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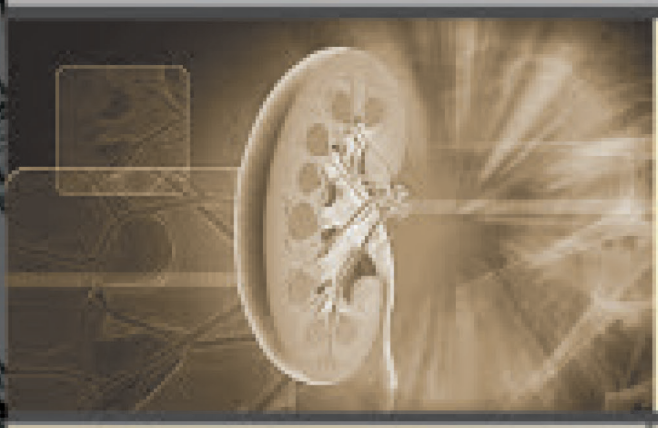

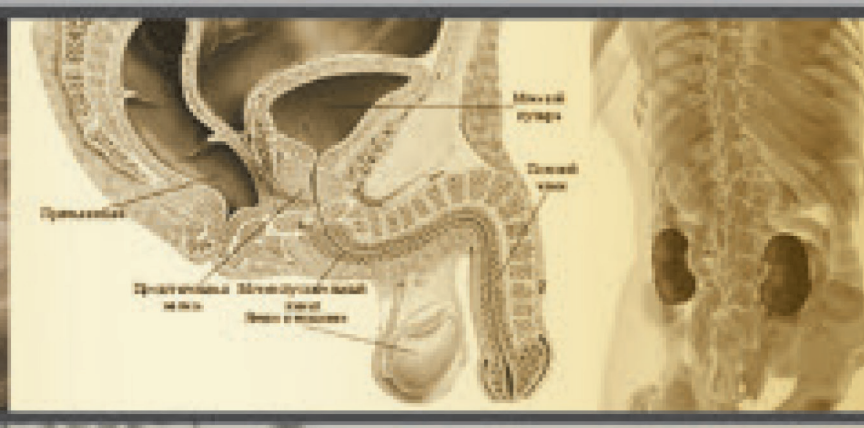

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Society of Urological Surgery

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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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Urooncology,

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Endourology,

Transplantation,

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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.

The journal should be abbreviated as "J Urol Surg" when referenced.

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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Following receiving of each manuscript, a checklist is completed by the Editorial Assistant. The Editorial Assistant checks that each manuscript contains all required components and adheres to the author guidelines, after which time it will be forwarded to the Editor in Chief. Following the Editor in Chief's evaluation, each manuscript is forwarded to the Associate Editor, who in turn assigns reviewers. Generally, all manuscripts will be reviewed by at least three reviewers selected by the Associate Editor, based on their relevant expertise. Associate editor could be assigned as a reviewer along with the reviewers. After the reviewing process, all manuscripts are evaluated in the Editorial Board Meeting.

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.

Urological Pathology

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.

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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

Acknowledge support received from individuals, organizations, grants, corporations, and any other source. For work involving a biomedical product or potential product partially or wholly supported by corporate funding, a note stating, "This study was financially supported (in part) with funds provided by (company name) to (authors' initials)", must be included. Grant support, if received, needs to be stated and the specific granting institutions' names and grant numbers provided when applicable.

Authors are expected to disclose on the title page any commercial or other associations that might pose a conflict of interest in connection with the submitted manuscript. All funding sources that supported the work and the institutional and/or corporate affiliations of the authors should be acknowledged on the title page.

Ethics

When reporting experiments conducted with humans indicate that the procedures were in accordance with ethical standards set forth by the committee that oversees human experimentation. Approval of research protocols by the relevant ethics committee, in accordance with international agreements (Helsinki Declaration of 197, revised 2013 available at http://www.wma.net/e/policy/b3.htm, "Guide for the Care and use of Laboratory Animals" www.nap.edu/catalog/5140.html/), is required for all experimental, clinical, and drug studies. Studies performed on human require ethics committee certificate including approval number. It also should be indicated in the "Materials and Methods" section. Patient names, initials, and hospital identification numbers should not be used. Manuscripts reporting the results of experimental investigations conducted with humans must state that the study protocol received institutional review board approval and that the participants provided informed consent.

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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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4. All authors are responsible for the manuscript's content

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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Online Article Submission Process

The Journal of Urological Surgery uses submission software powered by Online Article Submission articles the website for submissions to the Journal of Urological Surgery is http://submitjurolsurgery.org. This system is quick and convenient, both for authors and reviewers.

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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English Language Editing

All manuscripts are professionally edited by an English language editor prior to publication.

Journal of Urological Surgery: Video Article Author Information

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.

Video Format	
MP4	MP4 Preferred video format; H.264+AAC, max target 720p
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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.

Video materials of accepted manuscripts will be published online. Since video cannot be embedded in the print version of the journal, authors will be directed to the journal website by a QR code that can be scanned by a smart phone application.'

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ORIGINAL RESEARCH
General Urology

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J Urol Surg 2023;10(4):290-294

The Association Between *Sodium Citrate Cotransporter (NaDC-1)* Gene Polymorphism and Urinary Citrate Excretion in Patients with Calcium-containing Kidney Stones

Ahmet Çalışkan[1], Ömür Memik[2], Selma Düzenli[3], Ali Tekin[4]

[1]Akçakoca State Hospital, Clinic of Urology, Düzce, Turkiye
[2]University of Health Sciences Turkiye, Kocaeli Derince Training and Research Hospital, Clinic of Urology, Kocaeli, Turkiye
[3]Bolu Abant İzzet Baysal University Faculty of Medicine, Department of Medical Genetics, Bolu, Turkiye
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What's known on the subject? and What does the study add?

The I550V single-nucleotide polymorphism (SNP-rs11567842) has been associated with hypocitraturia and calcium kidney stones. Previous studies have reported that the rs11567842 mutation may be protective against hypocitraturia and kidney stones. However, in these studies, urine levels of oxalate, uric acid, and calcium in stone formers were higher than those in healthy individuals in the control group. This indicates that hypocitraturia cannot be the main factor in those who form stones. The current study investigated the relationship between patients with calcium-containing kidney stones and those with normal and low citrate excretion.

Abstract

Objective: To evaluate the relationship between *sodium citrate cotransporter (NaDC-1)* gene polymorphism and urinary citrate excretion in patients with kidney stones containing calcium.

Materials and Methods: Between June 2009 and August 2011, stone materials obtained from patients treated for nephrolithiasis at the Urology Clinic were examined using X-ray diffraction, and patients with calcium-containing stones (calcium oxalate and calcium phosphate) were identified. Patients were divided into two groups based on their 24-hour urine citrate levels: (1) those with normal urine citrate levels and (2) hypocitraturia. To analyze the rs11567842 mutation in the *NaDC-1* gene, their blood was collected in a Na-EDTA hemogram tube and stored at -40 °C. The genotypes of the cases were determined by analyzing the obtained genomic DNAs in real-time polymerase chain reaction.

Results: Ninety-six patients with calcium-containing nephrolithiasis were eligible for this study, 40 with normal urine citrate levels and 56 with hypocitraturia. The mean 24-hour urine citrate levels in the normal- and hypo-citraturia groups were 773 mg/1.73 m^2/24 hours and 152 mg/1.73 m^2/24 hours, respectively. Citrate measurements revealed a statistically significant difference between the two groups ($p<0.001$). Twenty-four-hour urine oxalate, magnesium, calcium, and uric acid levels did not differ significantly between the groups (all $p>0.05$). *NaDC-1* gene rs11567842 homozygous mutation (GG genotypes) was detected in 4 (10%) of normocitraturia and 4 (7%) of hypocitraturia. The normocitraturia group had a higher mutation rate than the hypocitraturia group, but this difference was insignificant ($p=0.618$).

Conclusion: This study suggests that the *NaDC-1* gene polymorphism does not cause hypocitraturia in calcium-containing kidney stones. Larger studies are needed to understand genetic disorders' impact on low urinary citrate excretion, with patient groups and healthy controls, and a standard diet.

Keywords: Citrate, hypocitraturia, NaDC-1, polymorphism, kidney stone, urolithiasis

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Introduction

Urinary citrate prevents the formation of calcium-containing kidney stones by inhibiting the crystallization and precipitation of calcium, so hypocitraturia, or low urinary citrate excretion, is an essential metabolic risk factor for the formation and recurrence of urinary stones (1). Hypocitraturia ranges from 20% to 60% among patients with calcium-containing kidney stones (2). The mechanisms underlying hypocitraturia in calcium-containing kidney stones still need to be fully clarified. Citrate's intestinal transportation, serum concentration, and filtered load do not differ between patients with kidney stones and healthy volunteers (3-5). But, metabolic abnormalities or a diet high in acid-producing foods affect the renal handling of citrate, resulting in alterations in citrate excretion levels in the urine (6-9). However, hypocitraturia can be observed in patients with calcium-containing kidney stones without any metabolic abnormalities, and despite urine collection being performed with fixed diets to minimize dietary factors in the studies, kidney stone formers still have lower citrate excretion compared to controls (4,5,10). These reports suggest that genetic predispositions play a role in the formation of kidney stones in patients with hypocitraturia (2).

