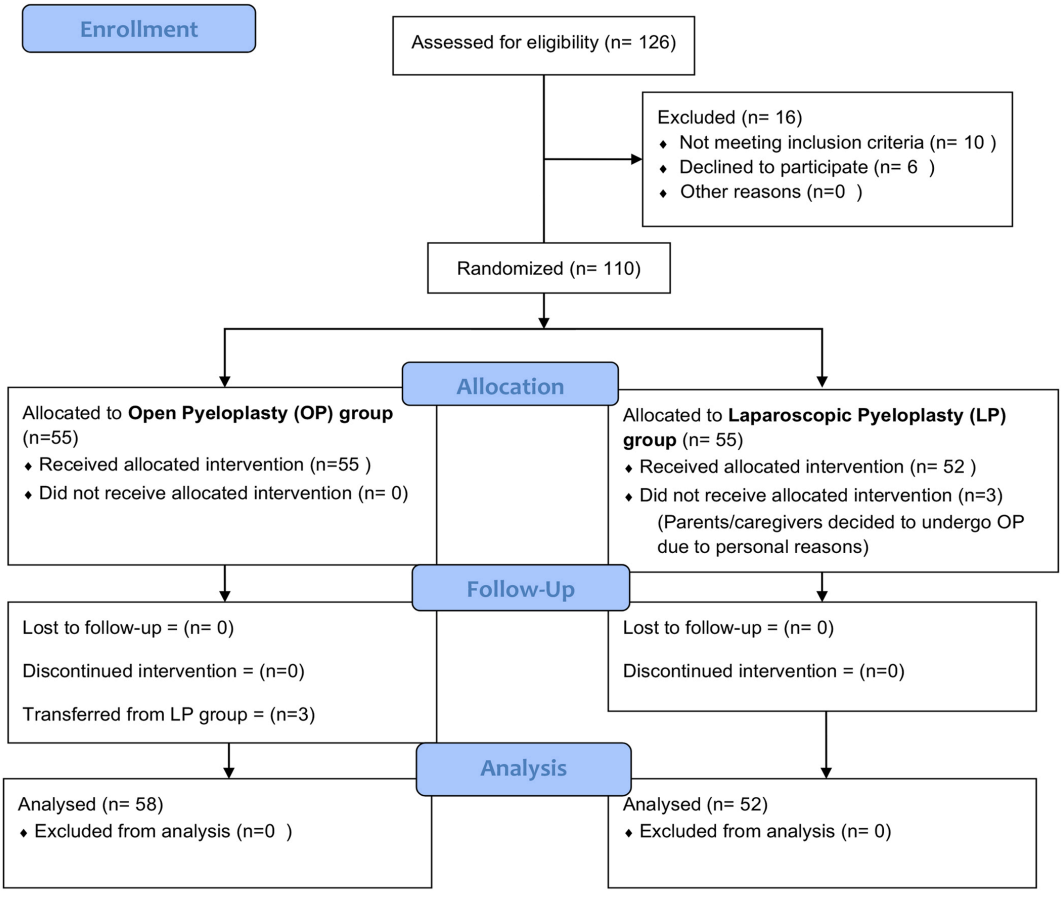

Figure 1. Flow diagram of the study

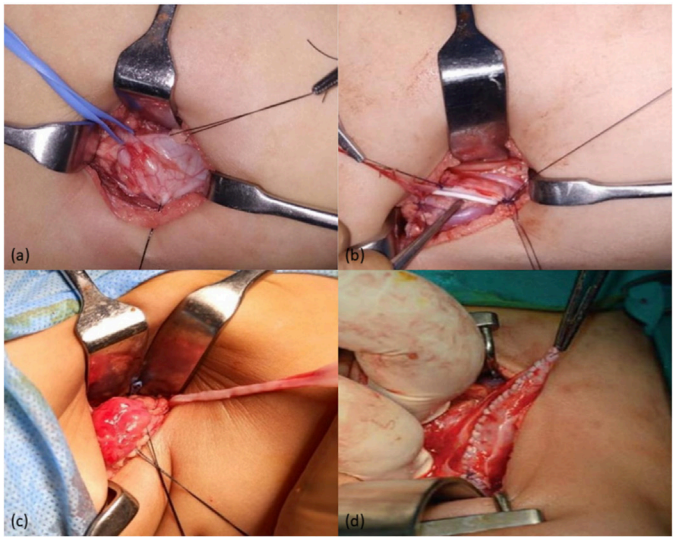

Figure 2. Intraoperative images of open pyeloplasty show (a) Dilated renal pelvis with an abrupt cut-off at PUJ (b) Placement of antegrade DJ stent (c) strictured segment of the ureter (d) Reduction pyeloplasty performed

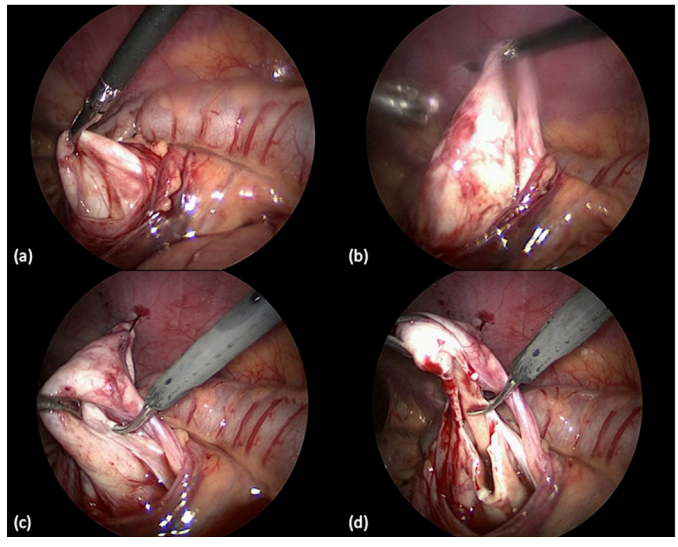

Figure 3. Intraoperative images of laparoscopic pyeloplasty show (a) Identification of dilated renal pelvis (b) Demonstration of an abrupt cut-off at PUJ (c) Hitching suture is taken (d) Reduction pyeloplasty being performed

Post-operative Analgesia: The anesthesiologist gave caudal block in all cases (both OP and LP groups) using a local anesthetic (2.5 mL/kg of 0.125% Bupivacaine) before starting the surgery.

Nurse-controlled analgesia was followed during the postoperative period as per the institutional protocol. Inj acetaminophen was administered at 12-15 mg/kg/dose, six-hourly for the first 24-48 hours and then on an SOS basis. We calculated the final analgesic requirement in both groups by adding up all the doses (standard and the SOS doses). Inj Tramadol was used @ 1 mg/kg/dose for breakthrough pain management.

Since parents are the primary source of subjective but fair inputs and opinions about their experience with the procedure and overall hospital stay, we asked the parents/caregivers of the operated children to reply to a simple, user-friendly questionnaire during the six-month follow-up visit. The same is listed in Table 1. This was to assess and compare the degree of satisfaction with the two different types of surgical procedures/treatments offered in the two groups. The identity of the parent/patient was kept hidden as the questionnaire only had LP or OP written on it. This resulted in removing any apprehension in the parents' minds about any backlash to their negative inputs (if any), and completely honest feedback was received.

Follow-up: All patients were followed up and assessed for improvement in HDN and AP diameter of the pelvis (APD) on USG KUB at 03 months, 06 months, and then at 01 years. RDS was done to assess functional status at three months, six months, and one-year post-op. Patients were evaluated based on the results of the follow-up APD by USG and findings RDS which were compared with pre-operative USG and RDS. Success was considered an asymptomatic child with a decrease in HDN on USG, improvement in renal function in the form of glomerular filtration rate, differential renal function (DRF), and a non-obstructive curve on diuretic renal scans, and high satisfaction score for the parents, as suggested by the questionnaire. Apart from comparing various parameters like mean operative time, mean operative blood loss, postoperative analgesia requirement, the duration of DJ stent placement, postoperative complications, and mean hospital stay, we also compared the two procedures for pre and post-operative difference in split renal function and APD of the renal pelvis on USG.

Statistical Analysis

The authors performed statistical analysis using SPSS statistical software (SPSS, Chicago, IL) Software Version 23.0. Descriptive statistics are expressed as frequencies and percentages of categorical variables. No advanced statistical tests were required in this study.

Results

The distribution of age and gender of the study population, as well as the side of PUJ obstruction in the OP and LP groups, are listed in Table 2. There were no statistically significant differences between the two groups in these parameters. The side with more severity was operated on during the study in patients with bilateral disease.

The differences in the OP and LP groups regarding mean operative time, operative blood loss, pre-and post-operative mean split renal function, and pre-and post-operative mean APD on USG KUB are listed in Table 3, along with the statistical significance.

In all patients, adequate post-op analgesia was ensured using nurse-controlled analgesia. The mean number of analgesic doses administered was 12 (range 9-15 doses) in the OP group and 9 (range 7-12 doses) in the LP group, where each dose amounted

Table 1. Questionnaire-based feedback from parents

Question	Scoring	Remarks	Mean score OP group	Mean score LP group
Are you satisfied with the surgical team's preoperative counseling and consent form?	1-5	Excellent- 5 Good- 4 Satisfactory- 2-3 Bad- 0-1	4.1	4.3
How well controlled was the post-op pain for your child?	1-5	Excellent- 5 Good- 4 Satisfactory- 2-3 Bad- 0-1	3.9	4.2
Would you prefer to undergo the same type of surgical procedure (given an opportunity to undergo a repeat surgery) or would you choose an alternative type of procedure?	0-2	Yes, same-2 Maybe/I don't know/Doctor's advice - 1 No, I would prefer the other procedure- 0	1.9	1.8
How was your overall experience concerning pre-op, the operative procedure offered, post-op recovery, and satisfaction with the surgical scar?	1-5	Excellent- 5 Good- 4 Satisfactory- 2-3 Bad- 0-1	4.3	4.4

Table 2. The difference in demographic and pre-operative parameters between OP and LP groups					
Parameter		**Open pyeloplasty (OP)**	**Laparoscopic pyeloplasty (LP)**	**p-value**	**Statistically significant difference between the two groups**
Gender	Boys	41	38	0.78	No
	Girls	17	14		
Age	0-6 months	15	13	0.98	No
	6 months - 2 years	21	19		
	2 years - 12 years	22	20		
Side	Right	14	11	0.51	No
	Left	41	39		
	Bilateral	3	2		

Table 3. The difference in various surgical parameters between OP and LP groups				
Surgical parameter	**Open pyeloplasty (OP)**	**Laparoscopic pyeloplasty (LP)**	**p-value**	**Statistically significant difference between the two groups**
Mean operative time	100 min (80-140 min)	170 min (120-240 min)	0.00001	Yes
Operative blood loss	15 mL (5-30 mL)	10 mL (5-20 mL)	0.06	No
Pre-operative mean split renal function	33.5% (19-40%)	35% (23-39%)	0.06	No
Post-operative mean split renal function (at six months)	40.5% (27-46%)	45.5% (30-48%)		
Pre-operative mean APD on USG KUB	38 mm (16-60 mm)	40 mm (16-60 mm)	0.06	No
Post-operative mean APD on USG KUB	11 mm (7-14 mm)	9 mm (6-11 mm)		
USG: Ultrasound, APD: Anteroposterior diameter, KUB: Kidney ureter bladder				

to 12-15 mg/kg of acetaminophen. Additionally, Inj Tramadol was used @ 1 mg/kg/dose for breakthrough pain management. The mean number of analgesic doses administered for Inj Tramadol was three in the OP group and two in the LP group. The calculated mean analgesic requirement also included the amount of analgesic drug given for excessive cry, tachycardia (having ruled out other causes for tachycardia), and irritability in children other than the routine analgesia. A student t-test was applied, and a p-value (0.01) was derived. This indicates that there was no statistically significant difference between the groups in the requirement of postoperative analgesia.

Among the postoperative complications, one case of OP developed an incisional hernia and one case of LP developed an anastomotic leak, but both were managed conservatively. One patient in each group developed Surgical Site Infection (SSI), who recovered successfully with regular dressings.

Parents/caregivers in both the groups expressed a 'good to excellent level of satisfaction with the surgical procedure, which their child was offered, which was assessed by the questionnaire at discharge. The mean score from the questionnaire was 14.2 (range 10-17) in the OP group and 14.7 (range 10-16) in the LP group. The same is listed in Table 1. It was noted that the LP group had slightly higher satisfaction with the postoperative analgesia. Overall, there was no statistically significant difference in the satisfaction levels of parents/caregivers between the two groups.

Discussion

In this study, in the OP group, the mean operative time was 100 (67-144) minutes, and in the LP group, the mean operative time was 170 (122-208) minutes. LP group had a longer operative time than the OP group and was statistically significant (p=0.0001). We ensured parity among the two groups even with respect to the extent of reduction pyeloplasty, with both groups having a significant reduction in the dilated pelves. This was evident by the fact that the post-operative APD on USG was remarkably reduced and comparable in both groups. The authors observed that the longer duration of operative time in the LP group may also have been attributable to the longer anastomotic intracorporeal suturing. As evident from various studies, LP has been accepted as a technically more challenging procedure compared to OP with a longer learning curve, which explains the skill-related cause of longer operative time (8-11).

Calvert et al. (12) compared 49 LPs with 51 OPs over 3 years. Compared with open procedures, laparoscopic procedures were

associated with a longer mean operating time (159 versus 91 min), a shorter mean time to a regular diet (38 versus 72 h), and a similar mean hospital stay (5 days).

In our study, the mean number of analgesic doses administered was 12 (range 9-15 doses) in the OP group and 9 (range 7-12 doses) in the LP group, where each dose amounted to 12-15 mg/kg of acetaminophen. Hence, the OP group had a mean requirement of approximately 180 mg/kg of total acetaminophen and the LP group had a mean requirement of approximately 135 mg/kg of total acetaminophen. The mean number of doses administered for Inj Tramadol (for breakthrough analgesia) was 3 in the OP group and 2 in the LP group. Thus, analgesic requirements in the OP group were noted to be slightly higher than those in the LP group.

Other studies also observed similar higher analgesic requirements in the OP group (7-10). In a study by Piaggio et al. (13), analgesia requirements were significantly higher in the OP group for intravenous and oral routes. Total narcotic intake (oral plus intravenous opioid) of morphine was 0.17 mg/kg (0.1-0.2) in the OP group compared with 0.07 mg/kg (0-0.2) in the LP group ($p<0.01$). The authors never used opioids in our study group.

The mean hospital stay in our study in the OP group ranged from 5 to 7 days with a mean stay of 6 days, whereas in the LP group, the hospital stay ranged from 4 to 21 days. The range of hospital stay was greater in the LP group because one patient with an anastomotic leak stayed in the hospital for 21 days. Otherwise, the mean duration of hospital stay in the LP group was 5 days only, which was slightly less than that in the OP group. This child with anastomotic leak was asymptomatic with no sepsis and could have been discharged with the drain *in situ*. However, due to parental apprehension and the distant place of his parent's residence, we resorted to keeping him in the hospital until full recovery. Other studies also observed shorter hospital stays in the laparoscopic group.

A study by Abdel-Karim et al. (14) and Badawy et al. (15,16) reported a statistically significant difference of higher blood loss in the OP group compared to the LP group. The study by Badawy et al. (15,16) also showed a similar trend of 3 times higher blood loss in the OP group (17,18). However, our study only showed a marginally higher amount of blood loss in the OP group (15 mL in the OP group and 10 mL in the LP group), which was not statistically significant.

The duration of keeping the DJ stent in situ for both groups was almost the same, with no difference between the two groups. In both groups, the duration of DJ stent ranged from 21 days to 28 with a mean of 23 days (The duration of DJ stent placement in the patient with the post-operative anastomotic leak was not considered for calculating the mean, since this patient was subjected to DJ stent removal after 8 weeks). In contrast, Badawy et al. (16) observed a longer time of DJ stent in situ for the OP group than the LP group, but the difference was not significant.

Several studies have quantified the steep learning curve for laparoscopy because skills for intracorporeal suturing require more time to perfect and need more practice (19). In a systematic review of literature by Klingler et al. (20), authors state that LP is a minimally invasive, safe, and effective therapy method for PUJ obstruction in children, with shorter hospital stay and excellent outcomes, and without additional risk of postoperative complications.

Study Limitations

We acknowledge that this study was not registered as a prospective clinical trial database, and the study protocol was not published before the start of the study. We also acknowledge the relatively small sample size of our and the difference in the number of patients who underwent LP (n=52) and OP (n=58).

Conclusion

Our study showed no significant difference between the two procedures, except for operative time. The analgesic requirement in the LP group was numerically less without being statistically significant. The authors emphasize that this difference in the operative time could be easily overcome by training the surgical residents & young pediatric surgeons well, in both Laparoscopic and OP. Additionally, similar training for the operating room technicians and the matrons would further reduce the operating time for LP, since the entire team being in sync with the surgeon is the key to a timely and successful procedure. Therefore, in our study, we did not find any one procedure superior to the other.

Claims of one procedure being clearly better than the other in all aspects and counterclaims of one being more complicated than the other are ill-founded and must be viewed with a completely unbiased approach. Hence, the decision between the two procedures should be left to the surgical team and the parents/caregivers according to the merit of each case.

Ethics

Ethics Committee Approval: The present study was approved by the Command Hospital Chandigarh Research Ethics Committee (REC) with reference number 2014/IEC/surg/10, date: 09.12.2014.

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K.K., Concept: S.K.K., Design: S.K.K., R.M., Data Collection or Processing: R.M., R.S., Analysis or

Interpretation: S.K.K., S.M., Literature Search: S.K.K., R.M., R.S., S.M., Writing: S.M.

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References

1. Liu DB, Armstrong WR 3rd, Maizels M. Hydronephrosis: prenatal and postnatal evaluation and management. Clin Perinatol 2014;41:661-678.
2. Chevalier RL, Thornhill BA, Forbes MS, Kiley SC. Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. Pediatr Nephrol 2010;25:687-697.
3. Yamaçake KG, Nguyen HT. Current management of antenatal hydronephrosis. Pediatr Nephrol 2013;28:237-243.
4. Cestari A, Buffi NM, Lista G, Sangalli M, Scapaticci E, Fabbri F, Lazzeri M, Rigatti P, Guazzoni G. Retroperitoneal and transperitoneal robot-assisted pyeloplasty in adults: techniques and results. Eur Urol 2010;58:711-718.
5. Senguttuvan P, Jigy J. Profile and outcome of pelviureteric junction obstruction. Open Urol Nephrol J 2014;7:67-70.
6. Polok M, Chrzan R, Veenboer P, Beyerlein S, Dik P, Klijn A, Kuijper C, de Jong T. Nondismembered pyeloplasty in a pediatric population: results of 34 open and laparoscopic procedures. Urology 2011;78:891-894.
7. Kirsch AJ, McMann LP, Jones RA, Smith EA, Scherz HC, Grattan-Smith JD. Magnetic resonance urography for evaluating outcomes after pediatric pyeloplasty. J Urol 2006;176:1755-1761.
8. Lucas SM, Sundaram CP. Transperitoneal robot-assisted laparoscopic pyeloplasty. J Endourol 2011;25:167-172.
9. Bansal P, Gupta A, Mongha R, Narayan S, Das RK, Bera M, Chakraborty SC, Kundu AK. Laparoscopic versus open pyeloplasty: comparison of two surgical approaches- a single centre experience of three years. Indian J Surg 2011;73:264-267.
10. Gadelmoula M, Abdel-Kader MS, Shalaby M, Abdelrazek M, Moeen AM, Zarzour MA, Mohammed N, Fornara P. Laparoscopic versus open pyeloplasty: a multi-institutional prospective study. Cent European J Urol 2018;71:342-345.
11. Fahad AH. A Comparative Study between Open and Laparoscopic Pyeloplasty. J Pharm Sci & Res 2017;9:1961-1965.
12. Calvert RC, Morsy MM, Zelhof B, Rhodes M, Burgess NA. Comparison of laparoscopic and open pyeloplasty in 100 patients with pelvi-ureteric junction obstruction. Surg Endosc 2008;22:411-414.
13. Piaggio LA, Corbetta JP, Weller S, Dingevan RA, Duran V, Ruiz J, Lopez JC. Comparative, Prospective, Case-Control Study of Open versus Laparoscopic Pyeloplasty in Children with Ureteropelvic Junction Obstruction: Long-term Results. Front Pediatr 2017;5:10.
14. Abdel-Karim AM, Fahmy A, Moussa A, Rashad H, Elbadry M, Badawy H, Hammady A. Laparoscopic pyeloplasty versus open pyeloplasty for recurrent ureteropelvic junction obstruction in children. J Pediatr Urol 2016;12:401-401.
15. Lekawa M, Shapiro SJ, Gordon LA, Rothbart J, Hiatt JR. The laparoscopic learning curve. Surg Laparosc Endosc 1995;5:455-458.
16. Badawy A, Badreldin M, Abdel Elbaky T, Abdallah M. Laparoscopic versus open pyeloplasty in the management of ureteropelvic junction obstruction. Menoufia Med J 2017;30:361.
17. Mei H, Pu J, Yang C, Zhang H, Zheng L, Tong Q. Laparoscopic versus open pyeloplasty for ureteropelvic junction obstruction in children: a systematic review and meta-analysis. J Endourol 2011;25:727-736.
18. Ravish IR, Nerli RB, Reddy MN, Amarkhed SS. Laparoscopic pyeloplasty compared with open pyeloplasty in children. J Endourol 2007;21:897-902.
19. Symons SJ, Bhirud PS, Jain V, Shetty AS, Desai MR. Laparoscopic pyeloplasty: our new gold standard. J Endourol 2009;23:463-467.
20. Klingler HC, Remzi M, Janetschek G, Kratzik C, Marberger MJ. Comparison of open versus laparoscopic pyeloplasty techniques in treatment of ureteropelvic junction obstruction. Eur Urol 2003;44:340-345.

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Evaluation of Factors Affecting Success Rate in Percutaneous Nephrolithotomy: A Five-Year Experience

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Abstract

Objective: To analyze the parameters that are believed to impact the success rate in patients undergoing percutaneous nephrolithotomy and to determine the factors that have a significant effect.

Materials and Methods: Success rates of 508 patients who underwent percutaneous nephrolithotomy were determined over a five-year period. Evaluation was performed with the medical history, non-contrast computerized tomography, and clinical research form in the first, third, and sixth months postoperatively. Patient characteristics, stone characteristics, and operation details were analyzed, and their effects on success were investigated. In the evaluation of the success rate, the results of the first month, were considered.

Results: No significant difference was shown between the successful and unsuccessful groups in terms of demographic features. Morbidities such as body mass index, hypertension, diabetes mellitus, hyperlipidemia, and heart disease had no effect on success. Solitary kidney or congenital renal anomaly, degree of hydronephrosis, and high preoperative serum urea creatinine levels did not have a significant impact on the success rate. Significant effects of parameters such as stone volume greater than 15 cm^2, complex stones, infection and cystine stones, intraoperative complication rate, and operation time on success were investigated ($p<0.001$, $p=0.038$, $p=0.014$, $p=0.010$, $p=0.022$, $p=0.030$, respectively). Success rates decreased statistically in cases with accompanying macroscopic hematuria ($p=0.032$). Previous surgery, extracorporeal shock wave lithotripsy history, and multifocal access had no effect however surgical experience increased the success rate ($p=0.036$).

Conclusion: The success rates in percutaneous nephrolithotomy can be enhanced by examining the factors that may have an impact and taking necessary precautions relevant to these factors.

Keywords: Percutan nephrolithotomy, success rate, predictive

Introduction

The goal of treatment selection in renal stones is to achieve the highest success rate with minimal complications and morbidity. Treatment options for kidney stones include extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy, percutaneous nephrolithotomy (PNL), and open or laparoscopic surgery. The main parameter in the selection of renal stone treatment is the stone size. In European and American urology guidelines, PNL is recommended as the first choice for the removal of kidney stones larger than 2 cm (1). PNL is almost completely replaced by open surgery for treating kidney stones bigger than 2 cm due to its advantages of being minimally invasive, cost-effective, short operative time, short hospital stay, lower complication rate, and high success rate. Although PNL is more invasive than other minimally invasive methods currently available, the trend in kidney stone surgery with advanced, more sophisticated equipment thanks to advancing technology is to use PNL more and more. In a recent meta-analysis by Chung et al. (2), the highest success and stone-free rate was achieved with PNL in kidney stones larger than 2 cm compared to other treatment modalities. Failure can lead to complications, increased additional treatment, and economic burden for the patients and the health system. Therefore, reliable prognostic parameters are needed to optimize the choice of treatment in patients, to plan the operation, to provide information about the operation and

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its results, and to evaluate the findings. In the current literature, the stone-free rate in PNL varies between 71% and 100% (3). This wide range in the success rates is due to the evaluation of stones of different sizes in studies and the different parameters and methods used in the assessment of success. Many factors such as stone size, density, complexity, anatomical variations, patient-related factors [age, body mass index (BMI), and comorbidities], as well as parameters such as entry point, access number, duration of operation, complication rates, and surgeon experience, are the main factors investigated regarding the success rates (4-6). Plain radiography, nephrography, or non-contrast abdominal computed tomography (NCCT) have been reported as diagnostic tools for detect stone -free rate after PNL in the current literature. In our study, the success rates following PNL were evaluated by CT.

In this retrospective study, we evaluated the stone-free rates and outcomes of patients who underwent PNL treatment in our clinic. We also analyzed factors related to the patient, stone, surgery, and several factors that may influence the success of PNL, with the aim of demonstrating which factors have a significant impact on the success rate. Identification and evaluation of these prognostic factors may play a prominent role in increasing the success of PNL.

Materials and Methods

The data of 508 patients who underwent PNL over a total of 5 years at our institute were analyzed retrospectively in terms of success rate. The demographic characteristics of the patients, accompanying comorbidities, stone characteristics, kidney characteristics, information on operation and hospitalization are shown in Table 1. Of the patients, 300 (59%) were male and 208 (41%) were female. The mean age was 42.89±16.57 years. In our study, various factors affecting the success rates of PNL operations were analyzed. These factors included patient's demographics, comorbidities, kidney features, stone characteristics, and operative information. The patients were evaluated with complete blood count, serum urea, creatinine, bleeding and coagulation profile, complete urinalysis, and urine culture before the operation. Detailed information about the operation was given to the patients, and informed consent forms were obtained from all patients. The patients were evaluated preoperatively with intravenous pyelography or non-contrast whole abdominal spiral tomography. The size of the stone is calculated by multiplying the maximum diameter by the diameter of the stone cut vertically with the help of a ruler in mm^2. Complex renal stones are defined as calculi greater than 3.0 cm in diameter with multiple renal stones, staghorn stones, abnormally positioned renal calculi, or horseshoe kidney calculi in a single kidney.

All patients were evaluated with NCCT scan for residual stones in the postoperative period. Post-PNL follow-up controls were performed at the 1st, 3rd, and 6th months. In the evaluation of success, the control results obtained in the first month, which is the period without any additional treatment, were taken as criteria. According to the postoperative period CT scan results, it was classified as "stone-free (SF)", "Clinically insignificant residual fragments (CIRFs)" and "failed (the presence of residual stones)". Asymptomatic, less than 4 mm, non-obstructing, and non-infected stones were evaluated as CIRF (7). Patients with SF and CIRF were considered successful cases.

Surgical Technique

All the operations were performed in the prone position. The pelvicalyceal system was visualized by administering radio-opaque material through the ureteral catheter under C-arm fluoroscopy. Under fluoroscopy, the relevant calyx was entered using 18 Gouge diamond-tipped percutaneous access needles (18G Percutaneous Access Needle, Boston Scientific). The tract was dilated through the guidewire using an 8F Amplatz dilator, 8F Teflon catheter, and 18F, 22F, and 30F Amplatz dilators over an 8F Teflon catheter, respectively. The access sheath (20-30F) (Amplatz sheat, Boston Scientific) was advanced up to the kidney and entered the collecting system. Under saline irrigation, the pelvicalyceal system was observed through the access sheath with a 26-F nephroscope. Stones detected in the pelvicalyceal system were fragmented with a pneumatic lithotripter (Vibrolith, Elmed).

Statistical Analysis

The analysis of the data was performed using the "SPSS for Windows 11.5" package program (185). Descriptive statistics were expressed as mean ± standard deviation or median (minimum-maximum) for continuous and discrete variables, and categorical variables as number of cases and percentile. The significance of the difference between the groups in terms of means was analyzed with the "Student's t-test" and the significance of the difference in terms of median values was investigated with the "Mann-Whitney U test". Categorical variables were evaluated with Pearson's "chi-square" or Fisher's "Exact Probability test". The significance of the linear relationship between continuous variables was analyzed by Spearman's "Correlation test". The combined effects of risk factors that had a significant effect on success and complications because of univariate statistical analyses or that were thought to have a significant effect in multivariate analyses were investigated with "Multiple Retroactively Eliminated Logistic Regression analysis". Odds ratio, 95% confidence interval, Wald statistics, and significance levels for each risk factor were calculated. Similarly, Multiple Linear Regression analysis was performed to determine the risk factors that had the most significant effect on the operation

and dilatation times. The regression coefficient, standardized regression coefficient, 95% confidence interval, and significance levels for each risk factor were calculated. Variables found to be p<0.25 because of univariate analyses were included in the multiple regression models as candidate risk factors. Because the operation and dilatation times were not normally distributed, logarithmic transformation values were used in multiple linear regression analyses. The results were considered statistically significant for p<0.05.

Results

The mean stone burden was 9.78±13.5 cm^2 (4-78). Sixty-one percent of the stones were within the range of 3-15 cm^2. While simple stones constituted 53,15% (n=270) of the cases, the rate of complex stones was 46,85% (n=238). Mean operation time, fluoroscopy time, and length of hospital stay were respectively 102.25±38.64 minutes (28-270), 9.53±6.1 minutes (3-15), and 3.43±1.11 days (1-8). In the first month-evaluation, success was achieved in 427 of 508 patients who underwent PNL. The success rate was calculated as 84%. After additional treatments (58 ESWL, 4 repeat PNL, 11 ureteroscopy) were applied to 73 of 81 patients who were evaluated as a failure, the success rate increased to 86% in the postoperative third month and to 88% in the sixth month.

In the evaluation of first-month success rates, no difference was observed between the success and failure groups in terms of age, gender, socioeconomic status, and family history of stone disease. Furthermore, morbidities such as high BMI, hypertension, diabetes mellitus, hyperlipidemia, and heart disease had no effect on success. It was observed that the success rate decreased statistically in cases with accompanying macroscopic hematuria. The stone-free rate found in patients with a solitary kidney or congenital renal anomaly was statistically similar to patients without these pathologies. The history of previous kidney surgery and ESWL had no impact on the success rate. The success rate was found to be similar in patients with various degrees of hydronephrosis (Table 2).

While the success rate was similar for stones with a stone volume of less than 3 cm^2 and those between 3-15 cm^2, it was observed that the success rate decreased statistically significantly in stones larger than 15 cm^2. Although the success rate was 90.3% for simple stones, it was 76.9% for complex stones. The success rate between simple and complex stones was statistically significant (p=0.038). The lowest success rate among complex stones was observed in complete staghorn stones. Although the calyx entry point did not have a significant effect on success, it was noted that the success rate decreased significantly in stones requiring multiple attempts for entry.

Table 1. The demographics and stone characteristics of patients

Number of patients (n)	**508 patients**
Mean age (years)	42.89±16.57
<14	32 patients (6.29%)
14-65	428 patients (81.10%)
>65	48 patients (7.94%)
Male/Female	300/208 (1.44)
Body mass index (BMI)	26.45±4.01 kg/m^2
<25	146 patients (28.74%)
25-30	282 patients (55.51%)
>30	80 patients (15.74%)
Hypertension	74 patients
Diabetes Mellitus	58 patients
Hyperlipidemia	56 patients
Heart disease	38 patients
Lung disease	18 patients
Solitary kidney	16 patients (3.1%)
Congenital renal anomaly	18 patients (5.5%)
Previous open surgery	78 patients (15.4%)
Previous ESWL	101 patients (19.9%)
Mean stone burden (cm^2)	9.78±13.5 (1-125)
<3 cm^2	n: 98 patients (19.29%)
3-15 cm^2	n: 314 patients (61.8%)
>15 cm^2	n: 96 patients (18.8%)
Simple Stones	n: 270 (53.15%)
Lower Calyx	n: 106 patients (20.9%)
Middle Calyx	n: 8 patients (1.5%)
Upper Calyx	n: 16 patients (3.5%)
Pelvis Renalis	n: 122 patients (20.3%)
Upper Ureter	n:18 patients (5.6%)
Complex Stones	n: 238 (46.85%)
Parsiel Coralliform	n: 56 patients (11%)
Complex Coralliform	n: 66 patients (13%)
Multiple Calyx	n: 116 patients (22.8%)
Mean operation time (minute)	102.25±38.64 (28-270)
Mean scopy duration (minute)	9.53±6.1 (3-15)
Mean nephrostomy time (day)	3.23±1.11 (1-8)
Mean hospitalization (day)	3.43±1.45 (1-14)

Table 2. Evaluation of factors on success rate					
Age (Years)					
<14	27	75.0	5	25.0	0.832
14-65	365	85.3	63	14.7	
>65	35	73	13	27	
Gender					
Male	249	83	51	17	0.534
Female	178	85	30	15	
Socioeconomic status					
High	200	79.7	51	20.3	0.114
Low	227	88.3	30	11.7	
Family Stone					
Yes	341	85.2	59	14.8	0.481
No	86	85.2	22	20.4	
Body mass index (BMI)					
<25	125	85.0	21	14.4	0.407
25-30	245	82	54	18	
>30	57	90.5	6	9.5	
Hypertension					
Yes	287	82.7	60	17.3	0.345
No	140	87.0	21	13.0	
Diabetes mellitus					
Yes	378	80.2	74	19.8	0.608
No	49	87.5	7	12.5	
Hyperlipidemia					
Yes	300	85.2	52	14.8	0.678
No	127	81.4	29	18.6	
Hearth disease					
Yes	382	81.4	74	18.6	0.123
No	45	86.5	7	13.5	
Lung disease					
Yes	404	83.5	80	16.5	0.351
No	23	95.6	1	4.4	
Macroscopichematuria					
Yes	352	88	48	12	**0.032**
No	75	69.4	33	30.6	
Serum urea					
<40	386	84.8	69	15.2	0.223
>40	41	77.3	12	22.6	
Serum creatinine					
<1.3	395	84.4	73	15.6	1.000
>1.3	32	84.2	6	15.8	
Solitary kidney					
Yes	414	84.1	78	15.9	0.489
No	13	81.3	3	18.7	
Congenital renal anomaly					

Table 2. continued					
Age (Years)					
Yes	402	83.8	78	16.2	0.234
No	25	89.3	3	10.7	
Previous open surgery					
Yes	362	82.1	68	17.9	0.224
No	65	83.3	13	16.7	
ESWL					
Yes	304	83.5	60	20.2	0.786
No	123	85.4	21	14.6	
Hydronephrosis grade					
0-1	200	87	30	13	0.178
2-3	227	81.6	51	18.4	
Stone Size (cm^2)					
<3	92	89.3	6	10.7	**<0.001**
3-15	294	89.8	20	10.2	
>15	41	48.1	55	51.9	
Simple Stone	244	90.3	26	9.7	**0.038ˆ**
Complex Stone	183	76.9	55	23.1	
Parsiel Coralliform	47	79.7	12	20.3	
Complex Coralliform	35	60.3	23	39.7	
Multiple Calyx	101	83.5	20	16.5	**0.023**[&]
Access Point					
Lower Calyx	310	87.8	43	12.2	**0.032**
Mid Calyx	55	82	12	18	
Upper Calyx	25	75.8	8	24.2	
Multiple Access	37	67.3	18	32.7	
Stone Composition					
Ca-phosphate	41	82	9	18	**0.014***
İnfection	23	62.2	14	37.8	
Ca ox monohydrate	184	89.3	22	10.7	**0.010+**
Cystine	16	59.3	11	40.7	
Others (Ca ox dihydrate, Uric acid, mix)	163	86.7	25	13.3	
Intraoperative complication					
Yes	360	88.5	47	11.5	**0.022**
No	67	66.3	34	33.7	
Operative time (minute)					
<100	264	88	36	12	**0.030**
>100	163	69.6	45	30.4	
Surgeon's experience					
0-254	190	74.8	64	25.2	**0.036**
255-508	237	93.3	17	6.7	

ˆ p value between simple and complex stones
[&] p value among complex stones
*p value between Ca-phosphate and infection stones
+ p value between Ca-phosphate and cysteine stones

It was also seen that the structure of the stone had an impact on the success. The lowest success rate was observed in cystine stones (59.3%) (p=0.010). The success rate was also found to be lower in infection stones compared with other types of stones (62.2%) (p=0.014). It was observed that intraoperative complications and long operation time significantly affected the success rate (p=0.022, p=0.030). The success rate was 74.8% in our first 254 cases, and it reached 93% in the last 254 cases. It was found that increased surgical experience was a factor that had a statistically significant effect on success (p=0.036). Combined effects of risk factors were also evaluated. According to the results of the retrospective logistic regression analysis, surgeon's experience, stone structure, complexity of the stone, and stone size were found to be independent factors affecting the success rate.

Complications associated with PNL were classified as major and minor complications. Major complications developed in 8.3% of the patients who underwent PNL operations, whereas minor complications occurred in 21.3%. As a major complication, bleeding requiring transfusion was encountered and 5.5% (n=28) of the cases. Three patients required conversion to open surgery due to bleeding and four patients due to access failure. Collecting system damage occurred in three patients, which required Double J insertion as an additional treatment. Hemothorax occurred in two patients which were managed with thoracal drainage. An arteriovenous fistula was observed in two patients and treated with superselective embolization.

Discussion

PNL provides the highest stone-free rate for treating kidney stones and with the effect of technological devices developed recently, has become the treatment of choice for complex and large kidney stones (3). The main goal of PNL is to achieve stone-free status with minimal morbidity with a high success rate. In a recent meta-analysis, PNL in the surgical treatment of kidney stones was shown to have the highest success and stone-free rate compared with other treatment options such as ESWL and retrograde intrarenal surgery (2). PNL has a near 100% success rate for treating non-staghorn stones, and up to 85% in staghorn stones (8). In our study, a total success rate of 84% was observed at 1-month follow-up in 508 patients undergoing PNL. In the current literature, different imaging techniques and success criteria's have been defined in the assessment of PNL success (9). In our study, success rates were assessed using NCCT because commonly used imaging modalities, such as plain abdominal radiography (KUB film) or ultrasonography were reported as deficient for the diagnosis of small residual fragments (10). The question of whether small stones that are not clinically important (i.e., do not cause obstruction, pain, and infection in the urinary system) overshadow the success of the operation has been enquired and the concept of clinically insignificant residual fragments (CIRFs) has been put forward. In this concept, the stone size was limited to 4 mm, and it was concluded that stones below this size had no effect on the success of the operation as it has been determined that 85% of stones of this size will pass without causing clinically symptomatic pain (11). We also evaluated stones below 4 mm as a successful group. Many factors shown in the literature to influence the success of PNL have been evaluated in various studies (5). We evaluated the impact of several factors on the success rate of PNL. A prospective study by Olbert et al. (12) showed that age and gender had no effect on success rates. We also found that age, gender, socioeconomic status, and family history has got no effect on the PNL success. No studies have investigated the impact of socioeconomic status and family history on PNL outcomes. In our study, similar to demographic characteristics, comorbidities such as hypertension, diabetes, hyperlipidemia, KVH, and BMI did not significantly affect surgical outcomes. Alyami et al. (13) found no difference on stone -free rate based on BMI. In a study of 430 cases conducted by Tefekli et al. (14), patients with metabolic syndrome and its components such as hypertension, diabetes, hyperlipidemia, and obesity were evaluated, and similar success rates were reported. We also did not demonstrate a significant effect of higher serum urea, creatinine levels, or presence of a solitary kidney and congenital renal anomaly on success rates. The global percutaneous nephrolithotomy study group showed that renal congenital abnormalities do not significantly impact treatment outcomes (15). It has also been also shown that PNL can be performed with similar success and complication rates in patients with solitary kidneys (16). In our study, we observed that previous surgery and a history of ESWL had no significant effect on the success rate. Patients with a history of open stone surgery reported as have a lower chance of stone-free rate in the current literature (4). Basiri et al. (17) stated that an open surgical history on the same side did not affect the success or complication rates in patients treated with PNL. Yuruk et al. (18) reported that similar success and complication rates could be achieved with PNL after failed ESWL, but it was usually more difficult with a prolonged operative time and fluoroscopic screening time. In our study, the success rate was significantly lower in cases with accompanying macroscopic hematuria. There was no statistically significant difference in success rates between patients with a higher degree of hydronephrosis and those with a lower degree of hydronephrosis. In hydronephrotic systems with stones, the entrance is easy, but the rate of failure increases because the stones can escape to other calyces (19). We found that stone size, complexity, and structure were the most important predictors of stone-free rate after PNL. Complex

stones accounted for almost half (46.85%) in our cases. Our results are consistent with those of Knox et al. (20), who revealed that stone sizeand number, are associated with reduced stone clearance. Bagrodia et al. (21) reported that stone size was the only independent predictor of treatment success. Yamasaki (22) reported that the size of the stone, the location, and the presence of multiple stones were prognostic factors for stone recurrence. Notably, in contrast to these observations, the European Association of Urology guidelines on urolithiasis discuss that the treatment success of PCNL is hardly affected by stone size (23). In our study, it was determined that the success rate in cysteine and infection stones was lower than other stone compositions. A reason for the low success rate of infected stones may be that these tend to be large and even coralliform. The best of our knowledge, there is no study evaluating the impact of stone composition on the success of PNL in the current literature. The success rate of multifocal access is expected to be lower as the stones-requiring multifocal intervention are larger and more complex. In this study, a higher number of accesses was performed in the failed group, confirming that a higher number of accesses was associated with less favorable outcomes. We demonstrated that higher intraoperative complication rates, prolonged dilation, and operative time reduced the success rate of PNL. The experience of the surgeon and learning curve are also important factors affecting the overall surgical success. In our series, the first 204 cases had a success rate of 73.8, whereas the latter 204 cases had a success rate of 93%. In line with our results, Tanriverdi et al. (23) reported a success rate of 73% for the first 60 cases and 85% after 60 cases. Although PNL is a significant treatment option with a high success rate, it should not be forgotten that serious complications can occur, even to the point of being life-threatening. The rate of major complications such as urosepsis, bleeding necessitating intervention, pleural injury, and colonic injury was reported to be between 0.2% and 4.7% fin a large study with 5803 cases (24). In our study, the rate of major complications was 8.3%. Bleeding was the most common complication. The rate of renal hemorrhage requiring transfusion and 5.5%. Transfusion rates ranging up to 20% have been documented with an overall of 7% demonstrated in a systematic review (25).

Study Limitations

Our study has some limitations that need to be considered while evaluating its findings. First, it is a retrospective study that can be affected by all potential weaknesses stemming from its retrospective design. Second, it has a relatively low number of cases and short evaluation time of success compared to clinical trials with high number of cases in the current literature.

Conclusion

PNL surgery is an effective and minimally invasive method that requires surgical experience and can be safely applied to stone treatment with adequate equipment and experience, at least as successfully as open surgery. After reviewing our experience with PNL, we showed several clinical and stone factors related to the success rate after PNL. Stone size, complexity, and composition, surgeon's experience were the independent predictors of stone-free status after PNL.

Ethics

Ethics Committee Approval: The study protocol was approved by Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (project no: 24/07, date: 18.04.2011).

Informed Consent: Informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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References

1. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol 2016;69:475-482.
2. Chung DY, Kang DH, Cho KS, Jeong WS, Jung HD, Kwon JK, Lee SH, Lee JY. Comparison of stone-free rates following shock wave lithotripsy, percutaneous nephrolithotomy, and retrograde intrarenal surgery for treatment of renal stones: A systematic review and network meta-analysis. PLoS One 2019;14:e0211316.
3. De S, Autorino R, Kim FJ, Zargar H, Laydner H, Balsamo R, Torricelli FC, Di Palma C, Molina WR, Monga M, De Sio M. Percutaneous nephrolithotomy versus retrograde intrarenal surgery: a systematic review and meta-analysis. Eur Urol 2015;67:125-137.
4. Smith A, Averch TD, Shahrour K, Opondo D, Daels FP, Labate G, Turna B, de la Rosette JJ; CROES PCNL Study Group. A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. J Urol 2013;190:149-156.
5. Jiang K, Sun F, Zhu J, Luo G, Zhang P, Ban Y, Shan G, Liu C. Evaluation of three stone-scoring systems for predicting SFR and complications after percutaneous nephrolithotomy: a systematic review and meta-analysis. BMC Urol 2019;19:57.

6. de la Rosette JJ, Zuazu JR, Tsakiris P, Elsakka AM, Zudaire JJ, Laguna MP, de Reijke TM. Prognostic factors and percutaneous nephrolithotomy morbidity: a multivariate analysis of a contemporary series using the Clavien classification. J Urol 2008;180:2489-2493.
7. Rassweiler JJ, Renner C, Eisenberger F. The management of complex renal stones. BJU Int 2000;86:919-928.
8. Falahatkar R, Shahraki T, Falahatkar S, Esmaeili S, Mashouf P. Evaluating outcomes of complete supine percutaneous nephrolithotomy for staghorn vs multiple non-staghorn renal stones: a 10-year study. World J Urol 2021;39:3071-3077.
9. Skolarikos A, Papatsoris AG. Diagnosis and management of postpercutaneous nephrolithotomy residual stone fragments. J Endourol 2009;23:1751-1755.
10. Pires C, Machet F, Dahmani L, Irani J, Dore B. Sensibilité de la radiographie de l'abdomen sans préparation par rapport à la tomodensitométrie dans l'évaluation des fragments résiduels après NLPC [Sensitivity of abdominal radiography without preparation compared with computed tomography in the assessment of residual fragments after percutaneous nephrolithotomy]. Prog Urol 2003;13:581-584.
11. Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, Macaluso JN Jr, McCullough DL. Nephrolithiasis Clinical Guidelines Panel summary report on the management of staghorn calculi. The American Urological Association Nephrolithiasis Clinical Guidelines Panel. J Urol 1994;151:1648-1651.
12. Olbert PJ, Hegele A, Schrader AJ, Scherag A, Hofmann R. Pre- and perioperative predictors of short-term clinical outcomes in patients undergoing percutaneous nephrolitholapaxy. Urol Res 2007;35:225-230.
13. Alyami FA, Skinner TA, Norman RW. Impact of body mass index on clinical outcomes associated with percutaneous nephrolithotomy. Can Urol Assoc J 2013;7:E197-201.
14. Tefekli A, Kurtoglu H, Tepeler K, Karadag MA, Kandirali E, Sari E, Baykal M, Muslumanoglu AY. Does the metabolic syndrome or its components affect the outcome of percutaneous nephrolithotomy? J Endourol 2008;22:35-40.
15. Osther PJ, Razvi H, Liatsikos E, Averch T, Crisci A, Garcia JL, Mandal A, de la Rosette J; Croes PCNL Study Group. Percutaneous nephrolithotomy among patients with renal anomalies: patient characteristics and outcomes; a subgroup analysis of the clinical research office of the endourological society global percutaneous nephrolithotomy study. J Endourol 2011;25:1627-1632.
16. Mahboub MR, Shakibi MH. Percutaneous nephrolithotomy in patients with solitary kidney. Urol J 2008;5:24-27.
17. Basiri A, Karrami H, Moghaddam SM, Shadpour P. Percutaneous nephrolithotomy in patients with or without a history of open nephrolithotomy. J Endourol 2003;17:213-216.
18. Yuruk E, Tefekli A, Sari E, Karadag MA, Tepeler A, Binbay M, Muslumanoglu AY. Does previous extracorporeal shock wave lithotripsy affect the performance and outcome of percutaneous nephrolithotomy? J Urol 2009;181:663-667.
19. Lu Z, Dong Z, Ding H, Wang H, Ma B, Wang Z. Tamsulosin for ureteral stones: a systematic review and meta-analysis of a randomized controlled trial. Urol Int 2012;89:107-115.
20. Knox ML, Cantor AM, Bryant JE, Burns JR. Predictive factors for percutaneous nephrolithotomy outcomes in neurogenic bladder population. J Endourol 2012;26:823-827.
21. Bagrodia A, Gupta A, Raman JD, Bensalah K, Pearle MS, Lotan Y. Predictors of cost and clinical outcomes of percutaneous nephrostolithotomy. J Urol 2009;182:586-590.
22. Yamasaki A. [Long-term results of endourological treatment of urinary calculi: multivariate analyses of the risk factors related to recurrence or re-growth]. Nihon Hinyokika Gakkai Zasshi 1994;85:1601-1609.
23. Tanriverdi O, Boylu U, Kendirci M, Kadihasanoglu M, Horasanli K, Miroglu C. The learning curve in the training of percutaneous nephrolithotomy. Eur Urol 2007;52:206-211.
24. de la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, Tefekli A; CROES PCNL Study Group. The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: indications, complications, and outcomes in 5803 patients. J Endourol 2011;25:11-17.
25. Seitz C, Desai M, Häcker A, Hakenberg OW, Liatsikos E, Nagele U, Tolley D. Incidence, prevention, and management of complications following percutaneous nephrolitholapaxy. Eur Urol 2012;61:146-158.