Citrate is reabsorbed in the proximal tubule apical membrane by the Na^+/$citrate^{2-}$ cotransporter, also known as Na^+/dicarboxylate cotransporter (NaDC-1). Therefore, NaDC-1 is a significant determinant of citrate excretion in the urine. The cDNA of the human *NaDC-1* gene contains 12 exons with 1.953 base pairs and encodes 593 amino acids (11-13). The genetic polymorphism of NaDC-1 (I550V or rs11567842) has been reported to be associated with urinary citrate excretion in Japanese patients with calcium stone formation (14). An *in vitro* experiment revealed that the single nucleotide polymorphisms (SNP) - rs11567842 in *NaDC-1* gene affects the function of NaDC-1, as it causes a decrease in protein expression and transport activity (15). Although the effect of the SNP - rs11567842 on citrate excretion has been demonstrated, its association with calcium stone formation remains unclear. In the current study, the relationship between *NaDC-1* gene SNP (I550V/rs11567842) and stone formation was evaluated by analyzing *NaDC-1* gene polymorphism in two separate patient groups with calcium-containing kidney stones and normal or low citrate excretion.

Materials and Methods

Between June 2009 and August 2011, stone materials obtained from patients treated for kidney stones at the Düzce University Faculty of Medicine Hospital, Clinic of Urology were examined using X-ray diffraction, and patients with calcium-containing kidney stones (calcium oxalate and calcium phosphate) were identified. The patients' weight and height were measured, a detailed medical history was obtained, and they were questioned about familial stone formation, recurrent stone formation, receiving treatment for the urolithiasis (surgical or medical), and systemic or metabolic disease. Excluded from the study were patients with any systemic disease (except hypertension), non-calcium component kidney stones, any treatment that could affect acid-base balance, diuretic treatment, and calcium or vitamin C supplements. For metabolic evaluation, serum creatinine, sodium, potassium, calcium, and uric acid levels were measured in each patient, as well as 24-hour urine citrate, oxalate, magnesium, calcium, and uric acid levels. In addition, a urinalysis and culture of the urine were conducted. Patients were instructed to avoid excessive consumption of red meat, salty foods, chocolate, leafy greens, tea, and coffee prior to the 24-hour urine test. Solute excretion in 24-hour urine samples were measured using the photometric method with Ben Biochemical Enterprise™ (CI8820, Milan, Italy) kits in the biochemistry laboratory of Düzce University Faculty of Medicine Hospital. Patients were divided into two groups based on their 24-hour urine citrate levels: normal and low. To analyze the rs11567842 mutation in the *NaDC-1* gene, their blood was collected in a Na-EDTA hemogram tube and stored at -40 °C.

The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the local ethics committee of Düzce University, Turkiye (approval no: 2010/102, date: 30.12.2010).

Real-time Polymerase Chain Reaction (PCR)

DNA isolation and PCR studies were conducted in the Molecular Genetics Laboratory of the Medical Genetics Department at the Bolu Abant İzzet Baysal University Faculty of Medicine Hospital. Genomic DNA was isolated and obtained using the High Pure PCR Template Preparation Kit-Roche™ kit. The genotypes of the cases were determined by analyzing the obtained genomic DNAs in real-time PCR (Light Cycler480 II™) using primers and probes covering the relevant polymorphism. Each sample was classified as wild type (AA), heterozygous type (AG), or homozygous type (GG) based on the results of the analysis

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 15 (IBM, Chicago, IL, USA). A $p<0.05$ indicated statistical significance. The Kolmogorov-Smirnov test was used to determine the normality of the numeric data. The two groups were compared using the Student's t-test for numerical variables and the Pearson chi-square test for nominal and ordinal variables, including genetic analysis results, gender, family history, and positive urine culture.

Results

Ninety-six patients with calcium-containing kidney stones were eligible for this study. Within the scope of the study, patients

were evaluated: 40 patients with normal 24-hour urine citrate levels and 56 patients with low levels. Twenty-four men and 16 women comprised the normocitraturia group, whereas 33 men and 23 women comprised the hypocitraturia group. The mean ages of the normocitraturia and hypocitraturia groups were 44.0 (9-72) and 43.3 (3-70) years, respectively (p=0.84). There were no statistically significant differences between the groups concerning age, gender, body mass index, or positive family history (all p>0.05, Table 1). The normocitraturia group had mean serum creatinine levels of 0.84 mg/dL, while the hypocitraturia group had mean serum creatinine levels of 0.88 mg/dL (p=0.417). Serum calcium and urine pH and density exhibited no statistically significant differences between groups (all p>0.05).

The mean 24-hour urine citrate level in the normocitraturia group was 773 mg/1.73 m^2/24 hours; in the hypocitraturia group, it was 152 mg/1.73 m^2/24 hours. Citrate measurements revealed a statistically significant difference between the two groups (p<0.001). The normocitraturia group had an average 24-hour urine oxalate concentration of 39.2 mg/1.73 m^2/24 hours, while the hypocitraturia group had an average 24-hour urine oxalate concentration of 33.3 mg/1.73 m^2/24 hours. Regarding oxalate measurement, there was no statistically significant difference between the groups (p=0.130). In addition, 24-hour urine magnesium, calcium and uric acid levels did not differ significantly between the groups (all p>0.05). The results of a 24-hour urine analysis (urine volume, oxalate, magnesium, calcium, and uric acid) are shown in Table 2.

Comparing the urine culture results of the normocitraturia and hypocitraturia groups, urine culture positivity was detected in 2 (5%) normocitraturia and 4 (7.2%) hypocitraturia patients. In terms of urine culture positivity, there was no statistically significant difference between the two groups (p=0.665). In 4 (10%) normocitraturia patients and 4 (7%) hypocitraturia

Table 1. Patient characteristics and familial stone formation rates

		Nephrolithiasis with normal citraturia (n=40)	Nephrolithiasis with hypocitraturia (n=56)	p-value*
Age (years)		44.0±15.0	43.3±15.0	0.839
Height (cm)		168.8±7.7	166.9±13.2	0.425
Weight (kg)		75.1±11.1	74.7±13.4	0.903
BMI (kg/m^2)		26.3±3.9	26.9±4.0	0.820
Gender	Male	24 (60)	33 (59)	0.916
	Female	16 (40)	23 (41)	
Familial stone formation	Yes	22 (55)	21 (38)	0.089
	No	18 (45)	35 (63)	

*: To compare mean values, the Student's t-test was used, and Pearson's chi-squared test was used to compare proportional values

Table 2. The outcomes of serum, spot urine, and 24-hour urine collection tests

	Nephrolithiasis with normal citraturia (n=40)	Nephrolithiasis with hypocitraturia (n=56)	p-value
Serum (blood)			
Creatinine (mg/dL)	0.84±0.1	0.88±0.2	0.417
Calcium (mg/dL)	10.1±3.8	9.5±0.5	0.224
Urinalysis			
pH	5.2±0.7	5.1±0.8	0.308
Density	1017±6.0	1016±6.0	0.377
24-hour urine collection			
Volume (mL)	2276±758	2075±925	0.264
Citrate (mg/1.73 m^2/24 hours)	773±301	152±87	**<0.001**
Oxalate (mg/1.73 m^2/24 hours)	39.2±19.5	33.3±18.0	0.130
Magnesium (mg/dL)	4.7±2.2	5.0±2.2	0.527
Calcium (mg/dL)	9.6±5.2	9.9±6.0	0.810
Uric acid (mg/dL)	23.4±9.6	23.8±12.5	0.859

Bold values denote statistical significance at the p<0.05

Table 3. Genotype frequencies of *NaDC-1 (SLC13A2/I550V)* gene polymorphism			
Genotypes, n, (%)	**Nephrolithiasis with normal citraturia n=40**	**Nephrolithiasis with hypocitraturia n=56**	**p-value**
AA genotype	20 (50)	29 (51.8)	0.618
AG genotype	16 (40)	23 (41.1)	
GG genotype (rs11567842 mutation)	4 (10)	4 (7.1)	

patients, the *NaDC-1* gene rs11567842 homozygous mutation (AA) was found. The hypocitraturia group had a higher mutation rate than the normocitraturia group, but this difference was not statistically significant (p=0.618, Table 3).

Discussion

The approximately 23.8 kb human *NaDC-1* gene is located on chromosome 17 p11.1-q11.1 and comprises 12 exons (16). The *NaDC-1* gene encodes the 592-residue NaDC-1 protein, which shares 54% and 43% sequence identity with the human NaCT and NaDC-3 proteins (17). The kidney and small intestine express NaDC-1 predominately. More specifically, NaDC-1 is localized on the apical membrane of renal proximal tubular and small intestine cells where it reabsorbs tricarboxylic acid cycle intermediates from urine and diet, respectively (18). According to *in vivo* and *in vitro* studies, acidosis stimulates both NaDC-1 function (citrate transport activity) and expression (mRNA and protein levels), whereas alkalosis only affects its citrate transport function (9,19). The primary physiological function attributed to NaDC-1 is citrate elimination in the kidneys. Urinary citrate is essential for preventing the formation of kidney stones by complexing Ca^{2+} ions, thereby preventing urine supersaturation and precipitation of Ca^{2+} salts-based calculi. This suggests that NaDC-1 is involved in the pathophysiology of kidney stones (18). Furthermore, the human *NaDC-1* gene I550V-SNP has been genetically related to hypocitraturia and kidney stones (14). Since citrate reabsorption by NaDC-1 determines urinary citrate concentration, inhibition of NaDC-1 is expected to increase urinary citrate excretion. However, potent specific NaDC-1 inhibitors are not yet available. A specific inhibitor could clarify the connection between NaDC-1-mediated urinary citrate excretion and calcium nephrolithiasis, and it could have been used as a treatment agent today. Therefore, additional research and evidence are required to conclude that NaDC-1-mediated hypocitraturia is a fundamental mechanism underlying calcium-containing kidney stones.