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Alleviating Effect of Alpha-Pinene on Testicular Torsion and Detorsion Injury in Rats

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What's known on the subject? and What does the study add?

Testicular torsion is one of the most important pediatric emergencies. The ischemia/reperfusion injury (IRI) that occurs during detorsion, which is a mandatory treatment, can adversely affect fertility. The search for compounds that can therefore eliminate reperfusion injury has gained momentum. Alpha-pinene (AP) is a monoterpene and is known for its strong antioxidant and anti-inflammatory properties. In this study, it was revealed that oxidative stress, inflammation, and endoplasmic reticulum stress increased and caused testicular damage in the testicular IRI model created in rats. It was determined that AP treatment eliminated this damage. This experimental study provides an important background for subsequent clinical trials on the protective efficacy of AP in cases of testicular torsion.

Abstract

Objective: It was aimed to evaluate whether alpha-pinene (AP) had a beneficial effect in the testicular ischemia/reperfusion injury (IRI) model for the first time.

Materials and Methods: Testicular malondialdehyde, total oxidant status, and total antioxidant status levels were determined using spectrophotometric methods. The superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), myeloperoxidase (MPO), 78-kDa glucose-regulated protein (GRP78), activating transcription factor 6 (ATF6), and C/EBP homologous protein (CHOP) levels were determined using the commercial enzyme-linked immunosorbent assay kits. Hematoxylin-eosin staining method was used in the histopathological evaluation.

Results: In the IRI group, testicular MDA, MPO, GRP78, ATF6, and CHOP levels were significantly increased, while GSH and GPx levels were decreased compared with the control group ($p<0.01$). AP application restored these levels significantly ($p<0.05$). Johnsen scores were also significantly lower in the IRI group compared the control group ($p<0.001$), and AP treatment increased these scores significantly ($p<0.001$).

Conclusion: These results suggest that AP can protect the testicular tissue against IRI by inhibiting oxidative stress, inflammation, and endoplasmic reticulum stress with its antioxidant properties, thus providing a molecular basis for a novel medical treatment of testicular IRI. Future studies are needed on other mechanisms of the protective effect of AP on the pathogenesis of testicular torsion.

Keywords: Alpha-pinene, endoplasmic reticulum stress, inflammation, oxidative stress, testicular torsion

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Introduction

Testicular torsion (TT) is a urological emergency that causes occlusion of blood vessels and prevents the perfusion of the testicles (1). The annual incidence of TT is reported to be 3.8-8.6 cases per 100,000 men younger than 18 years of age (2). Today, the only mandatory treatment method for TT is detorsion (1,2). However, reperfusion to cause tissue damage more severe than ischemia, this is known as ischemia/reperfusion injury (IRI) and is the main mechanism underlying the pathogenesis of TT (3). During reperfusion of ischemic tissue, excessive amounts of reactive oxygen species (ROS) are formed in the tissue, and these ROS cause endothelial dysfunction, inflammation, lipid peroxidation, and endoplasmic reticulum (ER) stress (3,4). The ER is a cellular organelle involved in protein synthesis, calcium storage, lipid synthesis, detoxification, and energy metabolism (5). Various pathological stimuli, such as increased pressure, temperature, trauma, ROS levels, and nutrient deficiency cause the accumulation of unfolded/misfolded proteins in the ER lumen, and this is known as "ER stress" (6). Cells activate the unfolded protein response (UPR) pathway, which is considered a protective mechanism for eliminate ER stress. In the case of mild ER stress, the activation of the UPR activates the cytoprotective mechanisms, while in the case of severe ER stress, the UPR activates apoptosis (5,6). Recent evidence has revealed that increased ER stress plays a role in the etiopathogenesis of IRI (7). It is therefore suggested that IRI-induced tissue loss can be prevented by identifying compounds with potential ER stress inhibitory activity (5,6).

Terpenoids are among the most abundant components in natural products, and more than 50,000 terpenoid derivatives have been isolated to date (8). Alpha-pinene (AP) is a monoterpene, especially abundant in plants of the *Pinus* genus (9). Today, it has a substantial area of use in the cosmetics, paint and food industries (10). Various pharmacological activities of AP, such as anticoagulant, anti-inflammatory, antimicrobial, antioxidant, antitumor, anti-apoptotic, analgesic, hypoglycemic, neuroprotective, and gastroprotective have been reported (8-10). Although AP protects brain and heart tissues in various experimental IRI models previously (11,12), there is no study examining the protective effect of AP against I/R-induced testicular damage. Protecting male reproductive health against IRI is critical for the continuation of fertility. This study therefore evaluated whether AP had a beneficial effect in a rat testicular IRI model for the first time, which had previously shown antioxidant and anti-inflammatory properties and tissue protective effects in various experimental IRI models.

Materials and Methods

Experimental Design

All experimental procedures were approved by the Animal Experiments Local Ethics Committee of Karadeniz Technical University in accordance with the international guidelines for the use and care of laboratory animals (protocol number: 2022/08, date: 02.03.2022). All surgical procedures were performed under general anesthesia provided by intraperitoneal (ip) administration of 60 mg/kg ketamine (60 mg/kg, Vem Pharmaceuticals, Ankara, Turkiye) and 12 mg/kg xylazine (10 mg/kg, Bayer, Leverkusen, Germany) combination. All applications to the rats were done by the ip route. The scrotal skin area was shaved and cleaned with a betadine antiseptic solution. The left testicle was entered with a scrotal incision, and the left testicle was made visible. The animals were divided into three groups (n=6): Group 1 (sham control), Group 2 (torsion/detorsion, T/D), and Group 3 (T/D+AP, 50 mg/kg). The experimental procedure is briefly summarized in Table 1. In the Group 1, the left testicle was removed and placed back into the scrotum to create surgical stress.

The experimental T/D procedure was performed according to the method by Turner et al. (13). In Groups 2 and 3, the left testicle removed by incision was rotated 720° clockwise and fixed to the scrotum (4,13). After 4 h of ischemia, the suture was removed and testicular reperfusion was achieved for 2 h based on previously described methods (4,14). AP (50 mg/kg) was administered 30 min before detorsion to Group 3. Simultaneously, dimethyl sulfoxide (DMSO) was administered to the Group 1 and Group 2. The dose of AP (Sigma-Aldrich, St. Louis, MO, USA) was determined considering previous studies and was prepared by dissolving in DMSO (12,15). After 2 h of detorsion, orchiectomy was performed. The removed testicles were homogeneously divided longitudinally two pieces, and one portion was frozen at -80 °C for biochemical analysis, and the other was stored in Bouin's solution for histological evaluation (Figure 1).

Histological Analysis

Routine histological tissue follow-ups were performed for testicular specimens fixed from Bouin's solution. Testicular specimens were cut in 5 µm sections, stained with H&E, and examined under a light microscope (Olympus BX50, Tokyo, Japan) (4,16). Later, seminiferous tubule architecture and the levels of spermatogenesis were graded with the scoring system defined by Johnsen (17). Scoring and histological evaluation were performed blindly by a pathologist unaware of the groups.

Biochemical Analysis

Testicle tissues were homogenized in cold saline at 9500 rpm using a homogenizer (IKA, T25 Ultra-Turrax, Staufen, Germany). The homogenates were centrifuged at 1800 x g for 15 min at 4°C. The supernatants were collected and the protein contents were determined using a commercial kit (Pierce BCA Protein Assay Kit, Thermo Scientific, Rockford, IL) according to the manufacturer's instructions and used for biochemical analysis. Testicular malondialdehyde (MDA) levels of all groups were determined according to the method described previously (18), while total oxidant status (TOS) and total antioxidant status (TAS) levels were determined using commercial colorimetric kits (Rel Assay Diagnostics, Gaziantep, Turkiye). The oxidative stress index (OSI) was determined using the following formula (19):

$$\text{OSI (arbitrary unit)} = \frac{\text{(TOS (µmoL hydrogen peroxide equivalent/L)}}{\text{(TAS (µmoL trolox equivalent/L)}} \text{ X } 100$$

Tissue superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione (GSH), myeloperoxidase (MPO), 78-kDa glucose-regulated protein (GRP78), activating transcription factor 6 (ATF6) and C/EBP homologous protein (CHOP) levels were determined using ready-to-use enzyme-linked immunosorbent assay (ELISA) kits (Finetest, Wuhan, China).

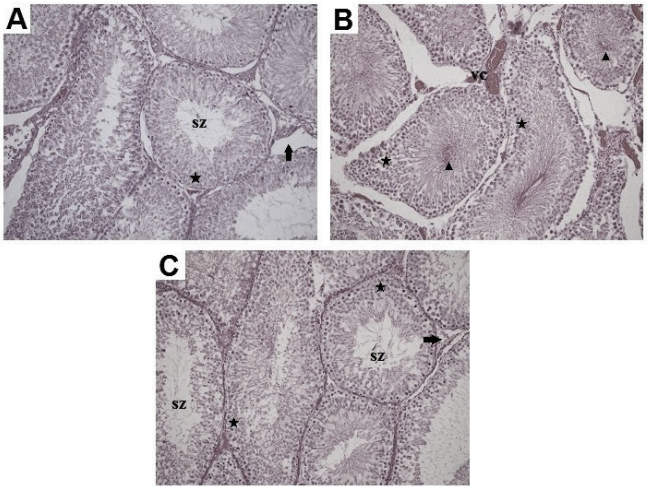

Figure 1. Histopathological images of testicular tissues of groups (×200, H&E staining). **Control Group (A)** SZ: spermatozoon, black star: seminiferous tubule germinal epithelium, black arrow: intertubular area. **T/D Group (B)** VC: vasocongestion in the intertubular area, arrowhead: germinal epithelial cells, black star: seminiferous tubule germinal epithelium. **T/D+AP Group (C)** SZ: spermatozoon, black star: seminiferous tubule germinal epithelium, black arrow: intertubular area

Statistical Analysis

All data are expressed as mean ± standard deviation. Statistical differences between the groups were assessed by ANOVA followed by Tukey's Post-hoc test. P was defined as statistically significant at <0.05.

Results

The levels of biochemical parameters and histological scores are presented in Table 2. The data showed that the MDA, TOS, OSI, and MPO levels in Group 2 were significantly more than Group 1 (p=0.0001, p=0.001, p=0.017 and p=0.0001, respectively). In contrast, the treatment of rats with AP, which was administered before reperfusion significantly lowered MDA, TOS, OSI and MPO levels compared to Group 2 (p=0.0001, p=0.003, p=0.025 and p=0.0001, respectively).

The results showed that the tissue levels of TAS, SOD, GPx, and GSH were significantly decreased in the Group 2 compared to Group 1 (p=0.0001, p=0.0001, p=0.003 and p=0.0001, respectively). In contrast, the administration of AP before reperfusion caused a significant increase in the tissue levels of TAS, SOD, GPx and GSH compared to Group 2 (p=0.0001, p=0.0001, p=0.006 and p=0.001, respectively).

Additionally, the GRP78, ATF6, and CHOP levels of the Group 2 were significantly increased compared with Group 1 (p=0.0001, p=0.001 and p=0.0001, respectively). Contrarily, treatment of rats with AP significantly decreased the tissue levels of GRP78, ATF6 and CHOP compared to Group 2 (p=0.0001, p=0.002 and p=0.0001, respectively). Furthermore, no significant difference was found between the Groups 1 and 3 in terms of biochemical parameters (p>0.05).

Johnsen scores were significantly lower in the Group 2 compared to Group 1 (p=0.0001), and AP treatment increased these scores significantly (p=0.0001).

Table 1. A summary of the procedures applied to the experimental groups

	Groups		
	Control	**T/D**	**AP + T/D**
Torsion 0 min	-	+	+
210 min after torsion	DMSO	DMSO	50 mg/kg
Detorsion (240 min after torsion)	-	+	+
Orchiectomy (360 min after torsion)	+	+	+

T/D: torsion/detorsion; AP: (+)-alpha-pinene

Table 2. The levels of oxidative stress, inflammation and ER stress markers and Johnsen scores of groups			
	Control	**T/D**	**AP + T/D**
MDA (nmol/mg protein)	4.53±2.91	14.9±3.08[a]	5.55±0.81[b]
TOS (μM H_2O_2 equivalent/L)	22.7±2.90	54.2±18.1[a]	26.6±8.82[b]
TAS (mM trolox equivalent/L)	1.18±0.12	0.62±0.23[a]	1.03±0.08[b]
OSI (arbitrary unit)	1.97±0.21	11.1±8.66[a]	2.53±0.81[b]
SOD (ng/mg protein)	0.24±0.05	0.09±0.03[a]	0.21±0.03[b]
GPx (pg/mg protein)	16.4±4.34	8.88±1.98[a]	15.9±3.09[b]
GSH (μg/mg protein)	4.82±1.42	0.85±0.26[a]	4.52±1.80[b]
MPO (ng/mg protein)	0.32±0.08	1.26±0.45[a]	0.33±0.09[b]
GRP78 (pg/mg protein)	51.7±7.81	160.3±38.2[a]	42.3±6.87[b]
ATF6 (pg/mg protein)	30.4±6.56	55.6±12.8[a]	33.9±6.54[b]
CHOP (ng/mg protein)	0.25±0.07	0.77±0.30[a]	0.21±0.04[b]
Johnsen Score	9.5±0.55	4.33±1.21[a]	8.0±0.63[a,b]

T/D: Torsion/detorsion, AP: (+)-alpha-pinene, MDA: Malondialdehyde, TOS: Total oxidant status, TAS: Total antioxidant status, OSI: Oxidative stress index, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, GSH: Glutathione, MPO: Myeloperoxidase, GRP78: 78-kDa glucose-regulated protein, ATF-6: Activating transcription factor-6, CHOP: C/EBP homologous protein, P-values according to one-way ANOVA test, post-hoc Tukey test. Data were expressed as mean±SD. [a]p<0.05 compared with control group, [b]p<0.05 compared with T/D group

Discussion

TT is one of the most serious pediatric emergencies, and IRI is central to its pathogenesis (1,2). The pathogenesis of IRI is complex and is related to various molecular mechanisms, such as oxidative/nitrosative stress, inflammation, ER stress, and mitochondrial dysfunction (3). In particular, MDA, a byproduct of the oxidation of fatty acids, acts as a potent chemoattractant and initiates the proinflammatory phase in tissues (20). It is therefore stated that there is a correlation between MDA levels and tissue oxidative stress level (4). TOS, TAS, and OSI are popular cumulative oxidative stress indicators that reveal the level of oxidative stress in biological samples (19,21). Increased MDA, TOS, and OSI levels and lower TAS levels in Group 2 indicated that the testicular IRI was mediated by oxidative stress, while AP treatment significantly reduced this damage in this study. Consistent with our results, AP has been previously demonstrated to prevent IRI-induced brain and heart injury by decreasing oxidative stress levels (11,12).

SOD is the primary step of the antioxidant defense mechanism in the organism and catalyzes the conversion of superoxide to hydrogen peroxide (22). GSH is a molecule synthesized from glutamic acid, cysteine and glycine, with a high antioxidant potential due to its sulfhydryl groups (23). GPx is an enzyme that reduces hydrogen peroxide to water with the antioxidant property of GSH (12). Measurements of GSH, SOD and GPx are therefore frequently preferred biochemical parameters to determine the level of antioxidant defense system in a biological sample (21). The results showed that decreased GSH, SOD and GPx levels in Group 2 could not protect the testicular tissue against ROS attacks (24), while AP treatment strengthened the antioxidant mechanism. This may be because AP protects antioxidant defense systems from attack by ROS. Similar to our results, AP has previously been demonstrated to prevent I/R, hydrogen peroxide, and scopolamine-induced intestine and brain injuries by increasing antioxidant enzyme levels (15,22,25).

Inflammation is an important biological reaction of the organism in response to external stimuli (26). Neutrophil infiltration is another characteristic of IRI-induced inflammatory tissue damage. Migration and activation of neutrophils into the ischemic tissue increase the amount of ROS, MPO, and pro-inflammatory cytokines and exacerbate tissue damage (20). While the increased MPO levels in Group 2 showed that testicular IRI was mediated by inflammation, it was determined that AP abolished this damage with its previously revealed anti-inflammatory properties. Similar to our results, terpenoids have previously been demonstrated to prevent I/R and cyclophosphamide-induced brain and testicular injuries via reducing the inflammation (20,27).

Recent studies highlight that ER stress comes to the forefront as an important molecular mechanism in IRI. ER stress from ischemic injury initiates the UPR, which is considered a protection mechanism (7). Three sensor proteins detect ER stress and initiate the UPR pathway: inositol-requiring enzyme-1 alpha (IRE-1α), protein kinase-like ER kinase (PERK), and ATF6 (28). Under physiological conditions, these three proteins are inactive and bound to GRP78, a large molecular ER chaperone. Under conditions of increased ER stress, GRP78 cleaves from PERK, IRE1, and ATF6, and this cleavage activates these sensor proteins (7). After ATF6 dissociates with GRP78, it is transported to the golgi in response to ER stress. Released ATF6 passes

into the golgi, where it is cleaved by proteases and activated. Activated ATF6 migrates from the golgi to the nucleus where it induces the expression of proteins in optimizing protein folding, maturation, and elimination of missense proteins (4). In the case of excessive ER stress, ATF6 induces CHOP expression, resulting in apoptosis and elimination of the cell whose ER stress cannot be reduced. Under increased ER stress conditions, increased CHOP suppresses Bcl-2 and GSH levels, increases Bax and ROS levels and causes the activation of apoptosis (4,28). Studies recently have focused on strategies that target the inhibition of ER stress in the I/R process. Among them, the treatment method with molecules with antioxidant and anti-inflammatory properties attracted great attention (29). However, there was no study examining the effect of AP on IRI-induced ER stress. The results showed that the levels of ER stress markers increased in the IRI group, whereas AP protected the testicular tissue against IRI by suppressing ER stress. Similar to our results, terpenoids have previously been demonstrated to prevent liver and lung IRI via reducing the ER stress (28,29).

Histological evaluation is a critical method in evaluating tissue damage caused by IRI and revealing the degree of the therapeutic effect of the investigated molecule (4,16). Histological analysis confirmed that functional testicular structures were damaged in the IRI group, while AP successfully attenuated this damage. In parallel with our results, it is previously shown histologically that various terpenoids, including eugenol and nerolidol, protect the testicular tissue against the damage caused by cisplatin and cyclophosphamide by modulating oxidative stress, inflammation, and apoptosis (20,30).

Study Limitations

There are also some limitations to our study. First, only one dose of AP was evaluated on the basis of literature data within the scope of this study. Second, the efficacy of AP at different times or in chronic T/D conditions was not evaluated in this study. The testicular protective effect of AP at different periods and doses should be evaluated in the next compherensive studies. Third, the effects of AP on fertility levels were not evaluated in the study. We believe that demonstrating the protective efficacy of AP against testicular IRI in long-term studies with physiological fertility behavior experiments will shed light on the clinical stages.

Conclusion

The results showed that AP reduced the testicular IRI for the first time. This protective effect of AP is thought to be due to its antioxidant, anti-inflammatory and ER stress inhibitor properties. Based on these findings, AP may be useful as a potentially effective adjunct to therapy for ischemic testicular injury before reperfusion.

Ethics

Ethics Committee Approval: This study was approved by the Animal Care Ethical Committee of Karadeniz Technical University (protocol number: 2022/08, date: 02.03.2022) and performed according to the animal research reporting of *in vivo* experiments (ARRIVE) guidelines.

Informed Consent: All institutional and national guidelines for the care and use of laboratory animals were followed. The rights of the animals were respected.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.O.K., Z.S.Y., S.D., R.S.T., Concept: S.D., İ.O.K., Design: S.D., İ.O.K., Z.S.Y., A.M., Data Collection or Processing: S.D., Z.S.Y., E.A.D., N.T.A., Analysis or Interpretation: S.D., İ.O.K., Z.S.Y., A.M., Literature Search: S.D., İ.O.K., E.A.D., N.T.A., Writing: S.D.

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References

1. Laher A, Ragavan S, Mehta P, Adam A. Testicular Torsion in the Emergency Room: A Review of Detection and Management Strategies. Open Access Emerg Med 2020;12:237-246.
2. Thaker H, Nelson CP. Adjuvant pharmacological and surgical therapy for testicular torsion: Current state of the art. J Pediatr Urol 2020;16:807-814.
3. Arena S, Iacona R, Antonuccio P, Russo T, Salvo V, Gitto E, Impellizzeri P, Romeo C. Medical perspective in testicular ischemia-reperfusion injury. Exp Ther Med 2017;13:2115-2122.
4. Kazaz IO, Demir S, Kerimoglu G, Colak F, Turkmen Alemdar N, Yilmaz Dogan S, Bostan S, Mentese A. Chlorogenic acid ameliorates torsion/detorsion-induced testicular injury via decreasing endoplasmic reticulum stress. J Pediatr Urol 2022;18:289.e1-289.e7.
5. Gao X, Xu Y. Therapeutic Effects of Natural Compounds and Small Molecule Inhibitors Targeting Endoplasmic Reticulum Stress in Alzheimer's Disease. Front Cell Dev Biol 2021;9:745011.
6. Ma RH, Ni ZJ, Thakur K, Zhang F, Zhang YY, Zhang JG, Wei ZJ. Natural compounds play therapeutic roles in various human pathologies via regulating endoplasmic reticulum pathway. Medicine in Drug Discovery 2020;8: 100065.
7. Han Y, Yuan M, Guo YS, Shen XY, Gao ZK, Bi X. Mechanism of Endoplasmic Reticulum Stress in Cerebral Ischemia. Front Cell Neurosci 2021;15:704334.
8. Yang W, Chen X, Li Y, Guo S, Wang Z, Yu X. Advances in pharmacological activities of terpenoids. Nat Prod Commun 2020;15:1-13.
9. Park BB, An JY, Park SU. Recent studies on pinene and its biological and pharmacological activities. EXCLI J 2021;20:812-818.
10. Allenspach M, Steuer C. α-Pinene: A never-ending story. Phytochemistry 2021;190:112857.
11. Choi IY, Lim JH, Hwang S, Lee JC, Cho GS, Kim WK. Anti-ischemic and anti-inflammatory activity of (S)-cis-verbenol. Free Radic Res 2010;44:541-551.

12. Zhang B, Wang H, Yang Z, Cao M, Wang K, Wang G, Zhao Y. Protective effect of alpha-pinene against isoproterenol-induced myocardial infarction through NF-κB signaling pathway. Hum Exp Toxicol 2020;39:1596-1606.
13. Turner TT, Tung KS, Tomomasa H, Wilson LW. Acute testicular ischemia results in germ cell-specific apoptosis in the rat. Biol Reprod 1997;57:1267-1274.
14. Mentese A, Demir S, Kazaz IO, Yulug E, Alemdar NT, Demir EA, Kartal MB, Durmus TB, Aliyazicioglu Y. Vanillic acid attenuates testicular ischemia/reperfusion injury in rats. Beni-Suef Univ J Basic Appl Sci 2022;11:155.
15. Khoshnazar M, Bigdeli MR, Parvardeh S, Pouriran R. Attenuating effect of α-pinene on neurobehavioural deficit, oxidative damage and inflammatory response following focal ischaemic stroke in rat. J Pharm Pharmacol 2019;71:1725-1733.
16. Demir S, Kazaz IO, Kerimoglu G, Ayazoglu Demir E, Colak F, Yilmaz S, Mentese A. Astaxanthin Protects Testicular Tissue against Torsion/Detorsion-Induced Injury via Suppressing Endoplasmic Reticulum Stress in Rats. J Invest Surg 2022;35:1044-1049.
17. Johnsen SG. Testicular biopsy score count--a method for registration of spermatogenesis in human testes: normal values and results in 335 hypogonadal males. Hormones 1970;1:2-25.
18. Mihara M, Uchiyama M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem 1978;86:271-278.
19. Ayazoglu Demir E, Mentese A, Kucuk H, Turkmen Alemdar N, Demir S. p-Coumaric acid alleviates cisplatin-induced ovarian toxicity in rats. J Obstet Gynaecol Res 2022;48:411-419.
20. Iqubal A, Syed MA, Najmi AK, Ali J, Haque SE. Ameliorative effect of nerolidol on cyclophosphamide-induced gonadal toxicity in Swiss Albino mice: Biochemical-, histological- and immunohistochemical-based evidences. Andrologia 2020;52:e13535.
21. Marrocco I, Altieri F, Peluso I. Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. Oxid Med Cell Longev 2017;2017:6501046.
22. Lee GY, Lee C, Park GH, Jang JH. Amelioration of Scopolamine-Induced Learning and Memory Impairment by α-Pinene in C57BL/6 Mice. Evid Based Complement Alternat Med 2017;2017:4926815.
23. Ma JQ, Liu CM, Qin ZH, Jiang JH, Sun YZ. Ganoderma applanatum terpenes protect mouse liver against benzo(α)pyren-induced oxidative stress and inflammation. Environ Toxicol Pharmacol 2011;31:460-468.
24. Manjunatha S, Shaik AH, E MP, Al Omar SY, Mohammad A, Kodidhela LD. Combined cardio-protective ability of syringic acid and resveratrol against isoproterenol induced cardio-toxicity in rats via attenuating NF-kB and TNF-α pathways. Sci Rep 2020;10:3426.
25. Porres-Martínez M, González-Burgos E, Carretero ME, Gómez-Serranillos MP. In vitro neuroprotective potential of the monoterpenes α-pinene and 1,8-cineole against H2O2-induced oxidative stress in PC12 cells. Z Naturforsch C J Biosci 2016;71:191-199.
26. Afolabi O, Alabi B, Omobowale T, Oluranti O, Iwalewa O. Cysteamine mitigates torsion/detorsion-induced reperfusion injury via inhibition of apoptosis, oxidative stress and inflammatory responses in experimental rat model. Andrologia 2022;54:e14243.
27. Mu L, Kou J, Zhu D, Yu B. Comparison of neuroprotective effects of flavonoids, terpenoids, and their combinations from Ginkgo biloba on ischemia-reperfusion-injured mice. Pharm Biol 2007;45:728-733.
28. Yang Y, Li C, Liu N, Wang M, Zhou X, Kim IH, Wu Z. Ursolic acid alleviates heat stress-induced lung injury by regulating endoplasmic reticulum stress signaling in mice. J Nutr Biochem 2021;89:108557.
29. Bouhlel A, Ben Mosbah I, Hadj Abdallah N, Ribault C, Viel R, Mannaï S, Corlu A, Ben Abdennebi H. Thymoquinone prevents endoplasmic reticulum stress and mitochondria-induced apoptosis in a rat model of partial hepatic warm ischemia reperfusion. Biomed Pharmacother 2017;94:964-973.
30. Ekinci Akdemir FN, Yildirim S, Kandemir FM, Aksu EH, Guler MC, Kiziltunc Ozmen H, Kucukler S, Eser G. The antiapoptotic and antioxidant effects of eugenol against cisplatin-induced testicular damage in the experimental model. Andrologia 2019;51:e13353.

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A Survey Study on Evaluation and Management of Nocturnal Enuresis in Pediatricians and Family Physicians

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What's known on the subject? and What does the study add?

Although nocturnal enuresis is a common disorder in pediatric urology practice, it can sometimes cause a challenge for both physicians and parents. However, it is known that most of the patients primarily refer to family physicians and pediatricians. This survey study, which included multiple-choice questions, showed that the participants felt inadequate during management of nocturnal enuresis. We believe that postgraduate training programs may increase the self-confidence of physicians in management of nocturnal enuresis.

Abstract

Objective: Nocturnal enuresis (NE) is one of the most common disorders in pediatric urology, and patients often turn to family physicians (FP) and pediatricians (P) initially. The aim of this study was to understand the awareness, self-confidence and suggestions of physicians regarding the management of NE.

Materials and Methods: In this study, 360 FP and family medicine residents (FMR), as well as 280 P and pediatrics residents (PR), were contacted through a cellular phone texting system. A simple multiple-choice questionnaire (Surveymonkey®) consisting of 10 questions was used to gather data. The survey included questions about their experience, training, evaluation, and management of NE.

Results: A total of 119 FPs and Ps (18.5%) filled the questionnaire. Thirty (25.21%) of the participants were P, 27 (22.69%) PR, 3 (2.52%) FP and 59 (49.58%) FMR. The rate of physicians who encounter at least 5 children with NE per month is 31.33%. The mean self-confidence in the management of NE was 4.5 out of 10. The self-confidence of pediatricians was significantly higher than that of PR and FMR ($p<0.001$, $p<0.001$). Most (n=78, 65.55%) of the participants stated that they received training on EN during medical faculty and 62 (52.10%) during residency. Psychological problems (89.92%), sleep disorders (78.15%), and excessive fluid intake (75.63%) were the most frequently considered factors in etiology. While most responders (75.63%) considered dietary regulation and behavioral interventions as the first-line treatment, 25.21% consult a pediatric urologist and only 1.6% recommend medical treatment.

Conclusion: Although FP and P admit they had training on NE, they mostly felt incompetent to manage NE and exclusively avoided pharmacological treatment.

Keywords: Children, enuresis nocturna, pediatric urology, physicians, survey

Introduction

Nocturnal enuresis (NE) is defined as involuntary urinary incontinence during sleep that occurs in children older than 5 years of age (1). Enuresis is classified as monosymptomatic NE and non-monosymptomatic NE according to daytime lower urinary tract (LUT) symptoms, such as urgency, voiding difficulties, abnormal daytime voiding frequency, and incontinence. Primary NE refers to a child who has not been dry for 6 months, whether secondary NE is symptom-free 6

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months before bedwetting. Around 10 to 15 percent of 7-year-old children experience primary NE, but it resolves at a rate of 15 percent per year, with approximately 99 percent of children becoming dry by the age of 15 (2). Although enuresis is three times more common in boys than in girls before the age of 10, this gender difference decreases with age. Nocturnal polyuria, nocturnal detrusor overactivity, low bladder capacity at night, high arousal thresholds, genetic factors, and psychological/psychiatric problems can be considered as etiological factors of NE (3).

A multicenter and multinational survey study concluded that there is no consensus among physicians on the etiology, diagnosis, and treatment of EN (4). Also, it is known that NE is often neglected by caregivers. Therefore, it may lead to low self-esteem, disturbed social life, and poor sleeping quality in untreated patients (5,6). Urotherapy, fluid restriction in the evenings, enuretic alarms, and desmopressin are first-line treatments for monosymptomatic NE (7-9). Also, LUT symptoms and constipation should be managed in patients with nonmonosymptomatic NE. Some patients should see a psychologist or psychiatrist for behavioral or antidepressant treatment (10,11).

Bedwetting is one of the most frequent complaints in pediatric urology outpatient clinics. However, patients often refer to family physicians (FP) and pediatricians (P) first. This study aims to understand the awareness, self-confidence, and suggestions of FP and P about the evaluation and management of NE in children.

Materials and Methods

Three hundred and sixty FP and family medicine residents (FMR) and 280 P and pediatrics residents (PR) were reached through a cellular phone texting system using a simple multiple-choice questionnaire (Surveymonkey®) consisting of 10 questions. Marking multiple answers was allowed for six of the 10 questions. However, 119 physicians filled out the questionnaire and were included in the study. Others were excluded from the study. The survey contained questions on the experience and training of the physicians, the frequency of seeing these patients, knowledge about the etiology, evaluation, and management of NE, and self-confidence to manage them. All questions in the survey are listed below.

1. What is your area of expertize (Only single response)

2. How many years have you been a physician? (Only single response)

3. How often do you encounter children with NE? (Only single response)

4. How confident are you in the management of NE? (Only single response)

5. Where did you get information about NE? (Multiple response available)

6. Which of the following sources did you use to learn about NE? (Multiple response available)

7. Which one(s) do you think is involved in the etiology of NE? (Multiple response available)

8. Which of the following do you use in the first evaluation? (Multiple response available)

9. What is your approach in the first-line treatment of children with NE who have never been managed before? (Multiple response available)

10. What is your approach in children who are resistant to first-line treatment? (Multiple response available).

Ethical approval was obtained from the local ethics committee (ethical number: 09.2023.01, date: 02.02.2023 - Marmara University Faculty of Medicine Clinical Research Ethics Committee).

Statistical Analyses

Data were analyzed using the IBM Statistical Package for the Social Sciences version 23 (IBM SPSS Statistics for Windows, Chicago, IL, USA). The normality of the distribution of the variables was evaluated using the Shapiro-Wilk test. As the distribution of continuous variables did not provide a normal distribution, continuous data were presented with a median, minimum and maximum. Independent groups were compared with Mann-Whitney U and Kruskal-Wallis tests. The Pearson chi-square and Fisher's exact test were used for binary categorical-dependent data. A p value <0.05 was set as statistically significant.

Results

A total of 119 participants (18.5%) filled out the questionnaire. Thirty (25.21%) of the participants were P, 27 (22.69%) PR, 3 (2.52%) FP and 59 (49.58%) FMR. While 74.79% (n=89) of participants had less than 5 years of experience, only 11.76% had more than 10 years (n=14). Most of the responders (n=55, 46.22%) rarely encounter children with NE (0-2 patients/month). The rate of physicians who encounter at least 5 children with NE per month is 31.33%. The mean self-confidence in the management of NE was 4.87 out of 10. The self-confidence score of pediatricians was significantly higher than PR and FMR ($p<0.001$, $p<0.001$) (6.86 ± 1.56, 4.96 ± 1.97, 3.86 ± 1.89, respectively). It was found to be higher in specialists than in residents ($p=0.0001$). When the self-confidence score was

compared according to experience and monthly case frequency, it was found to be statistically significant between the groups (p=0.001, p=0.001) (Table 1). Most (n=78, 65.55%) of the participants stated that they received training on EN during medical faculty and 62 (52.10%) during residency. Seventeen (14.29%) of them responded that they received information from postgraduate training. While 76 (63.87%) of the participants indicated faculty members as educational resources related to EN, 56 (47.06%) experts and senior assistants, 66 (55.46%) written training materials, 35 (29.41%) seminars and meetings, 26 (21.85%) personal clinical experience, and 14 (11.76%) internets. Psychological problems (89.92%), sleep disorders (78.15%), and excessive fluid intake (75.63%) were the most frequently considered factors in etiology (Table 2). In the subgroup analysis, preferences were similar in terms of disciplines and seniority, except for higher nocturnal urine production (p=0.017 for seniority) (Table 2). Urine analysis (86.44%), voiding diary (82.20%), and biochemical analysis (62.71%) were the main exams in the first evaluation (Table 3). In the subgroup analysis, preferences were similar in terms of disciplines and seniority, except for urinary system ultrasound (p=0.017 for seniority) (Table 3). While most of the responders (75.63%) considered dietary regulation and behavioral interventions as the first-line treatment, 25.21% consult a pediatric urologist and only 1.6% recommend medical treatment (Table 4). In the subgroup analysis, all preferences were similar in terms of disciplines

Table 1. Comparison of self-confidence scores in terms of disciplines, seniority, experience and case frequency

		n (%)	Self-confidence score (0-10) [Median (min-max)]	p-value
Discipline	Pediatrics	57 (47.9)	6.00 (1-10)	**0.001**
	Family medicine	62 (52.1)	4.00 (1-8)	
Seniority	Specialist	32 (26.9)	6.50 (3-10)	**0.0001**
	Resident	87 (73.1)	4.00 (1-10)	
Experience (year)	0-5	89 (74.8)	4.00 (1-10)	**0.001[#]**
	6-10	16 (13.4)	6.50 (4-10)	
	11-15	12 (10.1)	6.50 (5-10)	
	>16	2 (1.7)	7.50 (6-9)	
Case frequency (n/month)	0-2	55 (46.2)	4.00 (1-7)	**0.001[&]**
	3-4	26 (21.8)	5.00 (1-8)	
	5-6	23 (10.3)	6.00 (1-9)	
	7-10	11 (9.2)	7.00 (3-10)	
	>11	4 (3.4)	8.50 (4-10)	

([#]: 0-5 vs 6-10 = 0.001, 0-5 vs 11-15 = 0.0001; [&]: 0-2 vs 7-10 = 0.001, 0-2 vs >11 = 0.04), Min-max: Minimum-maximum

Table 2. Etiology of nocturnal enuresis according to participants and comparison of preferences in terms of disciplines, seniority (Multiple response available)

	n	%	Discipline		p-value	Seniority		p-value
			Pediatrics n (%)	Family medicine n (%)		Specialist n (%)	Resident n (%)	
Sleep disorders	93	78.15	43 (75.4)	50 (80.2)	0.492	28 (87.5)	65 (74.7)	0.134
Detrusor overactivity during sleep	72	60.50	33 (57.9)	39 (62.9)	0.577	17 (53.1)	55 (63.2)	0.318
Decreased bladder capacity	62	52.10	34 (59.6)	28 (45.2)	0.114	21 (65.6)	41 (47.1)	0.073
High nocturnal urine production	36	30.25	20 (35.1)	16 (25.8)	0.271	15 (46.9)	21 (24.1)	0.017
Excessive fluid intake	90	75.63	46 (80.7)	44 (71)	0.217	25 (78.1)	65 (74.7)	0.701
Obstructive sleep apnea	31	26.05	17 (29.8)	14 (22.6)	0.368	11 (34.4)	20 (23)	0.210
Psychological problems	107	89.92	51 (89.5)	56 (90.3)	0.878	28 (87.5)	79 (90.8)	0.596
Genetics	65	54.62	35 (61.4)	30 (48.4)	0.154	22 (68.8)	43 (49.4)	0.060

NA: Not available

and seniority (Table 4). Refractory cases of first-line behavioral treatment are vastly referred to pediatric nephrologists and urologists (Table 5). In the subgroup analysis, preferences were similar in terms of disciplines and seniority, except for I check compliance to treatment (p=0.048 for seniority) (Table 5).

Table 3. Diagnostic methods preferred by the participants in the first evaluation and comparison of preferences in terms of disciplines, seniority (Multiple response available)

	n	%	Discipline		p-value	Seniority		p-value
			Pediatrics n (%)	Family Medicine n (%)		Specialist n (%)	Resident n (%)	
I decide according to age	72	61.02	34 (59.6)	38 (61.3)	0.855	18 (56.3)	54 (62.1)	0.565
Child and family psychosocial development assessment	72	61.02	32 (56.1)	40 (64.5)	0.350	17 (53.1)	55 (63.2)	0.318
Urine analyses	102	86.44	51 (89.5)	51 (82.3)	0.261	30 (93.8)	72 (82.5)	0.129
Biochemical analysis	74	62.71	37 (64.9)	37 (59.7)	0.556	23 (71.9)	51 (58.6)	0.186
Urinary system ultrasound	51	43.22	26 (45.6)	25 (40.3)	0.560	22 (68.8)	29 (33.3)	**0.001**
Voiding diary	97	82.20	47 (82.5)	50 (80.6)	0.799	27 (84.4)	70 (80.5)	0.626
Uroflowmetry and measurement of residual urine	7	5.93	2 (3.5)	5 (8.1)	NA	2 (6.3)	5 (5.7)	NA
Invasive urodynamics	6	5.08	2 (3.5)	4 (6.5)	NA	2 (6.3)	4 (4.6)	NA
I do not make any examinations and refer to the expert	6	5.08	3 (5.3)	3 (4.8)	NA	0	6 (6.9)	NA

NA: Not available

Table 4. Approaches of the participants in first-line treatment and comparison of preferences in terms of disciplines, seniority (Multiple response available)

	n	%	Discipline		p-value	Seniority		p-value
			Pediatrics n (%)	Family Medicine n (%)		Specialist n (%)	Resident n (%)	
I decide according to the age of the child	82	68.91	40 (70.2)	42 (67.7)	0.774	20 (62.5)	62 (71.3)	0.360
I decide according to duration, frequency and severity of EN	69	57.98	31 (54.4)	38 (61.3)	0.446	15 (46.9)	54 (62.1)	0.137
Depends on the presence of daytime symptoms	80	67.23	40 (70.2)	40 (64.5)	0.511	22 (68.8)	58 (66.7)	0.830
I start with psychosocial support, diet, fluid restriction, and behavioral advice	90	75.63	45 (78.9)	45 (72.6)	0.419	25 (78.1)	65 (74.7)	0.701
I start with alarm therapy	18	15.13	10 (17.5)	8 (12.9)	0.480	8 (25)	10 (11.5)	0.068
I start with an anticholinergic agent	0	0	0	0	NA	0	0	NA
I start with desmopressin	2	1.68	2 (3.5)	0	0.227	1 (3.1)	1 (1.1)	NA
I start with imipramine	1	0.84	1 (1.8)	0	NA	0	1 (1.1)	NA
I do not treat and refer patients to the specialist	30	25.21	10 (17.5)	20 (32.3)	0.479	6 (18.8)	24 (27.6)	0.325

NA: Not available

Table 5. Approaches of the participants in cases resistant to first-line treatment and comparison of preferences in terms of disciplines, seniority (Multiple response available)

	n	%	Discipline		p-value	Seniority		p-value
			Pediatrics n (%)	Family Medicine n (%)		Specialist n (%)	Resident n (%)	
I check compliance to treatment	66	55.46	28 (49.1)	38 (61.3)	0.182	13 (40.6)	53 (60.9)	**0.048**
I check again daytime symptoms	54	45.38	21 (36.8)	33 (53.2)	0.073	13 (40.6)	41 (47.1)	0.528
If it is resistant to conservative and alarm treatment, I apply medical treatment	53	44.54	27 (47.4)	26 (41.9)	0.551	17 (53.1)	36 (41.4)	0.253
If I gave pharmacological treatment, I would change the dose	11	9.24	7 (12.3)	4 (6.5)	0.273	3 (9.4)	8 (9.2)	0.673
If I gave pharmacological treatment, I switch to another agent	7	5.88	2 (2.5)	5 (8.1)	NA	1 (3.1)	6 (6.9)	NA
If I gave pharmacological treatment, I add a second pharmacological agent	3	2.52	1 (1.8)	2 (3.2)	NA	0	3 (3.4)	NA
The drug I would just start or add would be anticholinergic	6	5.04	3 (5.3)	3 (4.8)	NA	1 (3.1)	5 (5.7)	NA
The drug I would just start or add would be desmopressin	5	4.20	3 (5.3)	2 (3.2)	NA	3 (9.4)	2 (2.3)	NA
The drug I would just start or add would be imipramine	1	0.84	1 (1.8)	0	NA	0	1 (1.1)	NA
The treatment I would just start or add would be enuretic alarm	7	5.88	3 (5.3)	4 (6.5)	NA	3 (9.4)	4 (4.6)	NA
I do not treat and refer to the relevant expert	80	67.23	38 (66.7)	42 (67.7)	0.910	18 (56.3)	62 (71.3)	0.122

NA: Not available

Discussion

In this study, we evaluated the NE management of P and FP using a questionnaire. To the best of our knowledge, this is the first study to assess the awareness and approach of primary care physicians toward NE in our country. Surprisingly, we found that this group, who regularly evaluates a large number of sick children in their daily practice, encountered fewer cases of NE than anticipated. About 68.07% of the participants reported encountering four or fewer children with NE per month. Another interesting point was that the vast majority of the participants received their NE-related training during their undergraduate education and residency, whereas only 14.29% of them benefited from postgraduate training. When asked about the etiology of NE, a significant number of participants (89.92%) attributed it to psychological and family psychosocial factors, which are causes of secondary NE. Notably, only 30.25% of participants identified nocturnal polyuria, one of the primary causes of NE. Moreover, in subgroup analysis, preferences for etiology and management of NE were similar between disciplines and seniority.

Although there are some studies in the literature evaluating the experiences of children suffering from NE and their parents (12,13), there are only a few studies examining the approach of physicians. One of them is a multicenter international survey study published in 2018, a total of 261 physicians' views on the etiology, diagnosis, and treatment of NE were evaluated (4). The percentage of participants with 10 or more years of experience was 70%. While the rate of participants with 10 or more years of experience was 70%, in this study, 88.24% were within the first 10 years. It was reported that 67% of the participants believed that monosymptomatic NE was due to ADH release variation, 64% to familial predisposition, and 48% to psychological reasons. In the same study, it was reported that bedwetting was the main complaint of only 32% of the patients and that the

majority of others were revealed by the physician's questioning during the appointment for another reason. In the treatment, restriction of fluid intake was preferred by 82%, pharmacologic intervention by 71%, urologic consultation by 59%, and family support by 54%. In the present study, psychological causes were prominent at 89.92%, sleep disorders at 78.15%, excessive fluid consumption at 75.63%, and detrusor overactivity at 60.50% in terms of etiology. Unlike this study, in our survey, participants were asked about their approach to NE, not monosymptomatic NE. Therefore, the difference in responses may have resulted from this situation. However, it is seen that psychological problems come to mind intensively in both studies. In the present survey, while supportive treatment such as psychosocial support, fluid restriction, and diet recommendation was considered as the primary treatment approach in 75% of cases, enuretic alarm was preferred only in 15.13% and desmopressin in 1.68%. Similar to the answers of our participants, supportive treatment for NE is recommended as first-line therapy in the The European Association of Urology pediatric urology guideline (Level of Evidence: 1, Strength Rating: strong) (14).

The other is a historical survey study published in 1996 and conducted with 61 primary care physicians (15). It was reported that 38% of the children treated by the participants in the last year showed complete remission, 41% showed partial remission, and 21% were resistant to treatment. 95% of the participants considered slow maturation of bladder control to be the cause of NE and 86% considered unusually deep sleep. According to the participants, 98% of the families had tried fluid restriction and 95% of the awakening method. It has been reported that behavioral treatments are used more commonly than pharmacological treatments and that 91% of the participants recommend the rewarding method to their families. Other methods used by the participants are postponing the problem to a later period and waiting for its development (80%), fluid restriction (80%), awakening (68%), and medication (52%). On the other hand, 36% of the physicians who recommended pharmacotherapy-prescribed imipramine. In this study, only one participant (0.84%) responded that imipramine could be recommended as a first-line treatment. Similarly, psychological disorders came to the fore in this study. It also gives an idea about the drug selection of that period.

Psychological stress or trauma and mood changes are known to cause NE or increase its symptoms (16,17). NE has also been reported to be associated with anxiety, depression and inferiority (18). Behavioral problems, which are seen in 10-15% of the general population, have been shown to be approximately twice as common in children with NE (10). Moreover, bedwetting causes additional psychological stress for children and reduces their quality of life (19). Also, it has been reported that mothers of children with NE have worse depression and anxiety scores than mothers of healthy children, and they seem more punishing (20,21). Therefore, a psychosocial assessment may be required in the management of NE. However, although psychological and behavioral disorders are important causes of NE, LUT functions should be evaluated in detail. Before treatment, it should be determined whether it is monosymptomatic or nonsymptomatic. Thus, detailed anamnesis, physical examination, and voiding diary should be performed, and if necessary, urine analysis, ultrasound, and uroflowmetry should be included (14).

Another important aspect of the study is assessing physicians' knowledge about NE and their self-confidence in managing it. Given that most of the participants have less than 10 years of experience, we believe that the results will provide insight into the current situation. The physicians NE-related self-confidence score average was only 4.87 out of 10, and the rate of physicians with a score of 8 and above was 10.92%. While 47.90% of the participants stated that they did not receive training on this subject during their residency, only 14.29% emphasized that they benefited from postgraduate training. While 63.87% of them received training on NE from faculty members, only 55.56% of them used printed training materials. It was stated that 25.21% of the participants referred the primary patient to the relevant specialist, while 67.23% referred the patient who was resistant to first-line treatment. These results suggest that physicians should be informed more about NE, which has a 15% incidence and can negatively affect the quality of life of both children and parents during their training and residency.

Study Limitations

The study has some limitations. Two different disciplines were chosen as the survey group, so it is important to consider that there may be different approaches. Unfortunately, we received feedback from only 119 of the 640 physicians which accounts for 18.59% of the response rate. While 52.1% of the participants were family practitioners, only 2.52% were FP specialists, with the remaining 49.58% being residents. Although residents were not authorized to prescribe medication, we included them in this study because we believe they play an important role in the initial evaluation of children suffering from bedwetting. It is worth noting that the question technique used in this survey allowed for multiple selection and interpretation, which may have influenced the participants' responses. Therefore, conducting face-to-face studies with a larger number of participants could provide more comprehensive information regarding the approach to NE.

Conclusion

While the majority of participants reported receiving information about NE at different stages of their education from various sources, they expressed a sense of inadequacy in assessing and

managing NE, often opting to avoid pharmacological treatment. We believe that postgraduate education programs aimed at enhancing physicians' self-confidence in dealing with NE would be beneficial.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the local ethics committee (ethical number: 09.2023.01, date: 02.02.2023 - Marmara University Faculty of Medicine Clinical Research Ethics Committee).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.A.Ş., Concept: Ç.A.Ş., Design: Ç.A.Ş., Data Collection or Processing: Ç.A.Ş., M.U.K., D.D., R.E., Y.T., Analysis or Interpretation: Ç.A.Ş., Y.T., Literature Search: Ç.A.Ş., Writing: Ç.A.Ş., H.K.Ç., T.T., S.Y.