A SNP (pI550V/rs11567842) in the *NaDC-1* gene causes a change from isoleucine (I) to valine (V) at amino acid 550th. Three genotypes have been identified in SNP. These are AA (wild type), AG (heterozygous mutant), and GG (homozygous mutant) genotypes. In the present study, 51.8%, 41.1%, and 7.1% of individuals with hypocitraturia had the AA, AG, and GG genotypes, respectively. Stone formers with normal citrate levels comprised 50% AA, 40% AG, and 10% GG genotypes. There was no statistical difference in the frequency of genotypes between groups.

Okamoto et al. (14) evaluated the effect of I550V-SNP on hypocitraturia and calcium stone formation and found that those with AA genotype had lower urinary citrate levels than other genotypes. They also detected AA genotypes at a higher rate in stone-forming patients than in healthy individuals. They demonstrated that the I550V polymorphism is associated with hypocitraturia and kidney stones and that having the AA genotype may be a risk factor for hypocitraturia and kidney stones. However, according to this study's 24-hour urine examination results, stone-forming groups had lower pH and citrate levels and higher calcium, oxalate, and uric acid levels than stone-free groups. The presence of these values, which may be a risk factor for the formation of kidney stones, makes it difficult to interpret the findings correctly, and it may not be accurate to state that stone formation is only due to low citrate levels.

Udomsilp et al. (20) evaluated the impact of the I550V polymorphism on hypocitraturia and recurrent calcium stone formation. They discovered that individuals with the AA genotype had lower urinary citrate levels than those with other genotypes. However, there was no noticeable distinction in the frequency of genotypes between stone-forming individuals and healthy individuals. They concluded that having the AA genotype is associated with hypocitraturia and may be a risk factor for kidney stone formation. This study did not report urinary levels of calcium, oxalate, and uric acid. In the present study, all I550V polymorphism-examined patients had calcium-containing kidney stones. In addition, pH, calcium, oxalate, and uric acid levels in urine were similar between groups. The current study design minimizes the influence of confounding variables and lacks the limitations of previous research.

Pajor and Sun (15) examined the effect of SNPs on NaDC-1 expression and function using the COS-7 cell heterologous expression system. They showed that the I550V variant had an increased sensitivity to lithium inhibition, although there was no significant effect on protein expression. They also concluded that all SNP mutations reduced the transport activity or expression of NaDC-1, leading to reduced intestinal and renal absorption

of citric acid cycle intermediates. In the current study, although those with *NaDC-1* gene rs11567842 mutation (GG genotype) were detected less frequently in the hypocitraturia group than those with normal urine citrate levels, this difference was not statistically significant. However, when evaluating the findings of our study, it must be kept in mind that no strict diet was adhered to during the research. As is well known, environmental factors, particularly foods that make the urine more acidic, also influence the urinary citrate excretion of individuals with normal renal function. Consequently, environmental factors cannot be ruled out as a cause of hypocitraturia in these patients.

Study Limitations

This study's most significant limitations are its small sample size and lack of a healthy control group. Comprehensive studies with larger patient groups, healthy controls, and a strict diet are required to clarify this relationship.

Conclusion

These results do not support a role for *NaDC-1* gene polymorphism in the etiopathogenesis of hypocitraturia in calcium-containing idiopathic kidney stones. Important limitations of this study include the absence of healthy control subjects and a standard diet. To further elucidate the role of genetic disorders in low urinary citrate excretion, comparative studies with larger patient groups and healthy controls, excluding environmental effects (with a standard diet), should be conducted.

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 Düzce University, Turkiye (approval no: 2010/102, date: 30.12.2010).

Informed Consent: The authors declare that they have no relevant financial.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Apparent Diffusion Coefficient of Variation (ADC_{cv}): A New Biomarker for Aggressiveness in Prostate Cancer?

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

Apparent diffusion coefficient (ADC_{cv}) could be benefical in improving future prostate cancer imaging. The validation of ADC_{cv} as an imaging biomarker may have important consequences for the detection and assessment of aggressiveness of prostate cancer.

Abstract

Objective: The aim of the study was to evaluate which apparent diffusion coefficient (ADC) parameter can predict the aggressiveness of prostate cancer in patients confirmed by radical prostatectomy specimens.

Materials and Methods: Patients who underwent radical prostatectomy for prostate cancer between October 2019 and June 2023 were retrospectively reviewed. Patients were separated into two groups based on the International Society of Urological Pathology (ISUP) classification, and the correlation between ADC metrics and ADC parameters, including ADC_{mean}, $ADC_{coefficient\ of\ variation}$ (ADC_{cv}), and ISUP classification the aggressiveness of prostate cancer was studied.

Results: Fifty-seven patients were included in the study. Patients were evaluated as low-risk (group 1) (n=40), and high-risk (group) (n=17). ADC_{mean} values for the two groups were not significantly different (p=0.218). ADC_{cv} values that can demonstrate tumour heterogeneity index were higher in group 2 than in group 1 (p<0.001). Multivariate analysis revealed that extracapsular extension, positive surgical margin, and ADC_{cv} values indicated tumour proliferation, whereas seminal vesicle invasion, prostate-specific antigen levels, and body mass index were not correlated with ISUP grade groups.

Conclusion: ADC_{cv} is a promising new biomarker for tumour aggressiveness in prostate cancer.

Keywords: Diffusion weighted imaging, apparent diffusion coefficient, ISUP grade group, prostate cancer, prostatectomy

Introduction

Prostate cancer is a leading cause of disease and death among men, with 1.6 million men being diagnosed annually and 366.000 men dying from the disease (1). In recent years, imaging has taken on more significance in the detection, staging, posttreatment evaluation, and detection of prostate cancer recurrence. Magnetic resonance imaging (MRI) offers the most exact representation of zonal anatomy and the highest soft tissue resolution of any imaging technique to date, allowing for a thorough anatomic evaluation of the prostate. The most effective MRI approach is multiparametric MRI (MpMRI). MpMRI combines T1-weighted and multiplanar T2-weighted images and functional diffusion-weighted imaging with apparent diffusion coefficient (ADC) maps and dynamic contrast-enhanced imaging sequences that can provide information about anatomy and function. Diffusion-weighted imaging (DWI), which uses the random mobility of water molecules to construct ADC maps, allows for both qualitative and quantitative assessments of prostate cancer (2,3). ADC is the net movement of molecules

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over a tissue area per second (mm^2/s) (4). In fact, the typical glandular morphology is changed in prostate cancer, with nests of cancer cells and fibrous stroma displacing the large interstitial gaps and glandular lumens, resulting in a decrease in unrestricted water circulation. Consequently, a high-signal-intensity zone on DWI pictures indicates clinically severe malignancy. In the monoexponential model, the ADC has a mean value that is connected to diffusion. The ADC value has proven to be an effective indicator of cancer aggressiveness, providing quantitative information on tumor characteristics (5). Many studies in the current literature indicate that the mean value of ADC reflects the degree of aggressiveness of prostate cancer (6-8). In contrast, a study that examined the ADC_{mean} and ADC_{ratio} values revealed no association with the aggressiveness of prostate cancer (9). However, there is still some uncertainty in this area, and no agreement has been achieved (6,10). This notion is related to some challenges. First, the ADC can differ greatly due to various factors. These are the b-values employed, MR scanner field strength, patient and coil geometry, temporal fluctuations in the magnetic field, and measurement differences between different readers. Furthermore, non-cancerous tumours, such as benign prostatic enlargement, may have lower ADC values. Consequently, various options beyond ADC_{mean} are needed to determine the aggressiveness of prostate cancer. Therefore, we intended to investigate the efficacy of $ADC_{coefficient\ of\ variation}$ (ADC_{cv}) measurement, a new biomarker of tumour heterogeneity index, in prostate cancer and examine, in a cohort of consecutive patients, the correlation between absolute ADC_{mean} and ADC_{cv} and the International Society of Urological Pathology (ISUP) grade following robot-assisted laparoscopic prostatectomy (RALP).

Materials and Methods

Patient Selection

The local ethics committee accepted this single-center retrospective study conducted between October 2019 and June 2023 and waived the requirement for informed consent (Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board - approval ID: 2023-13/466, date: 17.08.2023) because of the retrospective evaluation of anonymized medical data. The following were the criteria for inclusion: (1) prostate mpMRI collected on a 3.0 Tesla unit and (2) accessible serum prostate-specific antigen (PSA) levels at the time of prostate mpMRI. Patients with motion artifacts and inadequate imagesand a history of androgen deprivation therapy, radiation, or transurethral resection were also excluded. The cohort in our study was divided into two distinct groups based on the final whole prostate specimen obtained following radical prostatectomy. Group 1 was classified as the low-risk group, whereas Group 2 was categorized as the high-risk group. This classification was determined on the basis of the ISUP) grading system related to the pathology findings of the excised prostate specimen.