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References

1. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, Rittig S, Walle JV, von Gontard A, Wright A, Yang SS, Nevéus T. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. J Urol 2014;191:1863-5.e13.
2. Graham KM, Levy JB. Enuresis. Pediatr Rev 2009;30:165-72; quiz 73.
3. Nevéus T. Pathogenesis of enuresis: Towards a new understanding. Int J Urol 2017;24:174-182.
4. Maternik M. Understanding of and misconceptions around monosymptomatic nocturnal enuresis: findings from patient and physician surveys. J Pediatr Urol 2019;15:37.e1-.e8.
5. Hägglöf B, Andrén O, Bergström E, Marklund L, Wendelius M. Self-esteem before and after treatment in children with nocturnal enuresis and urinary incontinence. Scand J Urol Nephrol Suppl 1997;183:79-82.
6. Van Herzeele C, Dhondt K, Roels SP, Raes A, Hoebeke P, Groen LA, Vande Walle J. Desmopressin (melt) therapy in children with monosymptomatic nocturnal enuresis and nocturnal polyuria results in improved neuropsychological functioning and sleep. Pediatr Nephrol 2016;31:1477-1484.
7. Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 2002:Cd002112.
8. Alqannad EM, Alharbi AS, Almansour RA, Alghamdi MS. Alarm Therapy in the Treatment of Enuresis in Children: Types and Efficacy Review. Cureus 2021;13:e17358.
9. Kosilov KV, Geltser BI, Loparev SA, Kuzina IG, Shakirova OV, Zhuravskaya NS, Lobodenko A. The optimal duration of alarm therapy use in children with primary monosymptomatic nocturnal enuresis. J Pediatr Urol 2018;14:447.e1-.e6.
10. von Gontard A, Baeyens D, Van Hoecke E, Warzak WJ, Bachmann C. Psychological and psychiatric issues in urinary and fecal incontinence. J Urol 2011;185:1432-1436.
11. Glazener CM, Evans JH. Tricyclic and related drugs for nocturnal enuresis in children. Cochrane Database Syst Rev 2000:Cd002117.
12. Baek M, Park K, Lee HE, Kang JH, Suh HJ, Kim JH, Lee SD, Pai KS, Han SW, Park YH, Kim KD; Korean Children's Continence and Enuresis Society. A nationwide epidemiological study of nocturnal enuresis in Korean adolescents and adults: population based cross sectional study. J Korean Med Sci 2013;28:1065-1070.
13. Huang WJ, Liang YY, Yang Q, Ma X. Nocturnal enuresis in children: Parents' perspectives. Nurs Open 2022;9:2335-2341.
14. Radmayr C, Bogaert B, Burgu B, Dogan H, Nijman J, Quaedackers J, et al. EAU Guideline on Paediatric Urology, 2022.
15. Vogel W, Young M, Primack W. A survey of physician use of treatment methods for functional enuresis. Journal of Developmental & Behavioral Pediatrics 1996;17:90-93.
16. Akan S, Ürkmez A, Yildirim C, Sahin A, Yüksel Ö H, Verit A. Late-onset secondary nocturnal enuresis in adolescents associated with post-traumatic stress disorder developed after a traffic accident. Arch Ital Urol Androl 2015;87:250-251.
17. Haid B, Tekgül S. Primary and Secondary Enuresis: Pathophysiology, Diagnosis, and Treatment. Eur Urol Focus 2017;3:198-206.
18. Eray Ş, Tekcan D, Baran Y. More anxious or more shy? Examining the social anxiety levels of adolescents with primary enuresis nocturna: a controlled study. J Pediatr Urol 2019;15:343.e1-.e5.
19. Bachmann C, Lehr D, Janhsen E, Sambach H, Muehlan H, von Gontard A, Bachmann H. Health related quality of life of a tertiary referral center population with urinary incontinence using the DCGM-10 questionnaire. J Urol 2009;182:2000-2006.
20. Egemen A, Akil I, Canda E, Ozyurt BC, Eser E. An evaluation of quality of life of mothers of children with enuresis nocturna. Pediatr Nephrol 2008;23:93-98.
21. De Bruyne E, Van Hoecke E, Van Gompel K, Verbeken S, Baeyens D, Hoebeke P, Vande Walle J. Problem behavior, parental stress and enuresis. J Urol 2009;182:2015-2020.

ORIGINAL RESEARCH
General Urology

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Does Previous Open Nephrolithotomy or Failed Extracorporeal Shock Wave Lithotripsy Therapy Affect Percutaneous Nephrolithotomy Performance and Outcome?

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What's known on the subject? and What does the study add?

There are publications reporting that percutaneous nephrolithotomy is safe and effective after failed extracorporeal shock wave lithotripsy (ESWL) and a history of open surgery patients. Fluoroscopy time and hemoglobin drop are important parameters for percutaneous nephrolithotomy surgery. Most of the studies in the literature mentioned that the failed ESWL prolonged the fluoroscopy time, and open surgery history was linked to a significant drop in hemoglobin levels in patients that underwent percutaneous nephrolithotomy. In our study, it was found that percutaneous nephrolithotomy could be performed safely without prolonging the fluoroscopy time in the failed ESWL patients and without significant hemoglobin drops in the history of open nephrolithotomy patients.

Abstract

Objective: This study aimed to summarize our experience with patients undergoing percutaneous nephrolithotomy (PNL) with a previous history of extracorporeal shock wave lithotripsy (ESWL) treatment or open nephrolithotomy and compare them with patients who underwent PNL alone.

Materials and Methods: A total of 565 patients were treated with PNL from 2012 to 2022 at our center. These patients who underwent PNL were divided into three groups: Group 1 consisted of patients who had no medical history of previous ESWL or open kidney stone surgery, Group 2 consisted of those who had a history of previous ESWL, and Group 3 included patients with a history of previous open kidney stone surgery.

Results: Regarding age, there were no notable differences between the three groups, body mass index, gender, laterality, and stone density in Hounsfield Units. Group 3 had a significantly higher total operation fluoroscopy time than the other two groups, and Group 2 had a significantly lower total operation time than the other two groups. Regarding the postoperative parameters of all three groups, including hospital stay, time to nephrostomy removal, urinary leakage, hemoglobin decrease, blood transfusion, and stone-free rates, no statistically significant differences were found.

Conclusion: Our study demonstrates that PNL can be safely performed with a similar success rate and without a higher risk of problems in patients who have undergone open nephrolithomy or ESWL, as well as in primary PNL patients who have not undergone any previous interventions.

Keywords: Kidney stones, open stone surgery, extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy

Introduction

Kidney stones are a significant cause of morbidity worldwide and are a common urological illness that affects approximately 10-15% of the global population (1). Currently, the available management alternatives for the treatment of kidney stones include ureterorenoscopy (URS), percutaneous nephrolithotomy (PNL), extracorporeal shockwave lithotripsy (ESWL), open surgery, and laparoscopy. Nevertheless, depending on new technological and surgical advancements, open surgery has been replaced by less invasive procedures such as PNL (2,3). However, open kidney surgery has been performed in centers

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where there is a lack of experience or inadequate equipment for minimally invasive procedures (4).

In the guidelines provided by the European Association of Urology (EAU), ESWL is suggested as the first-line treatment method for stones smaller than 20 mm, whereas PNL is typically performed for stones larger than 20 mm (5). On the other hand, according to the EAU guidelines, if ESWL fails after 3 to 5 sessions of treatment, PNL is recommended as the next step (5). PNL is also performed for stones fragmented by ESWL but not suitable for spontaneous passage (6).

Nephrolithiasis is a recurrent and lifelong disease, and approximately half of the patients with nephrolithiasis will have a second renal colic attack within 10 years (7,8). A recent retrospective cohort study in Olmstead County, involving over 2.200 individuals who developed kidney stones for the first time, reported that the recurrence rates at 2, 5, 10, and 15 years were 11%, 20%, 31%, and 39%, respectively (9). Today, PNL is required in patients who have previously undergone ESWL or open nephrolithotomy. In patients who have previously undergone open stone surgery, there is often the presence of retroperitoneal scar tissue around the kidney, disruption of the pelvicalyceal anatomy, and in some cases, displacement of the intestines. Generally, when operating in a previously surgically treated anatomical region, the surgeon can expect technical challenges that may be associated with a longer surgical duration, higher complication rate, and potentially lower success rate (4).

Similarly, repeated ESWL can contribute to long-term fibrotic degeneration and impairment of the collecting system (6,10).

The objective of this study was to summarize our experiences with patients who underwent PNL after previous ESWL treatments (failure in stone fragmentation or stone clearance, and recurrences) and open nephrolithotomy and to compare them with patients who underwent PNL alone.

Materials and Methods

The study comprised 403 patients who received PNL at our clinic between 2012 and 2022. Three groups were created from the individuals who underwent PNL. Patients in Group 1 had never undergone ESWL or open kidney stone surgery, whereas those in Group 2 had undergone prior open kidney stone surgery and those in Group 3 had undergone prior ESWL. Patients under the age of 18, anatomical anomalies such as a duplicated collecting system or an obstruction at the ureteropelvic junction, skeletal deformities, impaired kidney function, a history of bleeding disorders, the presence of a solitary kidney, and patients who do not attend routine follow-up appointments are all excluded.

All patients underwent a routine preoperative evaluation, including a detailed history and physical examination, and laboratory tests such as blood biochemistry, urinalysis and culture. Non-contrast and contrast-enhanced abdominal tomography were performed. The stone burden of the patients was calculated using the Ackerman formula (volume = 0.6 x π x r2), where r represents half of the largest diameter of the stone. Demographic characteristics, such as stone burden and position, severity of hydronephrosis, number of tracts, past treatments for renal calculi, average length of the operation, average X-ray exposure, stone-free rates, hemoglobin levels, blood transfusion rates, and intraoperative and postoperative complications were compared among the groups. All patients underwent a follow-up evaluation with non-contrast computed tomography at one month after surgery. The indicators of operation success were the absence of stone or the presence of stone particles less than 4 mm. The Clavien-Dindo classification system, which has five grades, was used to classify complications (11). Grade 1 and 2 problems do not require surgical or radiological procedures; however, Grade 3 complications must. Total parenteral feeding and blood transfusion were categorized as Grade 2 problems.

We defined fluoroscopy time (FT) as the whole operation FT from the insertion of the needle to the implantation of the nephrostomy catheter because the term is used differently in the literature.

Surgical Technique

An open-ended 5 F ureteral catheter (MarflowTM, Marflow AG, Switzerland) was placed in the ureter and guided by cystoscopy with the patient in the lithotomy position under general anesthesia. After placement, the patient was moved to the prone position. All patients were operated on in the prone position. The anatomy of the pelvicalyceal system was visualized with radio-opaque material instilled using the ureteral catheter under C-arm fluoroscopy. A 19.5-gauge percutaneous needle (Percutaneous Access Needle, Boston Scientific Corporation, MA, USA) was introduced into the appropriate calyx system of the kidney. Fluoroscopy was used to place a guidewire (ZebraTM Niti- nol Guidewire, Boston Scientific Corporation, MA, USA) in the collecting system The tract was dilated up to 30 F using semirigid Amplatz dilators (Boston Scientific Microvasive Amplatz Tract- master TM, Boston Scientific Corporation, MA, USA), and an Amplatz sheath was inserted into the collecting system. Stone fragmentation was performed using a pneumatic lithotripter (CalculithTM Lithotripter, PCK, Turkiye) through a 28 F rigid nephroscope (Karl StorzTM Endoscopy-America Inc.) in all groups. Stone fragments were collected using forceps, and the operations were ended after the placement of a 14 F nephrostomy catheter.

Statement of Ethics

Ethical approval was obtained from the University of Health Science Turkiye, Kocaeli Derince Training and Research Hospital Ethics Committee (ethical number: 2022-110, date: 13.10.2022).

Written informed consent was obtained from all patients. All procedures related to humans abide by all applicable national laws, institutional guidelines, and tenets of the Declaration of Helsinki.

Statistical Analysis

SPSS for Windows was used for statistical analysis. v. 20.0 (SPSS Inc., Chicago, IL) of the Statistical Package for the Social Sciences. The Kruskal-Wallis test was used in the statistical analysis to assess differences, and the Mann-Whitney U test was used in paired comparisons (for independent non-parametric data). To compare categorical values between the groups, the chi-square test, performed. P 0.05 was chosen as the cutoff value for statistical significance.

Results

The data of 403 patients who were eligible for inclusion were analyzed in this study. Three groups of patients were created. Group 1 comprised primary PNL patients without a history of previous ESWL and open nephrolithotomy. Group 2 included patients with a history of previous ESWL who underwent PNL. Group 3 comprised patients with a history of previous open nephrolithomy who also underwent PNL. Group 1 had 275 patients (68.20%), Group 2 had 104 patients (25.81%), and Group 3 consisted of 24 patients (5.96%) (Figure 1).

Of the 403 patients divided into three groups, 305 (75.68%) were male and 98 (24.32%) were female, with a mean age of 47.29±13.44. There were no notable variations among the three groups in terms of age, body mass index, gender, laterality, and stone density in Hounsfield Units (p>0.05). However, when analyzing stone location, "pelvis and calyx" stone sizes were found to be much larger compared with group 2 (p=0.028). In terms of stone burden, Group 2 had a significantly lower stone burden than the other two groups (p=0.001). The preoperative data of the research groups and their statistical analyzes are presented in Table 1.

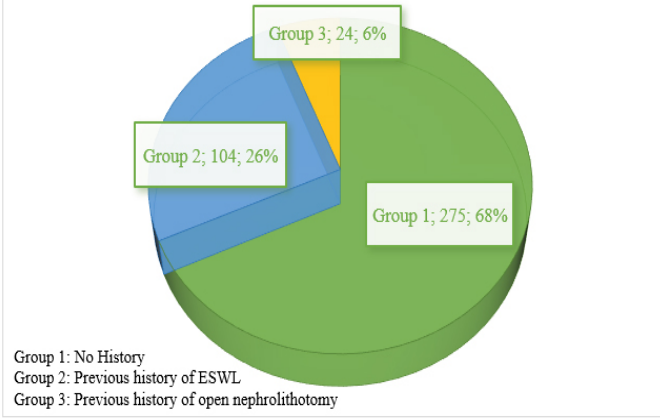

Figure 1. Number of patients in study groups

ESWL: Extracorporeal shock wave lithotripsy

Table 1. Demographic data and study group stone parameters

	Group 1	Group 2	Group 3	
	No History	Previous history of ESWL	Previous history of open nephrolithotomy	p
	(n=275)	(n=104)	(n=24)	
Age, mean ± SD (M)	46.93±13.78 (47)	47.85±12.85 (48)	48.92±12.15 (50.50)	0.638[1]
Gender (n)				0.850[3]
Male	209 (76.00%)	77 (74.04%)	19 (79.17%)	
Female	66 (24.00%)	27 (25.96%)	5 (20.83%)	
BMI (kg/m^2), mean ± SD, (M)	24.77±2.76 (25)	24.21±2.73 (24)	24.88±3.13 (24)	0.459[1]
Laterality (n)				0.329[3]
Right	140 (50.91%)	45 (43.27%)	10 (41.67%)	
Left	135 (49.09%)	59 (56.73%)	14 (58.33%)	
Stone location (n)				0.023[3]*
One calix	34 (12.36%)	22 (21.15%)	6 (25%)	
Pelvic	88 (32%)	38 (36.54%)	3 (12.5%)	
Multiple calyces	12 (4.36%)	8 (7.69%)	-	
Pelvic and calix	110 (40%)	30 (28.85%)	12 (50%)	
Staghorn	31 (11.27%)	6 (5.77%)	3 (12.5%)	
Stone burden mm^2, mean ± SD (M)	602.43±539.37 (423)	445.95±386.85 (287.5)	754.83±651.04 (570.5)	0.001[1]*
Statistical analysis	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3	
p	0.002[2]*	0.051[2]	0.001[2]*	
Stone density in Hounsfield Units, mean ± SD, (M)	1240.65±386.39 (1218)	1251.86±343.44 (1278)	1221.71±412.74 (1160)	0.556[1]

ESWL: Extracorporeal shock wave lithotripsy, BMI: Body mass index, SD: Standard deviation, M: Median, [1]Kruskal-Wallis H test, [2]Mann-Whitney U test [3]Chi-square test, *: Statistically significant (p<0.05)

A statistically significant difference was observed among the study groups according to total operation FT (p=0.003). Group 3 had a significantly higher total operation FT than the other two groups (p=0.031; p=0.003; Table 2). However, no change that was statistically significant was found in the total operation FT between Group 1 and Group 2 (p=0.064).

Regarding the total operation time, there was a statistically significant difference among the study groups (p=0.020). Group 2 had a significantly lower total operation time than the other two groups (p=0.001; p=0.020; Table 2, Figure 2). However, no statistically significant difference was discovered in total operation time between Group 1 and Group 3 (p=0.338).

When examining grade 1 complications, postoperative fever was observed in 9 patients in Group 1, 4 patients in Group 2, and 1 patient in Group 3. Regarding grade 2 complications, urinary tract infection was observed in 7 patients in Group 1 and 2 patients in Group 2. All patients were treated with appropriate antibiotic therapy. Additionally, 21 patients in Group 1, 7 patients in Group 2, and 1 patient in Group 3 required blood transfusion.

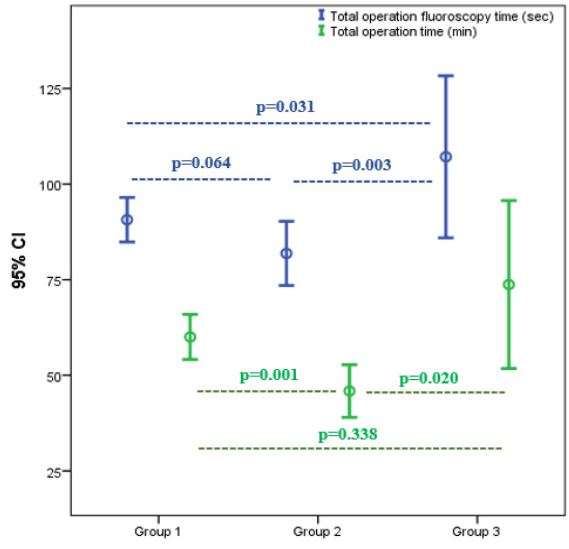

Figure 2. Fluoroscopy and operation times of the study groups

CI: Confidence interval

In terms of grade 3 complications, ureterorenoscopy was performed for 6 patients in Group 1, 3 patients in Group 2, and 1 patient in Group 3 because of stone migration into the ureter. Double-J stent insertion was performed in 4 patients in Group 1, 2 patients in Group 2, and 1 patient in Group 3 because of prolonged urinary leak after nephrostomy catheter removal. Selective angioembolization was performed for 2 patients in Group 1 due to uncontrolled bleeding. Colon perforation occurred in one patient each in Groups 1 and Group 2 and these patients were followed up with tube colostomy and discharged without any issues. One patient in Group 1 experienced continued bleeding and hematoma in the postoperative follow-up, leading to nephrectomy, whereas two patients developed pneumothorax and required chest tube insertion after discharge without complications. No Grade 4 or 5 complications were observed in any of the three groups (p=0.862) (Table 3).

Discussion

Our research is consistent with the current literature, showing that prior open surgery or ESWL for kidney stones does not significantly affect the subsequent outcomes of PNL in the same kidney. Studies in this area have compared the efficacy of PNL in primary patients with patients who have previously undergone open surgery. In a study which made by Tugcu et al. (12), PNL outcomes in 55 patients who had former open surgery compared with 105 patients who had no prior intervention and found no significant difference in success and complication rates, except for longer operation duration. The outcomes of PNL in 142

Table 2. Fluoroscopy and operation times of the study groups

	Group 1	Group 2	Group 3	
	No History	Previous history of ESWL	Previous history of open nephrolithotomy	p
	(n=275)	(n=104)	(n=24)	
Total operation fluoroscopy time[a] (sec), mean ± SD, (M)	90.69±40.79 (M: 81)	81.88±36.5 (M: 76)	107.14±47.82 (M: 98)	0.003[1]*
Statistical analysis	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3	
p	0.064[2]	0.031[2]*	0.003[2]*	
Total operation time[b] (min) mean ± SD, (M)	65.93±38.71 (55)	52.61±29.46 (45)	75.5±47.71 (67)	0.020[1]*
Statistical analysis	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3	
p	0.001[2]*	0.338[2]	0.020[2]*	

[a]total operation fluoroscopy time/[b]total operation time: (from the insertion of the needle to the nephrostomy catheter placement), ESWL: Extracorporeal shock wave lithotripsy, SD: Standard deviation, M: Median, [1]Kruskal-Wallis H test, [2]Mann-Whitney U test, *Statistically significant (p<0.05)

Table 3. Postoperative parameters of the study groups				
	Group 1	Group 2	Group 3	
	No History	Previous history of ESWL	Previous history of open nephrolithotomy	p
	(n=275)	(n=104)	(n=24)	
Time to nephrostomy catheter removal (day), mean ± SD, (M)	2.80±1.99 (3)	2.63±1.14 (3)	2.61±0.84 (3)	0.759[1]
Urinary leakage after nephrostomy removal (hour), mean ± SD (M)	6.12±9.40 (4)	5.35±7.57 (4)	8.75±14.96 (4)	0.529[1]
Hospital stay (day), mean ± SD (M)	3.77±1.50 (4)	3.49±1.39 (3)	4.17±2.43 (4)	0.216[1]
Haemoglobin drop in g/dL, mean ± SD (M)	1.50±1.19 (1)	1.44±1.08 (1)	1.58±1.35 (1)	0.946[1]
Blood transfusion, n (%)	21 (7.64%)	7 (6.73%)	1 (4.17%)	0.801[2]
Complications, n (%)				0.862[2]
Clavien grade 1	9 (3.27%)	4 (3.85%)	1 (4.17%)	
Clavien grade 2	28 (10.18%)	9 (8.65%)	1 (4.17%)	
Clavien grade 3	16 (5.82%)	6 (5.77%)	2 (8.33%)	
Stone free patients, n (%)	231 (84.00%)	88 (84.62%)	17 (70.83%)	0.233[2]

ESWL: Extracorporeal shock wave lithotripsy, SD: Standard deviation, M: Median, [1]Kruskal-Wallis H test, [2]Chi-square test

patients who had undergone open surgery in the past were compared with those in 186 patients who had not previously received treatment by Kurtulus et al. (13), who discovered no significant difference in the success of PNL. The results of patients who underwent PNL after open nephrolithomy were examined in a meta-analysis published in 2016 (4). PNL after open surgery was linked to a significant drop in hemoglobin levels, a greater need for angiographic embolization, and potentially longer operation times (4). In our research, statistically no significant drop was seen in hemoglobin levels in the group that underwent PNL after open nephrolithotomy. Except two patients in the primary PNL group, none of the patients required angiographic embolization due to the uncontrolled bleeding. Furthermore in PNL after open nephrolithotomy group, the operation durations were significantly longer than those in the primary PNL patients.

To the best of our knowledge, there are few studies in the literature that investigate PNL performed after open surgery or ESWL with similar study designs. According to Resorlu et al. (10) there were no appreciable differences in terms of these parameters between patients with a history of prior open surgery or failed ESWL when it came to operation duration (minutes), time needed to access the renal collecting system, FT, adverse PNL outcomes, and length of hospital stay. Yuruk et al. (6) evaluated the effectiveness of PNL after ESWL and found no significant differences except for prolonged FT in PNL following ESWL. Contrary to their findings, our study did not uncover a statistically significant difference between Groups 1 and 2 when compared with one another, although Group 2 had the shortest overall operation time. Türk et al. (3) found that PNL after ESWL treatment increased the amount of bleeding and the need for blood transfusion. However, in our study, no significant differences were found in terms of both hemoglobin decrease and transfusion rates.

One remarkable result of our study is that it is influenced by the stone 's size. Despite guidelines on the management of kidney stones, the widespread use of ESWL in non-academic centers does not always align with these guidelines. The approximately 4 cm stone size observed in the group with a history of failed ESWL is the best example of this.

Study Limitations

This study has a few limitations, such as being an individual center study and being retrospective.

Conclusion

Our study demonstrates that PNL can be safely performed with a similar success rate to PNL without a higher risk of complications in patients with a history of open nephrolithotomy or ESWL, as well as in patients who have not undergone any previous interventions. We believe that in such cases, instead of repeated ESWL applications, PNL should be performed or patients should be referred to centers where PNL is performed.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Science Turkiye, Kocaeli Derince Training and Research Hospital Ethics Committee (ethical number: 2022-110, date: 13.10.2022).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Desai M, Sun Y, Buchholz N, Fuller A, Matsuda T, Matlaga B, Miller N, Bolton D, Alomar M, Ganpule A. Treatment selection for urolithiasis: percutaneous nephrolithomy, ureteroscopy, shock wave lithotripsy, and active monitoring. World J Urol 2017; 35:1395-1399.
2. Ang AJS, Sharma AA, Sharma A. Nephrolithiasis: Approach to Diagnosis and Management. Indian J Pediatr 2020;87:716-725.
3. Türk H, Yoldaş M, Süelözgen T, İşoğlu CS, Karabıçak M, Ergani B, Ün S. Effects of previous unsuccessful extracorporeal shockwave lithotripsy treatment on the performance and outcome of percutaneous nephrolithotomy. Arab J Urol 2017;15:94-99.
4. Hu H, Lu Y, Cui L, Zhang J, Zhao Z, Qin B, Wang Y, Wang Q, Wang S. Impact of previous open renal surgery on the outcomes of subsequent percutaneous nephrolithotomy: a meta-analysis. BMJ Open 2016;6:e010627.
5. Tiselius HG, Ackermann D, Alken P, Buck C, Conort P, Gallucci M, Working Party on Lithiasis, European Association of Urology. Guidelines on Urolithiasis. Arnheim, The Netherlands: European As- sociation of Urology 2007.
6. Yuruk E, Tefekli A, Sari E, Karadag MA, Tepeler A, Binbay M, Muslumanoglu AY. Does previous extracorporeal shock wave lithotripsy affect the performance and outcome of percutaneous nephrolithotomy? J Urol 2009;181:663-667.
7. Zisman AL. Effectiveness of Treatment Modalities on Kidney Stone Recurrence. Clin J Am Soc Nephrol 2017;12:1699-1708.
8. Wang K, Ge J, Han W, Wang D, Zhao Y, Shen Y, Chen J, Chen D, Wu J, Shen N, Zhu S, Xue B, Xu X. Risk factors for kidney stone disease recurrence: a comprehensive meta-analysis. BMC Urol 2022;22:62.
9. Rule AD, Lieske JC, Li X, Melton 3rd LJ, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. J Am Soc Nephrol 2014;25:2878-2886.
10. Resorlu B, Kara C, Senocak C, Cicekbilek I, Unsal A. Effect of previous open renal surgery and failed extracorporeal shockwave lithotripsy on the performance and outcomes of percutaneous nephrolithotomy. J Endourol 2010;24:13-16.
11. Tefekli A, Ali Karadag M, Tepeler K, Sari E, Berberoglu Y, Baykal M, Sarilar O, Muslumanoglu AY. Classification of percutaneous nephrolithotomy complications using the modified Clavien grading system: Looking for a standard. Eur Urol 2008;53:184-190.
12. Tugcu V, Su FE, Kalfazade N, Sahin S, Ozbay B, Tasci AI. Percutaneous nephrolithotomy (PCNL) in patients with previous open stone surgery. Int Urol Nephrol 2008;40:881-884.
13. Kurtulus FO, Fazlioglu A, Tandogdu Z, Aydin M, Karaca S, Cek M. Percutaneous nephrolithotomy: Primary patients versus patients with history of open renal surgery. J Endourol 2008;22:2671-2675.

ORIGINAL RESEARCH
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Effect of Pfizer/BioNTech and Sinovac/CoronaVac Vaccines on Semen Parameters in Infertile Patients with Idiopathic Infertility: A Single-center Cohort Study

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What's known on the subject? and What does the study add?

Although it has been shown in many studies that COVID-19 vaccines have significantly reduced the risk of mortality and morbidity from the disease, vaccine hesitancy still exist among some individuals due to concerns about potential impacts on male fertility. Our study contributes to existing research by investigating the effects of COVID-19 vaccines on male fertility and semen paramaters, spesifically comparing the Sinovac/CoronaVAC and Pfizer/BioNTech vaccines and their impacts on semen parameters. The findings show that inactive and mRNA vaccines do not have a clinically meaningful affect on semen parameters in infertile men. Therefore, both vaccines can be considered safe for men's reproductive health.

Abstract

Objective: We investigated the effects of Coronavirus disease-2019 (COVID-19) vaccines on semen parameters in patients with idiopathic infertility who visited our urology clinic.

Materials and Methods: Patients who visited our andrology clinic between January 2021 and April 2022 after the vaccines were made available for the population aged 18 years and above were included in the study. Sperm parameters of patients before and after vaccination with two doses of Pfizer/BioNTech and Sinovac/CoronaVac were retrospectively evaluated and compared using the hospital's patient information system. Semen samples obtained from the patients were evaluated in our andrology laboratory. The age, body mass index (BMI), semen analyses, and intervals between the two doses of vaccines and the second semen analysis of the patients were recorded. Spermogram data before and after vaccination of 65 patients, including 17 Sinovac/CoronaVac and 48 Pfizer/BioNTech COVID-19 vaccinated patients, were divided into two groups and compared in terms of semen volume, semen pH, total sperm count, sperm motility, and morphology.

Results: There was no significant difference in terms of the vaccine interval, BMI, or age between the groups. Although no significant differences were found in terms of volume, pH, total motility, and percentage of motile sperm, the total sperm count and sperm count per milliliter decreased significantly in the Sinovac/CoronaVac group and increased significantly in the Pfizer/BioNTech group. Before and after vaccination, a decrease in total sperm count was observed in the Sinovac/CoronaVac group and a decrease in pH was observed in the Sinovac/CoronaVac and Pfizer/BioNTech groups.

Conclusion: Our findings show that the total sperm count and the sperm count per milliliter decreased significantly among idiopathic infertile patients who received Sinovac/CoronaVac but increased significantly among those who received Pfizer/BioNTech COVID-19 vaccines

Keywords: Andrology, COVID-19, infertility, Pfizer/BioNTech, Sinovac, spermogram

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Introduction

The novel Coronavirus disease-2019 (COVID-19) was declared the second pandemic of the 21st century by the World Health Organization (WHO) on March 11, 2020 (1) . It has been shown that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a new strain from the Coronaviridae family, causes COVID-19. Although the disease can be asymptomatic, it can also cause symptoms such as cough, fever, and chest discomfort. In severe cases, it can result in respiratory distress syndrome and death (2,3). Some studies have also reported negative effects of the disease on the male reproductive system (4-7).

To minimize the severity of the disease and its negative social and economic impacts during the COVID-19 pandemic, various types of vaccines have been produced, and vaccination programs have been initiated in some countries with emergency use approval. It has been shown that the inactivated vaccine Sinovac/CoronaVac, which is derived from a live virus, creates neutralizing antibodies against the SARS-CoV-2 virus in rats, mice and non-human primates, and phase 3 studies of Sinovac/CoronaVac have been conducted in Turkiye, Brazil and Indonesia. An interim analysis of studies in Turkiye reported the vaccine's efficacy as 91.25% (8). This inactivated vaccine began to be used in Turkiye and other countries in early January 2021 (9).

Considering the negative effects of live virus vaccines on fertility, similar results may also arise with inactivated vaccines, such as Sinovac/CoronaVac. Concerns about the potential negative effects of vaccines on human fertility and infant health are increasing, and this concern is becoming the most important reason for hesitancy toward vaccines (10). The SARS-CoV-2 mRNA vaccine (Pfizer/BioNTech), which contains BNT162b2, a modified RNA nucleoside in a lipid nanoparticle formulation, generates high levels of SARS-CoV-2 neutralizing antibody titers specific to the antigen with two doses of 30 microgram (g). The vaccine prevents infection at over 95% efficacy, with an average follow-up period of 2 months after the second dose (11). Despite emergency use approval in the United States of America (USA), 56% of individuals reported that they did not want to receive this vaccine, primarily because of concerns about possible negative effects on fertility (12,13). The Pfizer/BioNTech vaccine began to be used in Turkiye on April 2, 2021 (14).

There is limited scientific evidence in the literature regarding the effects of different types of vaccines on semen parameters and male fertility. In this study, we investigated the effects of these vaccines on semen parameters because of their active use in Turkiye.

Materials and Methods

We retrospectively investigated 118 sexually active male patients aged between 18 and 50 years whose partners had no problem and who attended Recep Tayyip Erdogan University Training and Research Hospital Andrology Laborotary between January 2021 and April 2022 and had received either Sinovac/CoronaVac vaccine (Group 1) or Pfizer/BioNTech vaccine (Group 2). Sixty-five patients were included in the study, and 53 patients who did not meet the inclusion criteria were excluded from the study (Figure 1). Ethical approval was obtained from the Recep Tayyip Erdogan University Non-Interventional Clinical Research Ethics Committee before the study (decision no: 2023/17 date: January 1, 2023). Anthropometric data of patients [age, body mass index (BMI)], the time of the second semen analysis after the second dose of vaccine, and semen analysis parameters (volume, pH, count, motility, and morphology) before and after two doses of vaccination were evaluated from the patient's files. Patients younger than 18 years old, older than 50 years old, using medication affecting spermatogenesis, diagnosed with endocrinological disease affecting spermatogenesis, presence of genetic disease, gender disorders, history of varicocele or cryptorchidism operations, having only one sample, and diagnosed with azoospermia according to the spermiogram analyzes were excluded from the study. After exclusion criteria, a total of 65 patients' data were recorded and analyzed Semen samples obtained by masturbation after 2-5 days of sexual abstinence were evaluated in the andrology laboratory by an experienced embryologist according to the guidelines of the WHO laboratory manual (6th edition) (Table 1) (15).

Patients who were azospermic (n=6), had not completed two doses of vaccine (n=6), or had a history of COVID-19 (n=41) were excluded from the study. The remaining 65 patients were divided into two groups: Group 1 (n=17) and Group 2 (n=48).

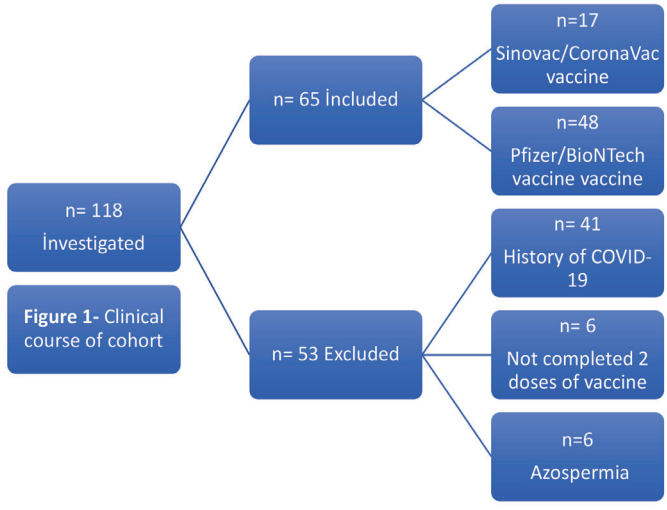

Figure 1- Clinical course of cohort

Figure 1. Clinical course of cohort

The pre-and post-vaccination BMI, semen volume, semen pH, sperm count per milliliter, total sperm count, sperm motility, and morphology values of patients in both groups were recorded and compared.

Statistical Analyses

Statistical analysis was performed using IBM SPSS Statistics (SPSS Inc., Chicago, IL, USA) software. After normality analysis of continuous numerical variables, the data showing the normal distribution were calculated as mean ± standard deviation and median (minimum-maximum). Differences between groups were evaluated using the independent samples t-test or Mann-Whitney U test, depending on the distribution of the data. Within-group and between-group pre- and post-vaccination comparisons in Sinovac/CoronaVac and Pfizer/BioNTech groups were performed using the Wilcoxon Signed-Rank test. For sperm morphology, 4 normal morphology was considered normal, and 4 was considered pathological. The McNemar test was used for comparisons made by dichotomizing the data. A $p<0.05$ was considered statistically significant.

Results

The mean ages of the patients in Groups 1 and 2 were calculated as 37±5 and 34±7 years, respectively. There was no significant difference between the groups in terms of BMI and duration. The mean time between vaccination and second semen analysis in Group 1 and Group 2 was 4±2.4 and 3.5±1.9 month (Table 2). No significant difference was found between Groups 1 and 2 in terms of volume, pH, total motility, the percentage of motile sperm changes, and morphology. We observed that the total sperm count (p=0.021) and sperm count per mL (p=0.014) significantly decreased in Group 1 and increased in Group 2 (Table 3).

Table 1. Normal value according to the World Health Organization

Semen volume (mL)	**≥1.4**
pH	7.2
Total sperm number (millions/ejaculate)	≥39
Sperm concentration (millions/mL)	≥16
Total motility (PR+NP, %)	≥42
Progressive motility (PR, %)	≥30
Sperm morphology (normal form, %)	≥4

PR: Progressive, NP: Non-progressive

Table 2. Comparison of the demographic characteristics of the groups

	Group 1 (n=17)	Group 2 (n=48)	p-value
	Mean ± SD; Median (min/max)	Mean ± SD; Median (min/max)	
Duration (month)	4 ±2.4	3.5±1.9	0.328
BMI*	25.9 (21.6-30.1)	27 (20.2-47.3)	0.135
Age (year)	37±5	34±7	0.073

*Body mass index, SD: Standard deviation, min: Minimum, max: Maximum

Table 3. Intergroupdifferences in sperm parameters

	Group 1 (n=17)	Group 2 (n=48)	p-value
	Mean ± SD; Median (min-max)	Mean ± SD; Median (min-max)	
*Volume (mL)	4 (1.8-6)	3.8 (1.1-8.1)	0.455
**Volume (mL)	4,1 (1.4-9.8)	3.4 (1-7)	
*pH	7.9 (6.9-8.5)	7.8 (6.7-8.5)	0.219
**pH	7.2 (7-8.1)	7.3 (6.8-8.5)	
*Total sperm count (millions/ejaculate)	125 (6-479)	121 (0.3-848)	**0.021**
**Total sperm count (millions/ejaculate)	102 (5-384)	152 (0.3-827)	
*Sperm count per mL (millions/mL)	36 (2-150)	32 (0.1-210)	**0.014**
**Sperm count per mL (millions/mL)	34 (1-105)	43 (0.1-167)	
*Total motility (PR+NP, %)	40 (18-65)	42 (2-71)	0.777
**Total motility (PR+NP, %)	38 (20-53)	42 (1-63)	
*Progresifmotility (%)	37 (15-62)	40 (1-68)	0.869
**Progresifmotility (%)	35 (16-48)	38 (1-61)	
*Sperm morphology (normal/pathological)	6/11	23/25	0.368
**Sperm morphology (normal/pathological)	8/9	17/31	0.397

*: Pre-Vaccination, **: Post-Vaccination, PR: Progressive, NP: Nonprogressive, SD: Standard deviation, min: Minimum, max: Maximum

In Group 1, no significant difference was observed in volume, sperm count per ml, motile sperm count, or total motility before and after Sinovac/CoronaVac vaccination. However, a statistically significant decrease was observed in pH (p=0.004) and total sperm count (p=0.019) due to the Sinovac/CoronaVac vaccine (Table 4). There was no significant difference in sperm morphology before or after the Sinovac/CoronaVac vaccine.

In Group 2, no significant differences were observed in volume, total sperm count, sperm count per mL, motile sperm count, or total motility before and after the vaccination. However, a statistically significant decrease was observed in pH because of the Pfizer/BioNTech vaccine (p<0.001) (Table 5). There was no significant difference in sperm morphology before and after administration of the Pfizer/BioNTech vaccine.

Discussion

This study was designed to identify the potential effects of Sinovac/CoronaVac and Pfizer/BioNTech vaccines on male fertility. Compared with previous studies that reported a decline in semen parameters in active COVID-19 and recovered patients (16,17), our study showed a significant decrease in total sperm count and sperm count per milliliter in infertile patients after Sinovac/CoronaVac vaccination but an increase in these parameters after Pfizer/BioNTech vaccination.

Gonzales and colleagues examined the sperm parameters of 45 patients before and after two doses of COVID-19 mRNA vaccines and reported a significant increase in all sperm parameters at an average of 75 days after the second dose (Pfizer/BioNTech n=21 and Moderna n=24) (18). In contrast, Barda's study showed no negative effect on sperm parameters in patients who received two doses of Pfizer/BioNTech and were evaluated 72 days after the second dose, and that total sperm and total motile sperm counts increased significantly after the second dose (19). A study by Myriam Safrai evaluated sperm parameters in 72 patients an average of 71 days after the second dose of the Pfizer/BioNTech vaccine and reported that it did not affect sperm parameters in normospermic or infertile patients (20). Similarly, Reschini et al. (21) reported that there was no negative effect on sperm parameters or fertilisation rates after PfizerBioNTech (n=73) and Moderna (n=20) vaccinations. Gat and colleagues examined semen samples after two doses of Pfizer/BioNTech vaccine on days 15-45, 75-125, and 145 and reported that the decreased sperm concentration and total motile sperm count in the first two-time intervals improved in the third time interval (22). Abd and colleagues compared semen samples before and after the second dose of the Pfizer/BioNTech vaccine 90 days after vaccination and found impaired total sperm motility and progressive motility, but other parameters were normal (23). In our study, we did not observe any changes in sperm parameters

Table 4. Intragroup differences in sperm parameters of the Sinovac/CoronaVac vaccine (group 1)

	Pre-Vaccination	Post-Vaccination	p-value
	Median (min-max)	Median (min-max)	
Volume (mL)	4 (1.8-6)	4.1 (1.4-9.8)	0.850
pH	7.9 (6.9-8.5)	7.2 (7-8.1)	**0.004**
Total sperm count (millions/ejaculate)	125 (6-479)	102 (5-384)	**0.019**
Sperm count per mL (millions/mL)	36 (2-150)	34 (1-105)	0.065
Progressive motility (%)	37 (15-62)	35 (16-48)	0.641
Total motility (PR+NP, %)	40 (18-65)	38 (20-53)	0.717
Sperm morphology (normal/pathological)	11/6	8/9	0.500

PR: Progressive, NP: Nonprogressive, min: Minimum, max: Maximum

Table 5. Intragroup differences in sperm parameters of the Pfizer/BioNTech vaccine (group 2)

	Pre-Vaccination	Post-Vaccination	p-value
	Median(min-max)	Median(min-max)	
Volume (mL)	3.8 (1.1-8.1)	3.4 (1-7)	0.064
ph	7.8 (6.7-8.5)	7.3 (6.8-8.5)	**<0.001**
Total sperm count (millions/ejaculate)	121 (0.3-848)	152 (0.3-827)	0.310
Sperm count per mL (millions/mL)	32 (0.1-210)	43 (0.1-167)	0.096
Progressive motility (%)	40 (1-68)	38 (1-61)	0.477
Total motility (PR+NP, %)	42 (2-71)	42 (1-63)	0.352
Sperm morphology (normal/pathological)	23/25	17/31	0.070

PR: Progressive, NP: Nonprogressive, min: Minimum, max: Maximum

before or after two doses of the Pfizer/BioNTech vaccine. Although normal sperm morphology decreased before and after vaccination, it was not statistically significant. Interestingly, the pH value was significantly lower after vaccination.

In a study of 128 individuals vaccinated with Sinovac/CoronaVac and Sinopharm inactivated vaccines in China, no difference in semen parameters was observed before or after the second vaccination within 90 days (24). In another study using Sinovac/CoronaVac vaccine, a slight decrease in motility and morphology was observed after the second dose, which was attributed to the length of time between semen collection before and after vaccination (10). Zhu Hong and colleagues examined semen parameters at an average of 60 days after inactivated vaccine administration in 43 healthy volunteers and observed no changes (25). In their study, Xia et al. (26) also showed that there was no difference in semen parameters or in vitro fertilization outcomes after vaccination with Sinovac (n=105) or Sinopharm (n=155) vaccines. In contrast to these studies, our study showed a decrease sperm count and pH values after Sinovac/CoronaVac vaccination.

In the first study in which Sinovac/CoronaVac and PfizerBioNTech vaccines were compared, we showed that sperm count per milliliter and total sperm count increased in favor of PfizerBioNTech. We did not detect any difference between the groups in other sperm parameters.

Study Limitations

The major limitation of this study was the retrospective design. Single-center design, heterogeneous sample distribution among the groups, and lack of serum testosterone values were the other limitations of our study. Pre-vaccination evaluation in idiopathic infertile men, evaluation of the same patient cohort, and comparison of two different vaccine groups were the strengths of our study.

Conclusion

We observed that the milliliter and total sperm count decreased in idiopathic infertile patients in the Sinovac/CoronaVac group, whereas it increased in the PfizerBioNTech group following COVID-19 vaccination. The findings show that inactive and mRNA vaccines do not significantly affect semen parameters in infertile men. Therefore, both vaccines can be considered safe for men's reproductive health.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Recep Tayyip Erdogan University Non-Interventional Clinical Research Ethics Committee before the study (decision no: 2023/17 date: January 1, 2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The author declare that they have no relevant financial.

References

1. Coronavirus disease (COVID-19) pandemic'. https://www.who.int/europe/emergencies/situations/covid-19 (accessed Dec. 12, 2022).
2. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Pei Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457-460.
3. Sun L, Shen L, Fan J, Gu F, Hu M, An Y, Yiran An, Zhou Q, Fan H, Bi J. Clinical features of patients with coronavirus disease 2019 from a designated hospital in Beijing, China. J Med Virol 2020;92:2055-2066.
4. Sheikhzadeh Hesari F, Hosseinzadeh SS, Asl Monadi Sardroud MA. Review of COVID-19 and male genital tract. Andrologia 2021;53:e13914.
5. Yao Y, Yuan X, Wu L, Guo N, Yin L, Li Y. COVID-19 and male reproduction: Current research and unknown factors. Andrology 2021;9:1027-1037.
6. Banihani SA. Human semen quality as affected by SARS-CoV-2 infection: An up-to-date review. Andrologia 2022;54:e14295.
7. Dil E. The Effect of the SARS-CoV-19 (COVID-19) Virus on Sperm Parameters of Patients with Male Infertility. International Journal of Current Medical and Biological Sciences 2023;3:34-37.
8. İnce U, Sayın F. COVID-19 Aşısında Güncel Uygulamalar. Sağlık Bilimleri Dergisi 2022;31:258-262.
9. Akova M, Unal S. A randomized, double-blind, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of SARS-CoV-2 vaccine (inactivated, Vero cell): a structured summary of a study protocol for a randomised controlled trial. Trials 2021;22.
10. Wang M, Yang Q, Zhu L, Jin L. Investigating Impacts of CoronaVac Vaccination in Males on In Vitro Fertilization: A Propensity Score Matched Cohort Study. World J Mens Health 2022;40:570-579.
11. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector A S, Rouphael N, Creech B C, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham S B, Bennett B, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403-416.
12. Szilagyi PG, Thomas K, Shah MD, Vizueta N, Cui Y, Vangala S, Vangala S,Kapteyn A. National Trends in the US Public's Likelihood of Getting a COVID-19 Vaccine—April 1 to December 8, 2020. JAMA 2021;325:396-398.
13. Berry SD, Johnson KS, Myles L, Herndon L, Montoya A, Fashaw S, Gifford D. Lessons learned from frontline skilled nursing facility staff regarding COVID-19 vaccine hesitancy. J Am Geriatr Soc 2021;69:1140-1146.
14. Cebeci Kahraman F, Savaş Erdoğan S, Aktaş ND, Albayrak H, Türkmen D, Borlu M, Arıca D A, Demirbaş A, Akbayrak A, Ekinci A P, Gökçek G E, Çelik H A, Taşolar M K, An İ, Temiz S A, Hazinedar E, Ayhan E, Hızlı P, Solak E Ö, Kılıç A, Yılmaz E. Cutaneous reactions after COVID-19 vaccination in Turkey: A multicenter study. J Cosmet Dermatol 2022;21:3692-3703.
15. WHO. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health

Organization, Department of Reproductive Health and Research. Geneva, Switzerland. WHO Press 2021.

16. Gacci M, Coppi M, Baldi E, Sebastianelli A, Zaccaro C, Morselli S, Pecoraro A, Manera A, Nicoletti R, Liaci A, Bisegna C, Gemma L, Giancane S, Pollini S, Antonelli A, Lagi F, Marchiani S, Dabizzi S, Degl'Innocenti S, Annunziato F, Maggi M, Vignozzi L, Bartoloni A, Rossolini R G, Serni S. Semen impairment and occurrence of SARS-CoV-2 virus in semen after recovery from COVID-19. Hum Reprod 2021;36:1520-1529.
17. Li H, Xiao X, Zhang J, Zafar MI, Wu C, Long Y, Lu W, Pan F, Meng T, Zhao K, Zhou L, Shen S, Liu L, Liu Q and Xiong C. Impaired spermatogenesis in COVID-19 patients. EClinicalMedicine 2020;28:100604.
18. Gonzalez DC, Nassau DE, Khodamoradi K, Ibrahim E, Blachman-Braun R, Ory J, Ramasamy R. Sperm Parameters Before and After COVID-19 mRNA Vaccination. JAMA 2021;326:273-274.
19. Barda S, Laskov I, Grisaru D, Lehavi O, Kleiman S, Wenkert A, Azem F, Hauser R, Nadav Michaan N. The impact of COVID-19 vaccine on sperm quality. Int J Gynaecol Obstet 2022;158:116-120.
20. Safrai M, Herzberg S, Imbar T, Reubinoff B, Dior U, Ben-Meir A. The BNT162b2 mRNA Covid-19 vaccine does not impair sperm parameters. Reprod Biomed Online 2022;44:685-688.
21. Reschini M, Pagliardini L, Boeri L, Piazzini F, Bandini V, Fornelli G, Dolci C, Cermisoni G C, Viganò P, Somigliana E, Coccia M E, Papaleo E. COVID-19 Vaccination Does Not Affect Reproductive Health Parameters in Men. Front Public Health 2022;10:839967.
22. Gat I, Kedem A, Dviri M, Umanski A, Levi M, Hourvitz A, Baum M. Covid-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. Andrology 2022;10:1016-1022.
23. Abd ZH, Muter SA, Saeed RAM, Ammar O. Effects of Covid-19 vaccination on different semen parameters. Basic Clin Androl 2022;32:13.
24. Huang J, Xia L, Tian L, Xu D, Fang Z, Lin J, Wu Q. Comparison of Semen Quality Before and After Inactivated SARS-CoV-2 Vaccination Among Men in China. JAMA Netw Open 2022;5:e2230631-e2230631.
25. Zhu H, Wang X, Zhang F, Zhu Y, Du MR, Tao ZW, Sun C, Ma T A, Li Y D, Liang G Q, Ren J, Feng B L, Jiang F. Evaluation of inactivated COVID-19 vaccine on semen parameters in reproductive-age males: a retrospective cohort study. Asian J Androl 2022;24:441-444.
26. Xia W, Zhao J, Hu Y, Fang L, Wu S. Investigate the effect of COVID-19 inactivated vaccine on sperm parameters and embryo quality in in vitro fertilization. Andrologia 2022;54:e14483.