- Grade Group 1: Very low-grade cancer with well-formed glands (corresponding to Gleason Score 6)
- Grade Group 2: Low-grade cancer with slightly irregular glands (corresponding to Gleason Score 3 + 4 = 7)
- Grade Group 3: Intermediate-grade cancer with irregular and fuzed glands (corresponding to Gleason Score 4 + 3 = 7)
- Grade Group 4: High-grade cancer with fused and poorly formed glands (corresponding to Gleason Score 8)
- Grade Group 5: Very high-grade cancer with no gland formation, characterized by sheets of tumor cells (corresponding to Gleason Score 9-10)

Specifically, Grade 1 and Grade 2 are considered low risk and assigned to Group 1, whereas Grade 3, Grade 4, and Grade 5 are categorized as high-risk and assigned to Group 2. This classification allows for the differentiation of prostate cancer cases based on their perceived risk levels according to the ISUP grading system. Table 1 shows patient distribution according to the ISUP grade

MRI Protocol

All patients underwent prostate mpMRI using a Siemens Medical Systems Skyra 3.0 Tesla MRI scanner with an 18-channel phased-array coil (Skyra, Siemens Medical Systems, Erlangen, Germany). Butylscopolamine bromide (Buscopan, Boehringer Ingelheim) was administered before all exams to reduce bowel motions, which could cause motion artifacts. The index lesion was assessed using prostate mpMRI by an abdominal radiologist with 10 years of experience. Our institution's mpMRI protocol for prostate imaging included tri-planar T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging. Echo-planar imaging in axial planes with b-values of 50, 500, 1.000, and 1.400 s/mm^2 was used for DWI. This was accomplished by merging data from all accessible b-values and fitting them using a least-squares monoexponential fitting

Table 1. Patient distribution according to ISUP grade groups

ISUP Grade groups	Number of patients	Percentage (%)
1	16	28.1
2	24	42.1
3	10	17.5
4	2	3.5
5	5	8.8

technique. This approach represents the diffusion properties of prostate tissue.

Image Analysis

To accurately evaluate prostate cancer lesions with true-positive findings, a free-form region of interest (ROI) was constructed. The ADC maps were generated automatically using the software (Syngo Via, Siemens Medical Systems) used in our facility. The radiologist evaluated the ADC maps and manually delineated an ROI on the tumour visible on the ADC map. Where ROI was entered, the software automatically calculated ADC_{mean} and standard deviation.This ROI, known as $ADC_{mean,}$ corresponded to the interior margin of the entire tumour outline. On the tumour segment with the greatest cross-sectional area, ROIs were carefully established. ADC_{cv} was computed using the formula Standard Deviation/ADC_{mean} on the ADC map, according to a previous study (11). The measurements of ADC_{mean} and ADC_{cv} are depicted in Figure 1. To ensure that only the tumor region was examined, normal tissue outside the borders of the lesion was excluded.

Statistical Analysis

To determine the normality of variable distribution, the Kolmogorov-Smirnov test was used. The chi-square test for categorical data was used to evaluate patient characteristics and postoperative pathological outcomes. For regularly distributed data, the Student's t-test was employed, whereas for non-normally distributed data, the Mann-Whitney U test was used. Variables less than 0.05 in the univariate analysis were investigated further in a multivariate logistic regression analysis to identify high-grade prostate cancer. In addition, receiver operating characteristic curve (ROC) analysis was performed on ADC_{cv} to determine its sensitivity, specificity, area under the curve (AUC), and cut-off value (Figure 2).

The data were analyzed using SPSS 22.0 (IBM SPSS Corp., USA). Variables less than 0.05 were accepted as statistically significant.

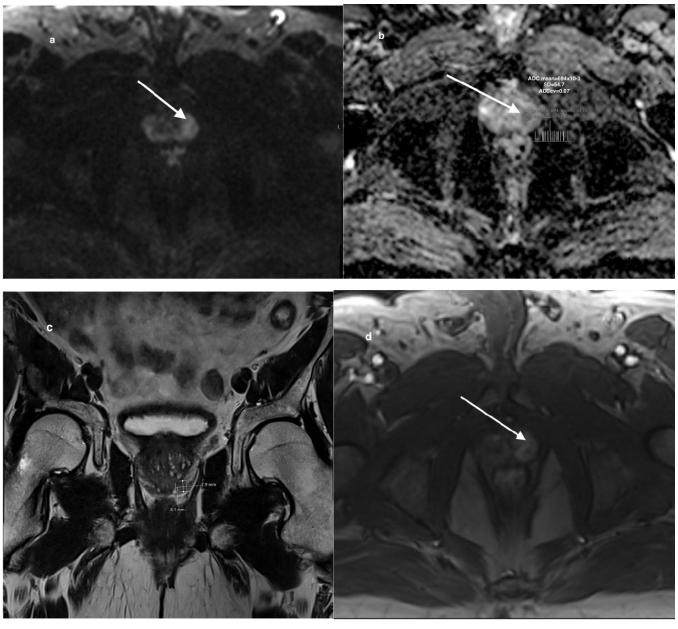

Figure 1. A 65-year-old patient with ISUP Grade Group 2 (Gleason Score 3+4) prostate cancer. On diffusion-weighted image (a) the tumour has hyperintensity signal. The apparent diffusion coefficient (ADC) map (b) demonstrates ADC_{mean} ($694x10^{-6}$) ADC_{cv} (54,7/694= 0.07) (white arrows). T2-weighted coronal (c) and post-contrast T1-weighted axial (d) images (white arrow) depict 8 mm diameter tumour

Results

Overall, 57 men with prostate cancer were enrolled in our dataset (age, 62.2±6.5; range, 51-76 years). The detailed patient distribution according to ISUP Grade Groups is shown in Table 2.

ADC_{mean} inverse correlation with ISUP (p=0.218) while ADC_{cv} showed a strong positive correlation with ISUP grade groups (p=0.041). Detailed information regarding the ADC metrics of the study sample is shown in Table 3. When ROC analysis was performed by evaluating ADC_{cv}, the threshold value was defined as 0.081 with 55% sensitivity and 82% specificity (p=0.010, AUC: 0.716).

However, bladder invasion, extracapsular extension (ECE), and positive surgical margin were correlated with ISUP grade groups, whereas seminal vesicle invasion, prostate-specific antigen (PSA) levels, and body mass index (BMI) were not correlated with ISUP grade groups. Table 2 demonstrates the laboratory and pathological findings of patients.

ADC_{cv} value of low grade group and high-grade groups were 0.099 0.099±0.06 and 0.174±0.12 respectively (p=0.041***). Figure 3 depicts the ADC metrics of a patient categorized as ISUP Grade

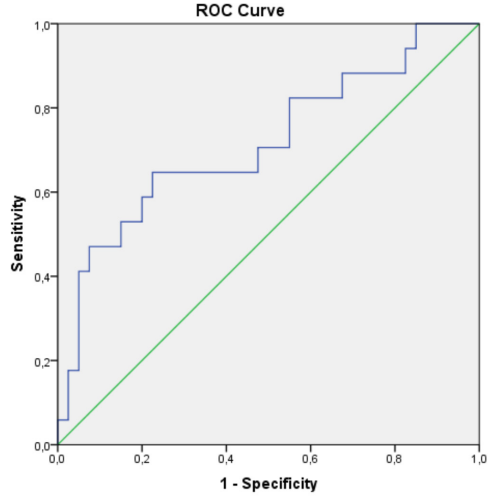

Figure 2. Receiver operating characteristic (ROC) analysis curve of high-risk prostate cancer detection with ADC_{cv}, AUC: 0.716 (p<0.010)

Group 3. ADC_{mean} value of low grade group and high grade group was 760.6±201.8×10^{-6} mm^2/s and 633.4±182.3×10^{-6} mm^2/s, respectively (p=0.218). In 13 patients (22.8%), surgical margins were positive. Seminal vesicle invasion was detected in 16 patients (28.1%), whereas bladder neck invasion was observed in 8 patients (14%). Extraprostatic extension was in 22 patients (38.6%). The ADC results for the two groups are shown in Table 3.

Discussion

In the present study, we validated the utility of two ADC parameters (ADC_{mean} and ADC_{cv}) as imaging biomarkers in patients who underwent 3-T mpMRI and radical prostatectomy with WM histopathologic analysis correlation.

Indeed, multiple previous studies with different cohorts have compared ADC_{min}, ADC_{mean}, and ADC_{ratios} in prostate imaging and reported conflicting results with varying endpoints. These studies have evaluated different clinical outcomes or endpoints, such as tumor detection, differentiation of malignant and benign lesions, and prediction of tumor aggressiveness or treatment response (10,11-13). The inconsistency of these studies' conclusions highlights the intricacy and diverse nature of prostate imaging, as well as the difficulties in establishing a clear superiority of one ADC parameter over another.

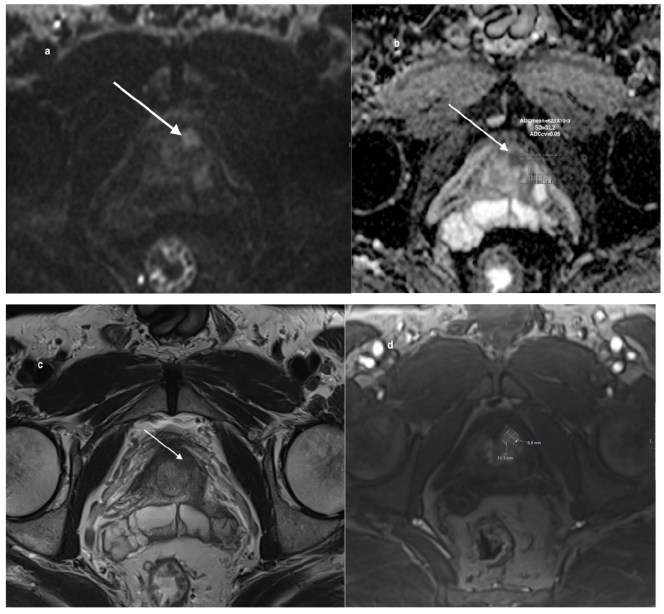

Figure 3. Prostate cancer ISUP Grade Group (Gleason score 4+3). The diffusion-weighted image (a) and ADC map (b) reveal an ADC_{mean} of 623 X 10^{-6} and an ADC_{cv} of 32/623 = 0.05 (white arrow). T2-weighted axial (c) and post-contrast T1-weighted axial (d) images depict a tumour with a 10 mm diameter

Table 2. Laboratory and pathological findings of patients according to ISUP grade groups

Parameters	ISUP 1-2	ISUP 3-4-5	P*	P**
	n=40	n=17		
Age (years)	61.47±6.18	63.94±7.2	0.202	
PSA (ng/mL)	8.31±5.83	13.72±15.84	0.120	
BMI (kg/m^2)	28.2±3.9	29.55±5.3	0.543	
Blood loss (cc)	318.7±178.1	288.2±182.4	0.539	
Seminal vesicle invasion	9 (22.5%)	7 (41.2%)	0.201	
Bladder neck invasion	1 (2.5%)	7 (41.2%)	**<0.001**	0.237
Extraprostatic extension	8 (20%)	14 (82.4%)	**<0.001**	**0.004**
Positive surgical margin	3 (7.5%)	10 (58.8%)	**<0.001**	**0.019**

*Univariate analyses
**Multivariate analyses
PSA: Prostate-specific antigen, BMI: Body mass index, ISUP: International Society of Urological Pathology

Table 3. ADC parameters according to ISUP grade groups

ADC parameters	ISUP 1-2 n=40	ISUP 3-4-5 n=17	P*	P**
ADC_{cv}	0.099±0.06	0.174±0.12	**0.010**	**0.041**
ADC_{mean}	760.6±201.8	633.4±182.3	**0.009**	0.218
SD	72.02±43.44	101.56±56.48	0.052	

ADC_{cv}: Apparent diffusion coefficient of variation, SD: Standard deviation

Recent publications have compared conventional ADC parameters with ADC_{ratios}. Many new studies have shown that ADC_{ratios}, particularly the ADC_{mean} ratio concerning the conventional parameter, exhibit the strongest negative correlation with prostate cancer aggressiveness (14).

Variability in study designs, patient populations, imaging protocols, and analysis methodologies may have contributed to the disparate findings. The inherent heterogeneity of prostate cancer, with its diverse histological subtypes and varying degrees of aggressiveness, further complicates the interpretation of ADC measurements.

Given the contradictory findings in the literature, additional research involving larger and more diverse cohorts is required to determine the clinical significance and optimal use of $ADC_{minimum}$ ($ADC_{min)}$ and ADC_{mean} in prostate imaging applications.

These studies should aim to address the limitations of prior research and establish robust correlations between these ADC parameters and clinically relevant endpoints, with the goal of improving diagnostic accuracy and patient management in prostate cancer. ADC_{min} and ADC_{ratio} (reported as the ratio of tumour and nontumour ADC values) are two of the metrics that have been investigated. According to studies, all of these variations have a substantial connection with the Gleason score; however, there are gaps in clinical relevance and aggressiveness. In the current study, we used 3-T mpMRI metrics and histopathological results acquired after radical prostatectomy to validate the usefulness of ADC_{cv} as an imaging biomarker.

The ADC_{cv} value represents a novel texture parameter that is utilized in cancer. Tissue heterogeneity has been proposed as a basis for a tumour biomarker in cancer investigations. Tissue heterogeneity is an emerging hallmark of tumour. Although numerous methods for measuring tissue heterogeneity using textural analysis tools have been described, they are frequently complicated and require sophisticated software (15). Stein et al. (11) reported that ADC_{cv} is a simple-to-calculate statistical parameter that indicates related variation. They evaluated the ADC_{cv} and maximum standardized uptake value (SUV_{max}) values using positron emission tomography MRI of liver metastases. As the outcome of this investigation, it was discovered that the SUV_{max} value and the ADC_{cv} value have a positive link. Overall, the study findings suggest that the ADC_{cv} value obtained from diffusion-weighted MRI can serve as a usef biomarker for predicting tumor aggressiveness in liver metastases. This information could aid in cancer investigations and treatment planning for patients with liver metastases. Sokmen et al. (16) confirmed with MRI fusion prostatic biopsy that ADC_{cv} is a tissue texture parameter in prostate cancer. However, our difference from their study is that our study was conducted after radical prostatectomy.

The multivariate analysis conducted in our study revealed that the ADC_{cv} parameter effectively predicts tumor aggressiveness. According to our findings, the ADC_{cv} parameter was suitable for regular inclusion in mpMRI reports. This parameter was considered easy to measure, facilitating its integration into radiology reports. Furthermore, integrating ADC_{cv} measurements into routine practice did not significantly increase the workload of radiologists. Throughout our investigation, ADC_{cv} demonstrated the highest efficacy in predicting tumor aggressiveness. Considering the ADC_{cv} cut-off value, it should be noted that prostate cancer may be highly aggressive with ADC_{cv} values higher than 0.081. Resection and lymph node dissection should be performed more carefully in these patients.

Nevertheless, it is important to note that other factors such as bladder invasion, extracapsular extension (ECE), and positive surgical margins were also correlated with ISUP grade groups.

Study Limitations

Our research has a few limitations. First, this is a retrospective study, and the data were collected from past medical records and imaging reports. This design has inherent limitations compared with prospective studies, where data are collected in real time. The study was conducted with a limited number of participants, which can impact the generalizability and statistical power of the findings. Due to the small sample size and retrospective nature of the study, there might be biases in the selection of participants, leading to a non-representative sample.

Overall, this study emphasizes the need for further research to enhance the understanding of ADC measurements in prostate cancer and their potential clinical applications. By addressing the study limitations and establishing stronger correlations, ADC values could be used more effectively for diagnostic accuracy and patient management in prostate cancer.

Conclusion

The statement suggests that the speed and accuracy of ADC_{cv} could be advantageous in enhancing future prostate cancer screening methods. The validation of ADC_{cv} as an imaging biomarker may have significant implications for the detection and assessment of prostate cancer aggressiveness, potentially aiding in more accurate diagnosis and treatment planning for patients. Our findings suggest that the ADC_{cv} parameter holds promise as a valuable tool for characterizing prostate cancer aggressiveness. Its simplicity of use and potential to provide clinically meaningful information make it a compelling candidate for integration into routine clinical practice.

Ethics

Ethics Committee Approval: The local ethics committee accepted this single-center retrospective study conducted

between October 2019 and June 2023 (Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation Board - approval ID: 2023-13/466, date: 17.08.2023).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL RESEARCH
General Urology

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Long-Term Outcomes of Pyeloplasty in Children with Poorly Functioning Kidneys

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

The studies of poorly functioning kidneys in children are limited. This article adds to the literature, long-term results on the renal function and parenchymal thickness of patients with poorly functioning kidneys in children, and details on those patients according to age.

Abstract

Objective: This study aimed to determine the efficacy and long-term outcomes of pyeloplasty in children with poorly functioning kidneys.

Materials and Methods: Twenty-six patient charts were reviewed who underwent pyeloplasty with poorly functioning kidneys from 2008 to 2020. Patients were divided into two groups based on DRF; Group 1: 0-10%, and Group 2: between 10-30%. Patient demographics, preoperative and postoperative anteroposterior diameter (APD), parenchymal renal thickness (PT) ratio, and differential renal function (DF) were analyzed to confirm the postoperative benefits and potential predictors of renal functional recoverability. The parameters of patients younger than one year of age were also compared to those of older patients.

Results: The renal function of 12 of 26 patients' was <10% (mean DF 4.9±3.8%) (Group I). The DF of the other 14 patients was between 10-30% (mean DF 22.6%) (Group II). Sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT ratio, and UTI were also evaluated using multivariate analysis, but none of the parameters were found to be predictable for renal function improvement (p>0.0001). The postoperative PT ratio and postoperative DF were increased in Group II, but not in Group I. DF and PT ratios also improved in Group II in patients younger than 1 year of age (p=0.014, p=0.032 respectively). Hypertension was detected in 5 patients (41.6%) during follow-up in Group I.

Conclusion: Pyeloplasty is recommended considering parenchymal and DF recovery in patients younger than 1 year of age with a DF of 10-30%. However, in patients with <10%, parenchymal or DF improvement was unsatisfactory, even in the late renogram.

Keywords: Differential renal function, poorly functioning kidney, parenchymal renal thickness, pyeloplasty, ureteropelvic junction obstruction

Introduction

Management of children with ureteropelvic junction obstruction (UPJO) and poorly functioning kidneys remains controversial. However, the definition of poorly functioning kidneys remains unclear. Some investigators consider a DF below 30% as poorly functioning (1), while others believe a DF of 20% (2,3). Stock et al. (4) concluded that patients with UPJO with a differential function of less than 35% have significant histological changes on biopsy and a low probability of postoperative improvement in DF (4). Ortapamuk et al. (5) reported no improvement in adult patients with DF <30%. Thus, we included patients with a kidney function of less than 30% in our study.