ORIGINAL RESEARCH
Basic Science

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Hydrogen Sulfide and Reactive Oxygen Species Scavengers Have a Protective Effect on Carbachol-Induced Contractions That are Impaired by High Glucose in Detrusor Smooth Muscle

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What's known on the subject? and What does the study add?

One of the most frequent diabetic complications is urinary bladder dysfunction, which is associated with increased bladder capacity and impaired smooth muscle contractions. It has been shown that smooth muscle tissues isolated from diabetic rats have altered contractile responses. However, the mechanisms responsible for altered smooth muscle contractility remain poorly understood. Increased production of reactive oxygen species (ROS) plays a role in bladder disorders, and H_2S has a cytoprotective effect that might have a scavenging effect on ROS. It is important to determine the effect of H_2S on impaired detrusor contractility caused by ROS in order to develop new treatment principles.

Abstract

Objective: Urinary bladder dysfunction, one of the most common diabetic complications, is associated with bladder overactivity, increased bladder capacity, and impaired bladder smooth muscle contractions. The involvement of hydrogen sulfide (H_2S) in pathological disorders such as diabetes mellitus has been suggested. Sodium hydrosulfide (NaHS)-treatment can distinctly reduce high glucose-induce cytotoxicity and oxidative stress. Reactive oxygen species (ROS) are produced in increased concentrations in diabetes and may cause tissue damage, thus impaired smooth muscle function. The aim of the study was to investigate the role of H_2S and ROS on carbachol-induced detrusor smooth muscle contractions under high glucose conditions.

Materials and Methods: Cumulative (10 nM-30 µM) carbachol contraction responses were obtained in bladder detrusor smooth muscle strips isolated from male New Zealand albino rabbit bladders in the control group and in high glucose conditions (30 min incubation in Krebs' Henseleit solution with high glucose). Responses were repeated in the presence of NaHS, catalase, superoxide dismutase (SOD), and their combinations. Contractions were expressed as a percentage of 80 mM K+ response and $p<0.05$ was accepted as statistically significant.

Results: Cumulative contractile responses were elicited with carbachol in control group and these responses were significantly increased in the presence of high glucose. Increased carbachol contractile responses in high glucose were significantly reduced in the presence of catalase, SOD and NaHS.

Conclusion: Based on these results, we propose that H_2S donors and ROS scavengers have probable benefits in treating diabetic complications such as urinary bladder dysfunction.

Keywords: Basic science, bladder, carbachol, high glucose, hydrogen sulfide, reactive oxygen scavenger

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Introduction

Urinary bladder dysfunction, which is one of the most common diabetic complications, is associated with bladder overactivity, increased bladder capacity, and impaired bladder smooth muscle contraction. The prevalence of dysfunction is between 43% and 87%. It is not life threatening but considerably affects life quality (1). Evaluation of bladder smooth muscle contractility is important for understanding the mechanisms underlying diabetic dysfunction. Alterations in contractile responses have been reported in smooth muscle tissues isolated from diabetic models. Increased carbachol-induced contraction was observed in bladder smooth muscle in streptozotocin-induced diabetic rats (2). Pretreatment of bladders under high glucose (HG) conditions enhanced carbachol-induced contraction in control animals (3). Nobe et al. (4) showed that glucose-dependent enhancement of contraction in the diabetic bladder is involved in the activation of the Rho kinase and calcium-independent PKC pathways. The increased vascular smooth muscle contraction, which was enhanced under HG conditions, was also reported in a type II diabetic mouse model (5,6). However, the mechanisms responsible for altered smooth muscle contractility remain poorly understood.

The involvement of hydrogen sulfide (H_2S) in pathological disorders such as diabetes mellitus has been suggested although its physiological role is still not known. Increased formation of H_2S and expression of endogenous H_2S-synthesizing enzymes, cystathionine γ-lyase (CSE) and cystathionine b-synthase (CBS), have been demonstrated in liver and pancreas of streptozotocin (STZ)-induced diabetic rats (7). Inhibition of CSE, a synthase of endogenous H_2S, promotes endothelial cell dysfunction induced by hyperglycemia (8) and reduces H_2S levels in streptozotocin-induced diabetic rats (9). In diabetic mice, treatment with H_2S can restore nitric oxide efficacy and decrease oxidative stress in the mouse aorta (10). However, possible accompanying changes in the functional effects of H_2S have not been enlightened.

The cytoprotective effect of H_2S may also be attributed to its scavenging effect on reactive oxygen species (ROS). ROS are produced in increased concentrations in pathological conditions such as cardiac ischemia, reperfusion or sepsis and cause tissue damage. ROS can alter smooth and striated muscle contraction by affecting many intracellular pathways associated with excitation-contraction coupling. It has been shown that carbachol and potassium-induced contractions reduced in the presence of hydrogen peroxide in rat urinary bladder detrusor muscle (11). In our previous study, H_2S reduced carbachol-induced contraction in the permeabilized guinea pig tenia cecum and that intracellular hydrogen peroxide formation and calcium storage mitochondria are responsible for this response (12). It is also known that superoxide anions reduce the release of calcium by preventing the opening of the calcium channels of the sarcoplastic reticulum in the myocardium (13).

The aim of this study was to investigate the role of H_2S and ROS scavengers in alterations of carbachol-induced detrusor smooth muscle contraction under HG conditions.

Materials and Methods

The study was approved by Hacettepe University Animal Ethics Committee (no: 2023/06-06, date: 23.08.2023). Male New Zealand albino rabbits (4-6 months old) were used in this study.

Tissue Preparation

Rabbits were euthanized with high-dose anesthesia (Ketamine/Xylazine, 50/5 mg/kg, i.p.) and the urinary bladders were isolated. Bladder strips were isolated and mounted in 5 mL3 organ baths containing Krebs' Henseleit solution under a resting tension of 800 mg. Tissues were equilibrated for 1 h and washed with Krebs' Henseleit solution every 15 min before each experimental procedure. Isometric changes in tension were recorded using an isometric force transducer (MP 150-Transducer Data Acquisition System; BIOPAC Systems).

Experimental Protocol

Sodium hydrogen sulfide (NaHS) is used as an H_2S donor, and its aqueous solution is introduced directly into the organ bath by an automated pipette. NaHS dissociates to Na^+ and HS^- in aqueous solution and then HS^- associates with H^+ to form H_2S (Hosoki et al., 1997).

At the beginning of each experiment, KCl (80 mM)-induced contractions were elicited in bladder strips. After a 30-min washout period, cumulative (10 nM-30 μM) carbachol-induced contraction responses were obtained in bladder strips in the control group and under HG conditions. The HG condition means 30 min incubation of bladder strips in Krebs' Henseleit solution with, 4.7; $MgSO_4$, 1.2; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; glucose, 11.6 and this was gassed with 95% O_2-5% CO_2 at 37°C and pH 7.4. The Krebs' Henseleit solution with HG contains 44 mM glucose. The cumulative carbachol-induced contraction responses were elicited in the presence of ROS scavengers catalase (1000 U/mL), superoxide dismutase (SOD; 150 U/mL), H_2S donor sodium hydrosulfide (NaHS, 300 μM), H_2S-synthesizing enzyme inhibitors propargylglycine (PAG; 300 mM) and aminooxyacetic acid (AOAA; 1 mM) in control and under HG condition.

Drugs and Solutions

Drugs used were carbamylcholine chloride (carbachol), catalase, SOD, NaHS, PAG and AOAA from Sigma (St. Louis, Missouri). All drugs and solutions were prepared by using distilled water.

Statistical Analysis

Contractions were expressed as a percentage of KCl (80 mM)-induced contraction. Data are represented as mean ± standard error of the mean. Statistical analysis was done by ANOVA/Newman-Keuls and Student's t-test by using GraphPad Prism9 software. P<0.05 was accepted as statistically significant.

Results

The Effect of High Glucose in Bladder Cumulative Carbachol Contraction

Cumulative contractile responses were elicited with carbachol (10 nM-30 µM) in control group. Bladder strips were incubated with HG (Krebs' Henseleit solution with 44 mM glucose). The contraction responses were significantly increased under HG conditions compared with the control group (Figure 1).

The Effects of ROS Scavengers Catalase and SOD on Cumulative Carbachol Contraction

Increased carbachol contractile responses under HG were significantly reduced in the presence of hydrogen peroxide (H_2O_2) scavenger catalase (1000 U/mL) and superoxide (O_2^-) scavenger SOD (150 U/mL) (Figure 2). There was no difference in the control group between the absence and presence of catalase or SOD (Table 1).

The Effects of H_2S Donor NaHS on Cumulative Carbachol Contraction

Cumulative carbachol (10 nM-30 µM) contractile responses were obtained in the presence of H_2S donor NaHS (300 mM) in control and under HG conditions. Increased carbachol contractile responses under HG were significantly reduced in the presence of NaHS. Contractile responses were also significantly decreased in the presence of NaHS in control group (Figure 3).

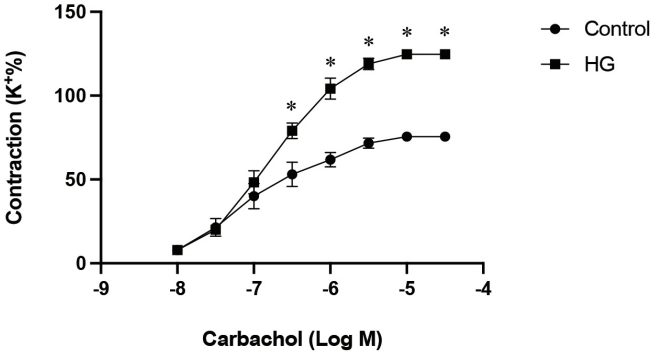

Figure 1. The cumulative contractile response elicited with carbachol (10 nM- 30 µM) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 significant compared to control; n=6)

HG: High glucose

Effects of Combination of H_2S Donor NaHS and ROS Scavenger Catalase or SOD on Cumulative Carbachol Contraction

To investigate the interaction between H_2S and ROS, bladder strips were incubated with NaHS and catalase or NaHS and SOD together. There is no further inbibition in cumulative carbachol (10 nM-30 µM) contractile responses incubated with the combination of NaHS and catalase or NaHS and SOD compared to incubation with NaHS alone in control group. In contrast, further inhibition was observed in carbachol contraction responses under HG conditions when bladder strips were incubated with the combination of NaHS and catalase or NaHS and SOD compared with incubation with NaHS alone (Table 1).

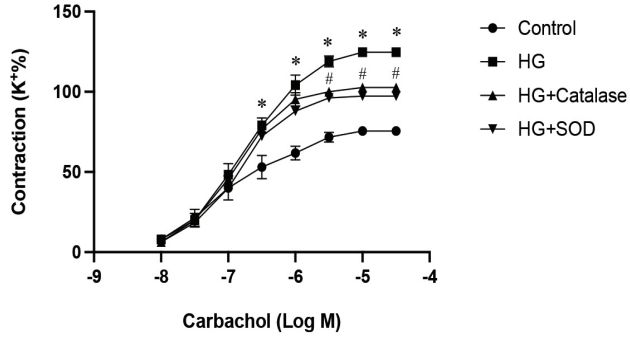

Figure 2. The cumulative contractile response elicited with carbachol (10 nM- 30 µM) in the absence and presence of catalase (1000 U/mL) and SOD (150 U/mL) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 significant compared to control, #p<0.05 significant compared to HG; n=5-6)

HG: High glucose, SOD: Superoxide dismutase

Table 1. Maximum contraction values (E_{max}) obtained with carbachol in the presence of catalase, SOD, NaHS and their combinations in the control and HG-incubated bladder detrusor smooth muscle

Group		E_{max}	n
Control		75.53±2.58	6
HG		124.65±2.36*	6
Catalase	Control	70.88±3.84	5
	HG	102.71±2.71#	5
SOD	Control	72.59±0.80	5
	HG	97.28±0.84#	6
NaHS	Control	64.03±1.72*	5
	HG	94.57±0.97#	5
NaHS+Catalase	Control	66.10±1.18	6
	HG	84.57±0.97#	5
NaHS+SOD	Control	65.47±1.75	5
	HG	85.51±1.26#	5

*: P<0.05 compared to control, #: P<0.05 significant compared to HG, HG: High glucose, SOD: Superoxide dismutase, NaHS: Sodium hydrosulfide, Max: Maximum

Effects of H_2S-synthesizing enzyme inhibitors PAG and AOAA on cumulative carbachol contraction

Increased carbachol contractile responses under HG conditions did not change in the presence of CSE enzyme inhibitor PAG (300 mM) and CBS enzyme inhibitor AOAA (1 mM) (Figure 4).

Discussion

Many neurological, cardiovascular, urological, gastrointestinal and biochemical complications develop in diabetic patients due to increased glucose. Bladder dysfunction is one of the most common diabetic complications associated with bladder overactivity, increased bladder capacity, and impaired bladder smooth muscle contractile function. Investigating the mechanism of impaired bladder smooth muscle contractility is important for understanding the underlying mechanisms of diabetes complications. Moreover, bladder dysfunction problems, especially those more common in women, lead to social problems as well. Our aim in this study was to elucidate the effect of ROS scavengers and H_2S on impaired contractile functions under HG conditions.

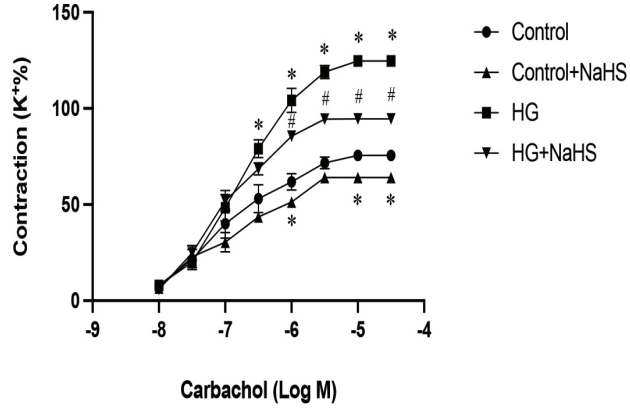

Figure 3. The cumulative contractile response elicited with carbachol (10 nM- 30 µM) in the absence and presence of NaHS (300 µM) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 compared to control, #p<0.05 significant compared to HG; n=5-6)

HG: High glucose, NaHS: Sodium hydrosulfide

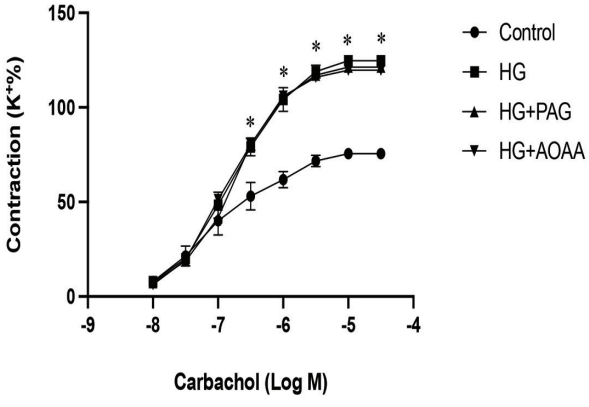

Figure 4. The cumulative contractile response elicited with carbachol (10 nM- 30 µM) in the absence and presence of PAG (300 µM) and AOAA (1 mM) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 compared to control; n=5-6)

HG: High glucose, PAG: Propargylglycine, AOAA: Aminooxyacetic acid

Changes in contractile responses in bladder smooth muscle experimentally induced or incubated with HG have been reported (2-4). In our study; cumulative carbachol contractile responses were significantly increased in the HG group compared with the control group. An increase in carbachol-induced contractile responses was demonstrated in bladder strips isolated from streptozotocin-induced diabetic rats and in tissues pretreated with HG (2,3). Many mechanisms are believed to be responsible for the impaired contractile response due to high glucose. The consequence of hyperglycemic stimulation is the increase of ROS, thus initiating oxidative stress, which causes bladder smooth muscle damage, resulting in impaired bladder function (14-16). Growing evidence has shown that high-glucose-related oxidative stress has an essential role in the remodeling of smooth muscle function that eventually results in the decompensation of the detrusor muscle (17-19). The complications of diabetes are thought to be the result of oxidative stress associated with HG in several tissues (20) including the detrusor smooth muscle (21). It has been reported that repeated stimulation of rabbit bladder strips leads to increased lipid peroxidation and impaired smooth muscle contractility in the ischemic and hypoxic media as well as in the normal physiological media (22).

Samples from rats with STZ-induced type 1 diabetes showed that genes involved in the production or enhancement of ROS and oxidative pathways are upregulated in the bladder of these rats, whereas antioxidative enzymes are downregulated (17-20). Xue et al. (23), 2021 showed that the viability of bladder smooth muscle cells significantly decreased and apoptotic cells increased after HG treatment, at the same time, the SOD level decreased and MDA increased. SOD is an important antioxidant enzyme, and its level decreases, suggesting a decline in antioxidant capacity. MDA is a lipid oxidative damage marker, and its increased level indicates a higher level of oxidative stress (23). In this study, we investigated the effects of ROS scavengers, O^{2-} radical scavenger SOD and H_2O_2 scavenger catalase, on increased carbachol contractile responses under high glucose. In the present study, we observed that contractile response under HG conditions was decreased in the presence of catalase and SOD. There was no difference in the control group in the presence of catalase and SOD. Consistent with previous studies, our results indicate that HG causes impaired contractile responses in the detrusor smooth muscle through oxidative stress.

Exogenous H_2S significantly prevented cell death, decreased the generation of apoptotic markers, and suppressed mitochondrial ROS production in rat aortic endothelial cells under HG conditions (24). NaHStreatment can distinctly reduce HG-induced cytotoxicity, apoptosis, oxidative stress, and inflammation in HUVECs (25). In diabetic mice, treatment with H_2S can restore nitric oxide efficacy and decrease oxidative stress in the mouse aorta (10). H_2S may act as a cytoprotective hormone in mouse islets and in MIN6 cells exposed to high glucose, fatty acids, or a mixture of cytotoxic cytokines (26,27). The effects of H_2S on increased carbachol contractile responses under HG conditions were also investigated. According to our results; increased carbachol contractile responses were significantly reduced under HG conditions in the presence of NaHS. Contractile responses were also significantly decreased in the control group in the presence of NaHS. Inhibition was seen in 14% (the control group) and 24% (HG group) ratios. In parallel with previous studies, our results suggest that H_2S reduces the oxidative stress caused by HG and, as a result, improves the impaired contractile responses. Moreover; when the combined effects of H_2S and ROS scavengers were examined under HG conditions, after incubation of NaHS and catalase or NaHS and SOD together, a further reduction 32% and 31% in carbachol contractile responses were obtained, respectively. According to studies examining the possible interaction of H_2S and ROS, Muzaffar et al. (28) showed that H_2S suppressed O^{2-} production in pulmonary artery endothelial cells. In another study, NaHS infusion decreased O^{2-} production in hypertensive rats (29).

H_2S-synthesizing enzyme inhibitors PAG and AOAA were examined to support the regulating effect of H_2S on deteriorated contractile responses in bladder smooth muscle under HG conditions. Increased carbachol contractile responses under HG were not change in the presence of CSE enzyme inhibitor PAG and CBS enzyme inhibitor AOAA.

Study Limitations

The fact that our study is an animal study is an important limitation. It is difficult to mimic hyperglycemia in animal tissues. Studies on the effects of H_2S and ROS on human should be conducted to strengthen these findings.

Conclusion

The study identified alterations in contractile responses in bladder smooth muscle under HG conditions. Cumulative carbachol-induced contractile responses were significantly increased in HG-incubated bladder detrusor muscle. These increased contractile responses decreased in the presence of catalase, SOD, and NaHS. Therefore, we can suggest that agonist-induced contractile functions in diabetes are related to H_2S and ROS such as H_2O_2 and O_2^-. In conclusion, these results may become a valuable source for assessing the probable benefits of H_2S donors and ROS scavengers in treating diabetic complications such as urinary bladder dysfunction.

Ethics

Ethics Committee Approval: The study was approved by Hacettepe University Animal Ethics Committee (no: 2023/06-06, date: 23.08.2023).

Informed Consent: Male New Zealand albino rabbits (4-6 months old) were used in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declare that they have no relevant financial.

References

1. Lee WC, Wu HP, Tai TY, Liu SP, Chen J, Yu HJ. Effects of diabetes on female voiding behavior. J Urol 2004;172:989-992.
2. Yang Z, Dolber PC, Fraser MO. Diabetic urethropathy compounds the effects of diabetic cystopathy. J Urol 2007;178:2213-2219.
3. Nobe K, Yamazaki T, Kumai T, Okazaki M, Iwai S, Hashimoto T, Kobayashi S, Oguchi K, Honda K. Alterations of glucose-dependent and -independent bladder smooth muscle contraction in spontaneously hypertensive and hyperlipidemic rat. J Pharmacol Exp Ther 2008;324:631-642.
4. Nobe K, Yamazaki T, Tsumita N, Hashimoto T, Honda K. Glucose-dependent enhancement of diabetic bladder contraction is associated with a rho kinase-regulated protein kinase C pathway. J Pharmacol Exp Ther 2009;328:940-950.
5. Nobe K, Sakai Y, Maruyama Y, Momose K. Hyper-reactivity of diacylglycerol kinase is involved in the dysfunction of aortic smooth muscle contractility in streptozotocin-induced diabetic rats. Br J Pharmacol 2002;136:441-451.
6. Nobe K, Suzuki H, Sakai Y, Nobe H, Paul RJ, Momose K. Glucose-dependent enhancement of spontaneous phasic contraction is suppressed in diabetic mouse portal vein: association with diacylglycerol-protein kinase C pathway. J Pharmacol Exp Ther 2004;309:1263-1272.
7. Yusuf M, Kwong Huat BT, Hsu A, Whiteman M, Bhatia M, Moore PK. Streptozotocin-induced diabetes in the rat is associated with enhanced tissue hydrogen sulfide biosynthesis. Biochem Biophys Res Commun 2005;333:1146-1152.
8. Degterev A, Huang Z, Boyce M, Li Y, Jagtap P, Mizushima N, Cuny GD, Mitchison TJ, Moskowitz MA, Yuan J. Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. Nat Chem Biol 2005;1:112-119.
9. Jain SK, Bull R, Rains JL, Bass PF, Levine SN, Reddy S, McVie R, Bocchini JA. Low levels of hydrogen sulfide in the blood of diabetes patients and streptozotocin-treated rats causes vascular inflammation? Antioxid Redox Signal 2010;12:1333-1337.