Poorly functioning renal units directly underwent pyeloplasty without prior placement of a PCN in our center for nearly

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15 years. In the present study, we reviewed this decision and determined the long-term efficacy of pyeloplasty in patients with poorly functioning kidneys as well as the factors that could predict improvement in DF after pyeloplasty.

Materials and Methods

We retrospectively reviewed the medical records of patients with UPJO and poorly functioning kidneys between 2008 and 2020. Patients with DF >30%, bilateral UPJO, solitary kidney, vesicoureteral reflux, ureterocele, megaureter, distal ureteral obstruction, bladder outlet obstruction, multicystic dysplastic kidney, or patients with less than 1 year follow-up period and incomplete investigations were excluded from the study. A diagnosis of UPJO was made with increased APD and thinning in parenchymal thickness on ultrasonography (USG) and the presence of an obstructive pattern (poor response to frusemide with a plateau and an up-raising curve with no response) on 99mTc-MAG3 scintigraphy. AP diameters were measured by a pediatric radiologist at the parenchymal edge in the transverse plane. The last imaging before surgery was included in the study.

Patients were divided into two groups: split renal function <10% (Group I) and 10-30% (Group II). Patient demographics, anteroposterior diameter, PT ratio (the ratio of the PT of the involved side to that of the contralateral side was measured as follows: involved side PT/contralateral side PT) on USG and postoperative drainage pattern on the 99mTc-MAG3 renogram were analyzed retrospectively and compared among the groups. The parameters that may affect recovery (sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT ratio, and UTI) were also evaluated using multivariate analysis. Preoperative and postoperative parameters were compared between the groups to clarify operative benefits. Patients were grouped by age (younger than one year of age and older than one year of age) to reveal the role of age in DF and PT recovery.

Percutaneous nephrostomy (PCN) was performed only to treat pyonephrosis or a huge renal pelvis before the operation. Open Anderson Hynes' pyeloplasty with a mini-incision was performed in all patients. Postoperative renal ultrasonography and clinical visits were performed at 1, 3, 6, and 12 months. A Tc-99m MAG3 renogram was routinely performed in all patients one year after surgery. The results of the cases in which scintigraphy was repeated for various reasons in the late follow-up period (2-8 years) were evaluated and compared with the postoperative results to determine whether there was any long-term improvement in DF. Since this was a retrospective study, the reasons for requesting late Mag III scintigraphy could not be determined.

Statistical Analysis

Data are presented as frequencies and percentages for categorical variables and medians for continuous variables. Comparisons between groups were performed using the chi-square test for qualitative variables and the Mann-Whitney U test for quantitative variables. Spearman's correlation analysis used coefficients for those with a skewed distribution. Binary logistic regression analysis was used for multivariate analysis. All reported p-values were 2-sided, and $p<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS Statistics 20.0.

Results

The case records of the 26 patients were analyzed (Table 1). 12 of the 26 patients' DF was <10% (Group I). The median age of the operation was 72.5 (4-156 months) months, the mean DF

Table 1. Comparison of the group's demographics, preoperative parameters and complications

	Group I	Group II	p-value
Number of the patients	12	14	
Age (month)	72.5	16	**0.009**
<1 year of age	4	10	
Laterality (L/R)	9/3	8/6	0.340
Antenatal diagnosis	3	9	**0.045***
PCN	2	1	
Preop DF (%)	4.9±3.8%	22.6±5.6	**<0.001**
Preoperative APD	30.7±16	43.7±17.2	0.076
Preoperative PT ratio	0.31±0.16	0.36±0.18	0.487
Complication (reop)	-	1	
Hypertension	5	0	**0.007***
UTI	8	4	0.052*
Follow-up (year)	9.8±2.8	6.5±3.8	

Mann-Whitney U test was used.* A chi-square test was used (a significance level of $p<0.05$)

was 4.96±3.8%, and the mean follow-up was 9.8±2.8 years (6-13 years). In the other 14 patients (Group II), DF was-10-30% (median age 16 months, mean DF 22.6±5.6%), and mean follow-up was 5.2±2.11 years (2-10 years). In Group I, the presenting symptoms were ANHN in 3 patients, abdominal pain in 4, palpable mass in 1, and UTI in 2. In Group II, the presenting symptoms were ANHN in 9, minor abdominal pain in 3, abdominal trauma in 1, and UTI in 2 cases.

99mTc-MAG3 scintigraphies of all patients before the operation showed a poor response to frusemide with a plateau and an up-raising curve with no response. After the operation, good drainage or moderately delayed drainage after frusemide was observed in all patients, except one who underwent redo pyeloplasty.

Three patients underwent percutaneous nephrostomy before the operation (pyonephrosis in 2, giant hydronephrosis in one). One patient was admitted to the hospital with a grade 4 renal injury due to minor trauma. A double-J stent was first inserted in this patient, and he underwent pyeloplasty three months later.

Preoperative APD and preoperative PT ratios were not statistically significant among the groups (Table 1), and parameters that may affect recovery (sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT, PT ratio, and UTI) were also evaluated, but none of the parameters were found to be significant (p>0.0001). However, a negative correlation was found between operative age and postoperative DF (Figure 1).

In Group I, the postoperative drainage pattern and APD of the patients improved, but DF and PT did not (Table 2). In Group II, PT ratios, APD, and DF were significantly improved during follow-up, in addition to the drainage patterns on 99mTc-MAG3 scintigraphy (Table 2).

Late 99mTc-MAG3 scintigraphy (2-8 years) was present in six patients in Group I and 11 patients in Group II. In Group II, DF remained the same in three of the cases with late 99mTc-MAG3 scintigraphy, while a slight decrease was found in eight of them compared to those performed in the postoperative 1st year. There was no long-term improvement in the DF (mean 6.7±4.7%) of the patients in Group I, as in the postoperative scans.

The patients in Group I were older (p=0.009). 75% of the patients in Group II were diagnosed antenatally (p=0.045) (Table 1). When the cases in Group II were classified according to age, the DF and PT ratios improved significantly in patients younger than 1 year of age (p=0.014, p=0.032 respectively) (Table 3). This improvement was not observed in older cases. On the contrary, although there was no significant increase in parenchymal thickness in patients older than 1 year of age in Group I (p=0.932), an improvement in DF was detected (p=0.012) (Table 3).

The perioperative and early postoperative course was uneventful. Anesthesia-related complications, including infantile age, were not observed. None of the patients had acute obstruction, urinary leakage, or unexpected readmissions. The success rate of the pyeloplasty was 96.1%. Except for one patient in Group

Table 2. Comparison of preoperative and postoperative DF, APD, and PT ratios in Group I and Group II

		Preoperative mean ± standard deviation	Postopertavite mean ± standard deviation	p-value
Group I	DF (%)	4.96±3.8	6.9±4.7	0.247
	PT ratio	0.31±0.16	0.27±0.20	0.875
	APD	30.7±16.0	12.2±11.4	**0.019**
Group II	DF (%)	22.6±5.6	27.5±10.9	**0.022**
	PT ratio	0.36±0.18	0.62±0.23	**0.007**
	APD	43.7±17.2	9.7±4.3	**0.001**

Table 3. Distribution of preoperative, postoperative DF and PT ratios by age among groups

	Age (year)		Preoperative mean ± standard deviation	Postoperative mean ± standard deviation	p-value
Group I	<1	DF (%)	6.0±4.8	3.25±2.7	0.109
		PT ratio	0.25±0.05	0.21±0.15	0.715
	>1	DF (%)	4.4±3.5	8.75±4.5	**0.012**
		PT ratio	0.34±0.18	0.31±0.22	1.000
Group II	<1	DF (%)	24.3±4.7	31.0±10.3	**0.014**
		PT ratio	0.39±0.17	0.66±0.24	**0.032**
	>1	DF (%)	18.3±5.9	19.0±7.8	0.715
		PT ratio	0.29±0.21	0.51±0.18	0.144

II who underwent redo pyeloplasty, the obstruction resolved postoperatively in all patients, as evidenced by a better drainage pattern on 99mTc-MAG3 renogram and a reduction in APD. The obstruction was relieved after the second operation in this patient, and DF improved during follow-up. Five patients in Group I developed hypertension that required medication after the operation; in Group II, no patient developed hypertension (p=0.007) (Table 1). Recurrent postoperative urinary tract infections (more than two) were less common in Group II but were not statistically significant.

Renal function improvement >5% was detected in two patients in Group I (16.6%) and in six patients (42.8%) in Group II postoperatively. DF improved by >5% in only 30.7% of the patients. The mean improvement in DF in Group I and Group II was 4.18% (0.5-13%), and 8.05% (2-20%), respectively.

Discussion

Several studies have been conducted both in favor of and against the preservation of poorly functioning kidneys. Early reports favored nephrectomy, especially if DF was <10%. Gupta recommended most of the poorly functioning UPJO kidneys show improvement in function and that not all such kidneys should be removed without a trial of PCN (6). Singh reported renal function improvement in only 24.1%, no improvement in 44.8%, and deterioration in 31.0% of older children after PCN replacement (7). However, PCN can cause infection, risk dislodgement, and require secondary scintigraphy.