10. Ng HH, Yildiz GS, Ku JM, Miller AA, Woodman OL, Hart JL. Chronic NaHS treatment decreases oxidative stress and improves endothelial function in diabetic mice. Diab Vasc Dis Res 2017;14:246-253.
11. Aikawa K, Leggett R, Levin RM. Effect of age on hydrogen peroxide mediated contraction damage in the male rat bladder. J Urol 2003;170:2082-2085.
12. Denizalti M, Durlu-Kandilci NT, Bozkurt TE, Sahin-Erdemli I. Hydrogen sulphide inhibits carbachol-induced contractile responses in β-escin permeabilized guinea-pig taenia caecum. Eur J Pharmacol 2011;658:229-235.
13. Holmberg SR, Cumming DV, Kusama Y, Hearse DJ, Poole-Wilson PA, Shattock MJ, Williams AJ. Reactive oxygen species modify the structure and function of the cardiac sarcoplasmic reticulum calcium-release channel. Cardioscience 1991;2:19-25.
14. Andersson KE. Oxidative stress and its possible relation to lower urinary tract functional pathology. BJU Int 2018;121:527-533.
15. Elrashidy RA, Liu G. Long term diabetes causes molecular alterations related to fibrosis and apoptosis in rat urinary bladder. Exp Mol Pathol 2019;111:104304.
16. Tsounapi P, Honda M, Hikita K, Sofikitis N, Takenaka A. Oxidative Stress Alterations in the Bladder of a Short-period Type 2 Diabetes Rat Model: Antioxidant Treatment Can Be Beneficial for the Bladder. In Vivo 2019;33:1819-1826.
17. Sullivan CJ, Teal TH, Luttrell IP, Tran KB, Peters MA, Wessells H. Microarray analysis reveals novel gene expression changes associated with erectile dysfunction in diabetic rats. Physiol Genomics 2005;23:192-205.
18. Hipp JD, Davies KP, Tar M, Valcic M, Knoll A, Melman A, Christ GJ. Using gene chips to identify organ-specific, smooth muscle responses to experimental diabetes: potential applications to urological diseases. BJU Int 2007;99:418-430.
19. Kanika ND, Chang J, Tong Y, Tiplitsky S, Lin J, Yohannes E, Tar M, Chance M, Christ GJ, Melman A, Davies KD. Oxidative stress status accompanying diabetic bladder cystopathy results in the activation of protein degradation pathways. BJU Int 2011;107:1676-1684.
20. Poladia DP, Bauer JA. Oxidant driven signaling pathways during diabetes: role of Rac1 and modulation of protein kinase activity in mouse urinary bladder. Biochimie 2004;86:543-551.
21. Changolkar AK, Hypolite JA, Disanto M, Oates PJ, Wein AJ, Chacko S. Diabetes induced decrease in detrusor smooth muscle force is associated with oxidative stress and overactivity of aldose reductase. J Urol 2005;173:309-313.
22. Ohnishi N, Liu SP, Horan P, Levin RM. Effect of repetitive stimulation on the contractile response of rabbit urinary bladder subjected to in vitro hypoxia or in vitro ischemia followed by reoxygenation. Pharmacology 1998;57:139-147.
23. Xue J, Liu Y, Zhang S, Ding L, Shen B, Shao Y, Wei Z. CGRP protects bladder smooth muscle cells stimulated by high glucose through inhibiting p38 MAPK pathway in vitro. Sci Rep 2021;11:7643.
24. Liu J, Wu J, Sun A, Sun Y, Yu X, Liu N, Dong S, Yang F, Zhang L, Zhong X, Xu C, Lu F, Zhang W. Hydrogen sulfide decreases high glucose/palmitate-induced autophagy in endothelial cells by the Nrf2-ROS-AMPK signaling pathway. Cell Biosci 2016;6:33.
25. Lin F, Yang Y, Wei S, Huang X, Peng Z, Ke X, Zeng Z, Song Y. Hydrogen Sulfide Protects Against High Glucose-Induced Human Umbilical Vein Endothelial Cell Injury Through Activating PI3K/Akt/eNOS Pathway. Drug Des Devel Ther 2020;14:621-633.
26. Kaneko Y, Kimura T, Taniguchi S, Souma M, Kojima Y, Kimura Y, Kimura H, Niki I. Glucose-induced production of hydrogen sulfide may protect the pancreatic beta-cells from apoptotic cell death by high glucose. FEBS Lett 2009;583:377-382.
27. Taniguchi S, Kang L, Kimura T, Niki I. Hydrogen sulphide protects mouse pancreatic β-cells from cell death induced by oxidative stress, but not by endoplasmic reticulum stress. Br J Pharmacol 2011;162:1171-1178.
28. Muzaffar S, Jeremy JY, Sparatore A, Del Soldato P, Angelini GD, Shukla N. H2S-donating sildenafil (ACS6) inhibits superoxide formation and gp91phox expression in arterial endothelial cells: role of protein kinases A and G. Br J Pharmacol 2008;155:984-994.
29. Yu H, Xu H, Liu X, Zhang N, He A, Yu J, Lu N. Superoxide Mediates Depressive Effects Induced by Hydrogen Sulfide in Rostral Ventrolateral Medulla of Spontaneously Hypertensive Rats. Oxid Med Cell Longev 2015;2015:927686.

CASE REPORT
Pathology

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Chronic Urinary Outflow Obstruction Resulting from Prostatic Neurofibromatosis

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Abstract

Neurofibromatosis type 1 is a disorder characterized by tumors of autonomic peripheral nerve sheaths. Visceral involvement is infrequent, with genitourinary involvement being rarer. Presented here is a case of a 52-year-old male who presented with an acute renal injury secondary to renal tract obstruction. Transurethral resection of the enlarged prostate demonstrated neurofibromatosis with no signs of malignant transformation.

Keywords: Neurofibroma, prostatomegaly, bladder outflow obstruction

Introduction

Genitourinary manifestations of neurofibromatosis type 1 are rare, with purely prostatic involvement being even rarer. We report a case of prostatic neurofibromatosis presenting with acute renal failure due to bladder outlet obstruction.

Case Presentation

A 52-year-old male was admitted to the intensive care unit for type 2 respiratory failure requiring non-invasive ventilation in the setting of urosepsis with an *Escherichia coli* bacteremia. His past medical history was significant for obstructive sleep apnea, hypertension, type 2 diabetes and neurofibromatosis type 1. He had an associated acute kidney injury with creatinine of 193 umol/L from a baseline of 60 umol/L (Reference range: 60-110), prompting a non-contrast computerized tomography scan of the renal tract, which demonstrated gross hydroureternephrosis bilaterally and prostatomegaly (Figure 1). Upon further history, he had longstanding symptoms of urinary frequency, urgency and nocturia. On digital rectal examination, he had an enlarged, but soft and benign prostate. He improved clinically following the insertion of an indwelling urinary tract catheter and intravenous antibiotics. He was weaned off oxygen and discharged one week later. Ultrasound following this demonstrated a markedly enlarged 100 cc prostate. Cystoscopy and transurethral resection of the prostate were performed approximately six weeks following his initial admission; the bladder mucosa was moderately trabeculated, and the prostate was enlarged and occluded. Histopathological analysis revealed pieces of a spindle cell tumour with elongated and bent nuclei that appeared diffusely infiltrative. There were a few scattered mast cells and eosinophils in the stroma with no normal prostatic glands. Immunohistochemistry confirmed that the spindle cells were positive for the neural markers, SOX10 and S100 (Figure 2). The patient successfully passed a trial of void post-operatively with the return of normal renal function, and resolution of his lower urinary tract symptoms after six weeks.

Discussion

Neurofibromatosis type 1 (NF1) is an inheritable autosomal dominant disorder with nearly 100% penetrance and markedly varied expressibility (1-4). It is caused by genetic mutations of the tumour-suppressor gene located on 17q11.2, which result in increased cellular proliferation.

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It is relatively common, with an incidence of 1 in 3000 live births and affects both sexes and races equally. It is characterized by multiple neurofibromas, which are tumors of autonomic peripheral nerve sheaths, mainly arising from Schwann cells, but may also originate from the perineurium or endoneurium.

Diagnosis involves two or more of the following seven criteria: six or more café au lait macules, two or more neurofibromas or one plexiform neurofibroma, axillary or inguinal freckling, optic pathway glioma, two or more iris hamartomas (Lisch nodules), bony dysplasias, or a first-degree relative with NF1 (3).

Visceral involvement is infrequent, but if present, the gastrointestinal tract is the most common site of occurrence (2). Genitourinary tract involvement is even rarer, with approximately only 70 cases reported in the literature, approximately 50 of these involving the bladder (2). To date, there have only been 10 cases of neurofibromatosis of the prostate reported in the literature (3). Neural tumors that involve the genitourinary tract have been postulated to arise from the anatomically adjacent autonomic plexuses, which innervate the tract. With time, the tumors enlarge and extend into the contiguous organs (1-3).

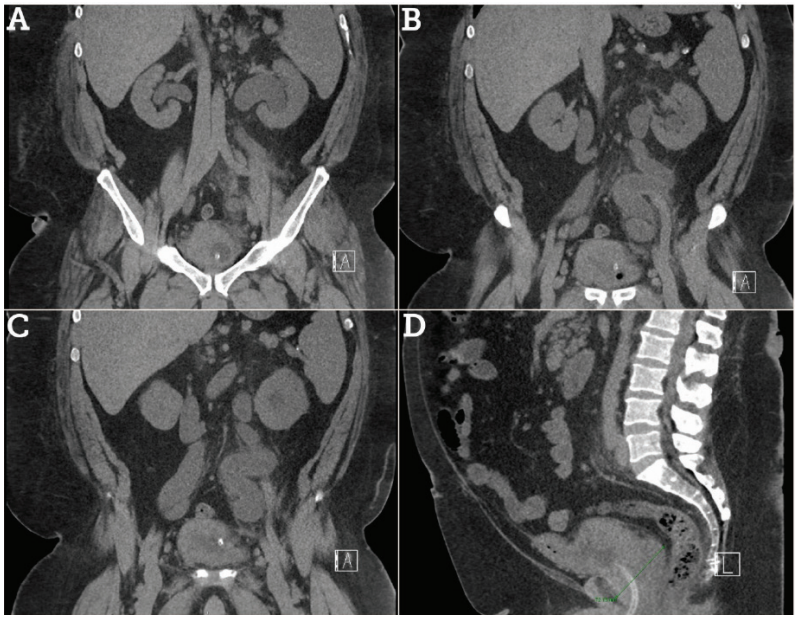

Figure 1. Coronal (A, B and C) and sagittal (D) computed tomography images demonstrating severe bilateral hydroureternephrosis and prostatomegaly

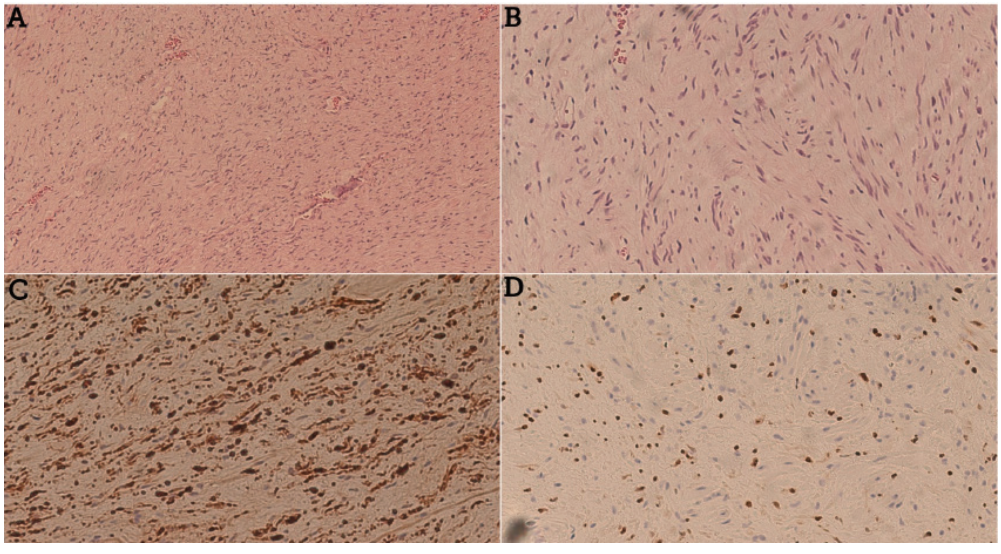

Figure 2. Microscopic prostatic chip histopathological images. H&E staining at x10 (A) and x20 (B) magnification demonstrating presence of spindle cells and scattered mast cells and eosinophils. Immunoperoxidase staining demonstrating presence of S100 (C) and SOX10 proteins (D)

The natural history of neural tumors in the pelvis is one of slow, contiguous growth, and lesions can become quite extensive before producing symptoms, such as in our case. Previous reports of prostatic neurofibromas elicit clinical histories of bladder outlet obstruction with frequency and nocturia, with some reports of prostatodynia, and a perineal or periprostatic mass palpated on a digital rectal exam (4).

Imaging techniques such as ultrasound, computerized tomography and magnetic resonance imaging, as well as the use of cystoscopy, can guide the diagnosis and determine the extent of the tumor and the presence of bladder involvement. However, a definitive diagnosis can only be obtained through histopathology, either by biopsy or the evaluation of prostatic chips obtained by resection. In many cases, diagnosis is achieved only after surgery through histopathological analysis of surgical specimens, with spindle cells expressing the S-100 protein characteristic for the tumour (4).

The mainstay of treatment remains undetermined. Chemotherapy and radiotherapy are both ineffective in managing tumor lesions (2-4), with radiotherapy being associated with the development of malignant peripheral nerve sheath lesions (4). Currently, surgical excision remains the only potential treatment for a cure, but such may not be viable when considering the removal of all cutaneous and visceral neurofibromas. Additionally, recurrence rates are high, with up to 45% of patients having local recurrences following surgical removal, many of which occur within the first year (2).

Additionally, patients with NF1 are at an increased risk of developing benign and malignant tumors, with rapid tumour growth potentially being a sign of malignant transformation. Malignant peripheral nerve sheath lesions are found in 3-15% of patients, and of these lesions, 22% present as metastases (5). Life expectancy in patients with NF1 is approximately 15 years shorter than in the general population, with the main cause of death being consequences from malignant tumors (5).

As such, the most appropriate management would be close monitoring and surgical excision of any large neurofibromas that cause bothersome symptoms or increase rapidly in size.

Conclusion

In conclusion, this is a very unusual case of a relatively young man presenting with bladder outlet obstruction and bilateral gross hydroureteronephrosis caused by prostatomegaly resulting from the presence of a neurofibroma. The diagnosis of prostatic neurofibromatosis, albeit rare, needs to be considered with those with stigmata of neurofibromatosis type 1 with urinary signs and symptoms, to organize prompt surgical management with transurethral resection and routine follow-up.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.V.B., E.H., P.G., C.S.L., Concept: S.V.B., P.G., Design: L.V., Data Collection or Processing: L.V., Analysis or Interpretation: L.V., S.V.B., E.H., P.G., C.S.L., Literature Search: L.V., Writing: L.V., S.V.B., E.H., P.G., C.S.L.

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

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References

1. Rober PE, Smith JB, Sakr W, Pierce JM Jr. Malignant peripheral nerve sheath tumor (malignant schwannoma) of urinary bladder in von Recklinghausen neurofibromatosis. Urology 1991;38:473-476.
2. Chung AK, Michels V, Poland GA, King BF, Wojno KJ, Oesterling JE. Neurofibromatosis with involvement of the prostate gland. Urology 1996;47:448-451.
3. Lindor NM, McMaster ML, Lindor CJ, Greene MH; National Cancer Institute, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr 2008;1-93.
4. Paner GP, Aron M, Hansel DE, Amin MB. Non-epithelial neoplasms of the prostate. Histopathology 2012;60:166-186.
5. Przybylik-Mazurek E, Palen J, Pasternak-Pietrzak K, Sowa-Staszczak A, Brzozowska-Czarnek A, Hubalewska-Dydejczyk A. Coexistence of neurofibromatosis type 1 with multiple malignant neoplasia. Neuro Endocrinol Lett 2018;39:149-155.

CASE REPORT
Urooncology

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Open Approaches to Radical Nephrectomies: A Case Report of Bilateral T3b Renal Cell Carcinoma

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Abstract

A case report describing the surgical challenges of an open approach bilateral T3b renal cell carcinoma with bilateral renal vein involvement. This is the second reported case of bilateral renal cell carcinoma with extension into bilateral renal veins and inferior vena cava. This case highlights how good outcomes can be achieved with open surgical approach.

Keywords: Nephrectomy, renal cell carcinoma, renal vein thrombus

Introduction

A 67-year-old male presented to the emergency department with a two-day history of hematuria and dysuria. Both kidneys were ballotable on examination. His past medical history included hypertension, and he was an ex-smoker. The patient's older brother had prior treatment for bilateral renal cell carcinoma (RCC).

Investigations revealed a mildly elevated white cell count of $11.1*10^9$ cells/L, C-reactive protein of 22 mg/L, and decreased renal function with a serum creatinine of 138 mg/dL. Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a 53 mm right-sided interpolar mass and a 121 mm left-sided multilobulated mass replacing most of the renal parenchyma (Figure 1). Additionally, CT showed enhancing tumor thrombus extending into both the left and right renal veins, extending into the inferior vena cava to the level of hepatic vein insertion (Figure 2). No evidence of metastatic disease was identified on CT.

CT - guided left renal biopsy confirmed clear cell RCC. Multidisciplinary consensus was to proceed with bilateral radical nephrectomy (RN), and the patient was prepared for postoperative dialysis via a central venous catheter.

Figure 1. Axial cross-section from CT imaging demonstrated large bilateral renal masses and renal vein tumour thrombus extending from right renal mass

CT: Computed tomography

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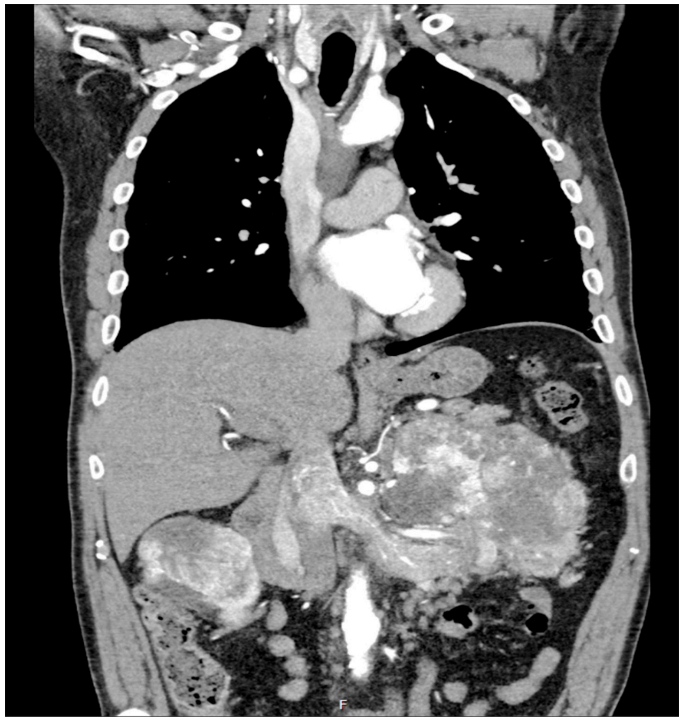

Figure 2. Coronal cross-section from arterial phase CT demonstrating renal vein and inferior vena cava tumour thrombus from left renal mass

CT: Computed tomography

Case Presentation

Due to extensive tumor burden, an open surgical approach was undertaken with upper midline laparotomy. Intraoperatively, a large left upper pole tumor with profound neovascularisation and adherence to the splenic capsule was identified and concurrent splenectomy was performed. Level 2 caval thrombus was identified with the bilateral renal vein involvement. Proximal and distal control of the inferior vena cava (IVC) was obtained, and the proximal tumor thrombus was identified and milked inferiorly, followed by cavotomy and extraction of the tumor thrombus. A small portion of the caval wall was resected to ensure the complete removal of the tumor thrombus. The vascular surgical team then performed caval reconstruction using bovine pericardium graft. A limited retroperitoneal lymph node dissection of the paracaval, interaortocaval, and paraaortic chains was performed at the level of the renal hilum. Postoperatively, he was instituted on hemodialysis, made an uneventful recovery, and was discharged home on day nine. He has been referred to the familial cancer unit because of his family history of bilateral clear cell RCC.

Pathological examination of the left and right renal tumors demonstrated International Society of Urological Pathology grade 3 and grade 2 clear cell RCC, respectively, with no involved lymph nodes and clear surgical margins (American Joint Committee on Cancer 8th edition staging pT3bpN0 bilateral clear cell RCC).

Discussion

Here we present a unique case of bilateral RCC with bilateral renal vein and inferior vena cava tumor thrombus (1). Renal cancer accounts for 2.9% of all new cancer diagnoses in Australia, making it the 7th most diagnosed cancer in 2021 (2). Bilateral RCC occurs in less than 5% of all RCC cases, with most cases having a genetic etiology such as Von-Hippel Lindau syndrome (3).

Although genetic etiology accounts for 3-5% of RCC presentations and is associated with a higher degree of locally advanced disease, there is no statistical analysis of incidence of venous involvement in genetic syndromes (4). However, the rate of IVC thrombus involvement in RCC cases is estimated to be between 5-20% of RCC diagnosed each year (5).

To our knowledge, there has been only one other reported case of bilateral RCC with extension into bilateral renal veins and the IVC (5). It was postulated that the reported case was a nongenetic instance of bilateral RCC, in contrast to our case (5). Nephron-sparing surgery is often preferred in genetic RCC syndromes because the tumors are often bilateral, multifocal, and recurrent (6). While there is some evidence that in stage 3 tumours, nephron-sparing surgery can have similar outcomes to RN (6), in our case, multidisciplinary consensus deemed this inappropriate as remaining renal function was estimated not to be sufficient to avoid haemodialysis. Nephron-sparing surgery may also decrease the five-year life expectancy of patients due to a risk of incomplete tumour resection in previous cases of T3a tumours (7).

As robotic and laparoscopic approaches continue to become more commonplace in RN (8), this case demonstrates the role of open RN techniques when complete oncological clearance is required in cases of extensive RCC. Although there may be perioperative advantages with minimally invasive techniques, such as reduced blood loss, shorter convalescence, and a shorter hospital length of stay (8), there is yet to be definitive evidence of improvements in oncological outcomes (8). Additionally, due to the higher hospital cost combined with limited access to robotic techniques in many healthcare systems, an open approach still remains a relevant and viable option in a case such as that presented with extensive bilateral and locally advanced disease.

A number of studies have found less surgical time and blood loss in thrombectomy-first compared to thrombectomy-last approaches to patients with IVC thrombus in RCC (9).

However, a thrombectomy-last approach was required in this case as access to IVC was most optimal after bilateral RN. This case demonstrates that good outcomes can be achieved with thrombectomy-last approaches (10).

Conclusion

This is the second reported case of bilateral renal cell carcinoma with extension into bilateral renal veins and IVC and the first to report a history suggestive of a hereditary familial syndrome. Additionally, this case highlights the surgical approach taken and challenges faced due to incredible size and infiltration into local vasculature and tissues, emphasizing the continued relevance of an open surgical approach in obtaining an optimal oncological outcome, despite the increasing popularity and experience with minimally invasive techniques for complex renal surgery.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.J.H.K., J.L.K., A.R.S., M.W.W., A.D., Concept: J.L.K., M.W.W., Design: J.L.K., Data Collection or Processing: A.D., Literature Search: P.J.H.K., Writing: P.J.H.K., J.L.K., A.R.S., M.W.W., A.D.

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References

1. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Kuusk T, Lam TB, Marconi L, Merseburger AS, Powles T, Staehler M, Tahbaz R, Volpe A, Bex A. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol 2019;75:799-810.
2. Kidney cancer in Australia statistics. 2022. https://www.canceraustralia.gov.au/cancer-types/kidney-cancer/statistics
3. Qi N, Li T, Ning X, Peng X, Cai L, Gong K. Clinicopathologic Features and Prognosis of Sporadic Bilateral Renal Cell Carcinoma: A Series of 148 Cases. Clin Genitourin Cancer 2017;15:618-624.
4. Haas NB, Nathanson KL. Hereditary kidney cancer syndromes. Adv Chronic Kidney Dis 2014;21:81-90.
5. Lin W, Watts KL, Davuluri M, Aboumohamed A. Non-Familial Synchronous Bilateral Renal Cell Carcinoma with Bilateral Synchronous Renal Vein Extension and Inferior Vena Cava Thrombus. Curr Urol 2019;13:51-53.
6. Herring JC, Enquist EG, Chernoff A, Linehan WM, Choyke PL, Walther MM. Parenchymal sparing surgery in patients with hereditary renal cell carcinoma: 10-year experience. J Urol 2001;165:777-781.
7. Liu H, Kong QF, Li J, Wu YQ, Pan KH, Xu B, Wang YL, Chen M. A meta-analysis for comparison of partial nephrectomy vs. radical nephrectomy in patients with pT3a renal cell carcinoma. Transl Androl Urol 2021;10:1170-1178.
8. Crocerossa F, Carbonara U, Cantiello F, Marchioni M, Ditonno P, Mir MC, Porpiglia F, Derweesh I, Hampton LJ, Damiano R, Autorino R. Robot-assisted Radical Nephrectomy: A Systematic Review and Meta-analysis of Comparative Studies. Eur Urol 2021;80:428-439.
9. Ishiyama Y, Kondo T, Yoshida K, Iizuka J, Tanabe K, Takagi T. "Thrombus-first" or "thrombus-last" approach for surgical management of renal cell carcinoma with inferior vena cava thrombus. Int J Urol 2022;29:559-565.
10. Hevia V, Ciancio G, Gómez V, Álvarez S, Díez-Nicolás V, Burgos FJ. Surgical technique for the treatment of renal cell carcinoma with inferior vena cava tumor thrombus: tips, tricks and oncological results. Springerplus 2016;5:132.