In recent years, many authors have recommended renal salvage over nephrectomy even if DF <10% (1,2,8). Therefore, in the last decade, especially in infants, most pediatric urologists have preferred to perform pyeloplasty (1). Lone recommended performing a pyeloplasty straightaway to preserve the kidney, which is much easier and feasible without prior PCN (9). In this study, renal units with <30% split function directly underwent pyeloplasty without prior placement of a PCN, except in three patients because of pyonephrosis in two patients and giant hydronephrosis in one patient.

Grimsby et al. (10) claimed that the pyeloplasty success rate is low in patients with poorly functioning kidneys. However, impaired DF was not associated with a high incidence of complications or failure rates in this study, similar to those in the literature (9). Anesthesia-related complications were not observed, including infantile age in our series. There were no patients with acute obstruction, urinary leakage, or unexpected readmissions. The absence of these complications in the early postoperative period may be related to the routine use of intraureteral stents. However, urinary infections after pyeloplasty were not uncommon, and five patients in Group I experienced hypertension, although they could be controlled with medication (Table 1).

Recent reports seem to agree that DF can markedly improve in patients with poorly functioning kidneys (2,11-14) after pyeloplasty. Bansal et al. (1) reported a 14% mean increase in DF in patients with DF <30%, and a 13.9% mean increase in DF in patients with DF <10% after pyeloplasty. Wagner et al. (8) reported that a DF of less than 10% was associated with the greatest degree of improvement, but their series included only four patients with less than 10% DF. The DF and PT ratios improved significantly in patients with DF between 10 and 30% in our study. However, our results are not as optimistic as those of previous reports in patients with DF <10%. Similarly, Nayyar et al. (15) reported that pyeloplasty was followed by an improvement in DF in only one-third of the cases. The overall improvement of poorly functioning kidneys' function >5% was found in 30.7% of the patients in our series too, only two patients in Group I (16.6%), and six patients in Group II (42.8%). The mean improvements in Group I and Group II were found 4.18% (0.5-13%), and 8.05% (2-20%), respectively.

Many factors have been studied regarding the degree of improvement after pyeloplasty, such as age, sex, antenatal diagnosis, APD, and PT on USG and preoperative DF (16). In our study, sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT, PT ratio, and UTI were not predictive of DF improvement. Thus, based on our study and published data, it is not possible to predict which patients' PT or DF will improve after pyeloplasty. On the other hand, five of six patients in whom DF improved by >5% were under one year of age in Group II. The patients in Group II were younger than those in Group I and were mostly diagnosed antenatally (Table 1); a negative correlation was found between operative age and postoperative DF (Figure 1).

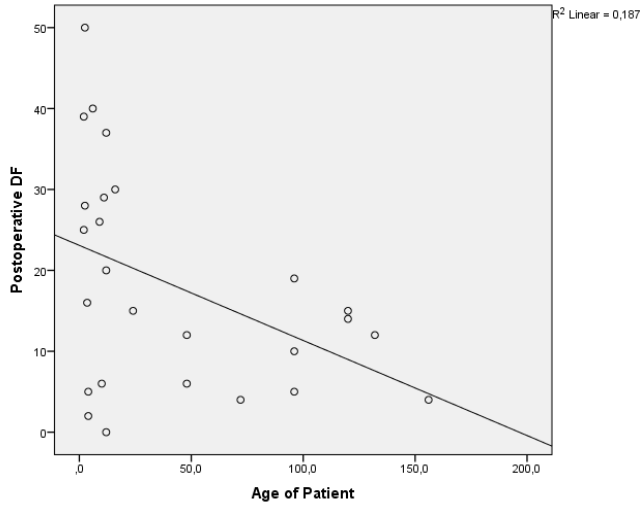

Figure 1. Postoperative differential renal function and the age of the patients (months) have a negative correlation

Gench reported better improvement in DF of the patients with poorly functioning kidneys who were postnatally diagnosed (3). Chandrasekharam et al. (17) reported that infants aged <1 year showed a significant improvement in renal function after pyeloplasty compared with older children. They suggested that the potential recovery of renal function is dependent on the timing of the surgery. When patients were grouped according to their age in our study, it was found that older patients in Group I had significant DF improvement after the operation (Table 3). However, parenchymal improvement was not observed in these patients. In older patients with a DF improvement >5%, infection at the time of diagnosis may have caused false DF impairment. Perhaps after infection treatment and surgery, the actual DF of the patients was measured. DF or PT improvement was not detected in four patients younger than one year of age in Group I (Table 3). Menon et al.'s (2) series, comparing different age groups consistent with our results, showed a significant increase in mean DF in infants with preoperative 10-20%, in older patients with 0-9% DF, but not in infants. This finding, evident in both series, suggests that some infants with DF below 10% may have congenital dysplastic kidneys. In contrast, in patients with DF 10-30% and younger than one year of age, DF and PT improvements were found to be significant. In patients with 10-30% DF and older than one year of age, DF improvement was not observed, and PT improvement was not significant (Table 3). Therefore, considering that there is a negative relationship between age and postoperative DF according to our study, early diagnosis is important in patients with 10-30% DF.

Late scintigraphy was not routinely performed in UPJO patients at our institution and was available in only 61% of cases in this series. In most cases, DF decreased slightly in the late scintigraphies compared to the postoperative values. Menon et al. (2) reported a minor fall in DF with time in their series too and attributed this result to better growth of the opposite kidney and a reduction in the size of the baggy kidney.

Song et al. (18) showed that PT might be useful for distinguishing between the true and false estimation of differential renal function in a study that investigated the changes in DF before and after pyeloplasty in renal units with unilateral UPJO and supranormal function (18). Kim et al. (19) reported that pyeloplasty performed at <1 year of age was a significant factor for recovery of PT (17). However, PT was not mostly reported in studies on low-functioning kidneys (1,2,8,14). PT varied significantly with the age of the children at the time of surgical repair. For this reason, we also evaluated the PT ratios in our study which were defined by Kim et al. (19). Our study showed parenchymal improvement in patients with DF 10-30% and younger than one year of age, and parenchymal thickness may be a better parameter for demonstrating kidney recovery (20,21).

A third treatment option for patients with very poorly functioning kidneys (DF <10%) is to leave the kidney *in situ* if the patient does not suffer from infection or pain. However, no series or comparative studies support this option. In the pediatric age group, the risk of trauma or developing hypertension must be considered. Minor trauma may threaten the life of the patient and complicate surgery in these patients, as in one patient in our series.

Study Limitations

The limitations of the present study are its retrospective design and the small number of cases. However, considering that patients with low-functioning kidneys comprise a small group of UPJO patients, we believe that our series of patients treated in a single center with long-term follow-up is valuable.

Conclusion

The surgical outcomes of pyeloplasty in poorly functioning kidneys have been satisfactory. In our study, a significant improvement was found in PT and DF in patients with 10-30% DF and younger than 1 year of age after pyeloplasty, and a negative correlation was found between postoperative DF and age at surgery. Antenatal and postnatal USG needs to become widespread for the early diagnosis of these patients. Based on our results and recent literature, we recommend pyeloplasty in infants with 10-30% DF. However, in infants with 0-10% DF, our results and the literature are more confusing. Unfortunately, PT and DF did not improve significantly in the early and late terms in kidneys functioning below 10%, especially in infants, even though the obstruction was resolved. It should be kept in mind that have a risk of hypertension in these patients and postoperative renal recovery may not always be as good as desired, and parents should be informed accordingly.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of the hospital with the decision number 746, 2022/15-05 (University of Health Sciences Turkiye, Dr. Behçet Uz Training and Research Hospital Clinical Research Ethics Committee, date: 15.09.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH
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A Pilot Study on Sex Hormones and Cognition in Men with Multiple Sclerosis

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

A relationship between sex hormone levels and disease course is known in MS. However, the relationship between sex hormones and both physical and cognitive parameters in male MS patients was mentioned in this study, and for the first time, the AMH hormone was studied in male MS patients. Additionally, the relationship between sexual functions and cognitive tests has also been stated.

Abstract

Objective: The presence of sexual dysfunction in male patients further exacerbates the adverse impressions of multiple sclerosis (MS) on the quality of life. The goal of our study was to evaluate the relationship between sex hormons and disease severity, sexual dysfunction, and cognition in male MS patients.

Materials and Methods: Twenty-eight MS patients and 14 age- and education-matched healthy controls were included in the study. To assess the cognitive status: California verbal learning test, symbol digit modalities test, revised brief visuospatial memory test, trail-making test, and to evaluate sexual function, male sexuel healt questinore (MSHQ) and international index of erectile function (IIEF) scales were used. Serum Anti-Mullerian hormone level, follicle-stimulating hormone, luteinizing hormone, and total testosterone levels were evaluated.

Results: Serum testosterone levels were significantly lower in the MS group than in the healthy group (4.28±1.20 and 4.50±2.24, respectively; p=0.012). Sexual functions were evaluated using the MSHQ and IIEF, and the MSHQ-ejaculation function scores were statistically significantly lower in the patient group than in the control group (p=0.014). Erectile function was assessed using the IIEF. Erectile dysfunction (ED) was detected in 11 (39%) patients, and four patients could not provide semen analysis specimens due to severe ED. Brief visuospatial memory test and California Verbal Learning test scores were statistically significantly lower in the ED group than in non-ED group (p=0.008, p=0.008, and p=0.026).

Conclusion: The importance of sexual functions and hormones during MS has been demonstrated by both laboratory and cognitive tests.

Keywords: Multiple sclerosis, testosterone, cognition

Introduction

Multiple sclerosis (MS) is a chronic autoimmune central nervous system disease that causes cognitive problems along with physical impairment and is often detected in young adults. As with many autoimmune diseases, it is more common in women, but tends to have a more severe course in men. MS harms the quality of life for several reasons (1). The presence of sexual dysfunction, adding to physical problems in male patients in early adulthood, further exacerbates the adverse impact of MS on the quality of life. Sexual dysfunction can assume various forms in male patients, such as reduced libidoand

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erectile/ejaculatory dysfunction, and it is frequently correlated with decreased serum testosterone (2-4). Sexual dysfunction correlate with urinary problems in MS, and sexual functions correlate with both motor and emotional symptoms (5).

An association between low testosterone and high expanded disability status scale (EDSS) scores has previously been shown in MS (6). Studies have reported that testosterone possesses anti-inflammatory and neuroprotective properties, can protect against glutamate toxicity through neurons and is an antioxidant (6,7). Anti-Mullerian hormone (AMH) is a dimeric glycoprotein and is involved in growth and differentiation. AMH released from Sertoli cells from the intrauterine eighth gestational week causes the regression of Mullerian structures in males, while in females, it is released from birth from the granulosa cells in the small antral follicles to both the follicular fluid and the systemic circulation (8).

AMH levels in males are regulated by intratesticular testosterone (9). After puberty, it is released into the seminiferous tubule lumen and is restricted within the testis-blood barrier. Hence, it is detected at higher levels in the seminal plasma than in serum (10,11). Although the relationship between spermatogenesis, testosterone, and AMH remains partially understood, seminal AMH can be a potential non-invasive marker of permanent hypospermatogenesis (12). In women, AMH levels are closely related to follicular reserves (13). The purpose of this study was to examinate the relationship between serum testosterone, serum AMH levels, spermiogram features, and severity of disease, sexual dysfunction, cognition, fatigue, and depression in patients with male MS patients.

Materials and Methods

Patient Enrollment

Male patients aged 18-65 diagnosed with progressive MS (PMS) or relapsing-remitting MS (RRMS) based on the McDonald 2017 MS diagnostic criteria and age-and education level-matched healthy individuals representing the control group were included in this study. The control group were healthy volunteers who applied to the neurology outpatient clinic with complaints such as headache or dizziness and had no chronic disease. The patient group without erectile dysfunction (ED) and the healthy control group were sexually active.

Patients lacking sufficient cognitive levels to provide information about their past histories, using drugs capable of affecting clinical evaluations (antipsychotic medicine use, corticosteroid use in the previous three months, and other neurological/autoimmune or urological diseases), were excluded from this study. Verbal informed consent forms were obtained from all patients and the healthy control group, and ethical approval for this study was granted by the university's ethical committee to which the clinic belonged.

Clinical Assessment

The main aim of our study was to define the tie between the clinical status of patients with MS patients and AMH levels. Therefore, a detailed cognitive evaluation was performed. BICAMS was used because it was validated in Turkish (14); it was easy to use, including the essential cognitive domains retained in MS. Three tests of BICAMS, the California verbal learning test II, the symbol digit modalities test (SDMT), and the revised brief visuospatial memory test, were administered by the same person trained in the administration of neuropsychological tests. Adding to BICAMS, trail-making testing was also implemented to further evaluate executive functions. The presence of depression was evaluated using the Beck depression inventory (BDI), whereas fatigue levels were assessed using the fatigue impact scale (FIS). To achieve standardization, whole cognitive tests were carried out in the same order, in a quiet room and in the morning.

The male sexual health questionnaire (MSHQ) and the international index of erectile function (IIEF) were used to assess sexual functions in the study group. Because serum AMH levels, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and total testosterone levels exhibit a diurnal rhythm, they were measured before 10:00 am to ensure standard and accurate measurement. Routinely investigated serum glucose, complete blood count, and thyroid-stimulating hormone (TSH) levels were also included in the analysis. Study group semen analysis, sperm quality, and numbers were also investigated. Semen analysis data were assessed in compliance with the World Health Organization criteria of a semen volume of 1.5 mL, sperm concentration 15 million/mL, total sperm count 39 million/ejaculate, total motility 40%, normal morphology 4%, and vitality 58%. Serum FSH levels of 1.5-12.4 mIU/mL, LH levels of 1.7-8.6 mIU/mL, PRL levels of 4.6-21.4 ng/mL, and testosterone levels of 2.5-8.4 ng/mL were evaluated as reference ranges. Patients' erectile functions were assessed using the validated, six-question Turkish-language version of the IIEF (15). Each question was scored from 1 (never or seldom) to 5 (always or almost always), and the total scores were recorded. The severity of ED was assessed as severe (total score=0-6), moderate (total score=7-12), mild-moderate (total score=13-18), mild (total score=19-25), or no ED (total score =26-30). The ejaculation function was classified using the Turkish-language version of the short form of the MSHQ, comprising four questions scored between 0 and 5. The first three questions assessed ejaculatory function, frequency, and force (MSHQ-123) (0-15), while the fourth evaluated ejaculation bother (MSHQ-EjD) (0-5) (16). A higher total score for the first three questions was relevant with better ejaculatory function, whereas higher scores on the fourth question were associated with poor ejaculation bother.

Statistical Analysis

The study data were analyzed using the SPSS 22.0 software. The normality of the distribution of continuous variables was assessed both visually and using normal distribution tests. The independent sample t-test was applied to two-group comparisons of normally distributed variables, and the Mann-Whitney U test was applied to two-group comparisons of non-normally distributed variables. Categorical variables were compared using the chi-square tests. This was evaluated using Spearman's correlation analysis since the relationship between continuous variables was not normally distributed. P-values of less than 0.05 were considered statistically significant for all analyses.

Results

Twenty-eight male patients with RRMS-PMS diagnosed with MS based on the McDonald criteria, aged 40.89±10.93 years, and 14 men with no additional disease, aged 36.27±4.86, representing the control group, were included in the study. No difference was determined between the two groups concerning age or education levels (p=0.085 and p=0.262, respectively). The mean age at MS onset was 33.39±1.55 (18-49), and the mean EDSS score was 2.35±1.55 (0-5.5).

The patient and control groups' serum glucose, TSH, FSH, LH total testosterone, and PRL levels were investigated. Serum testosterone levels were statistically significantly lower in the MS group than in the control group (4.28±1.20 and 4.50±2.24, respectively; p=0.012) (Table 1). Testosterone levels were at the lower limit of the normal value in 3 patients in the study group and 1 participant in the control group. The presence of depression in the study group was investigated using the BDI, and no significant difference was observed between the two groups (p=0.152). Fatigue levels were assessed by the FIS, with both subscores and total fatigue levels being compared. The total FIS scores and the physical and social subscores were statistically higher in the MS patient group than in the control group (p=0.037, p=0.008, and p=0.014) (Table 2).

Sexual functions were analyzed using the MSHQ and IIEF, and the MSHQ-ejaculation function scores were statistically significantly lower in the patient group than in the control group (p=0.014) (Table 2). Erectile function was assessed using the IIEF. ED was detected in 11 (39%) patients, and four patients could not provide semen analysis specimens due to severe ED (Figure 1). Sperm counts were 30±9.4 million in the MS group and 24±6.5 million in the healthy control group; the difference was not statistically significant (p=0.452). Sperm motility was 42.50±18.67 in the MS group and 45.87±15.52 in the control group. The difference was insignificant (p=0.362).

The patients with and without ED in the MS group were compared regarding clinical characteristics, cognitive involvement, and other features. Mean EDSS scores were 2.7±2.03 in the ED group and 1.62±0.80 in the non-ED group (p=0.001). BVMT and CVLT scores were significantly lower in the ED group than in the non-ED group, while trail-making

Table 1. Sex hormone levels, glucose, and TSH levels of the study group

	MS group	Healthy group	p-value
FSH level Mean ± SD median, range (min-max)	5.43±3.23	5.52±4.67	0.426
LH level Mean ± SD median, range (min-max)	5.01±2.21	5.65±3.14	0.068
Prolactin level Mean ± SD median, range (min-max)	7.77±3.88	10.85±3.87	0.841
Total testosterone level Mean ± SD median, range (min-max)	4.28±1.20	4.50±2.24	**0.012**
Plasma AMH level Mean ± SD median, range (min-max)	8.86±5.29	10.02±2.74	0.215
Serum glucose level Mean ± SD median, range (min-max)	95.32±8.60	92.22±5.06	0.319
Serum TSH level Mean ± SD median, range (min-max)	1.80±1.26	1.96±0.60	0.264

SD: Standard deviation, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, AMH: Anti-Mullerian hormone, TSH: Thyroid-stimulating hormone

Table 2. MSHQ, IIEFQ, and fatigue impact scale scores of the study group

	MS group	Healthy group	p-value
FIS-total score Mean ± SD	34.7±23.33	17.67±6.57	**0.037**
FIS-cognitive subscale Mean ± SD	7.30±6.24	5.78±4.57	0.112
FIS-psychosocial subscale Mean ± SD	18.00±13.53	8.67±5.54	**0.018**
FIS-physical subscale Mean ± SD	9.57±7.63	3.22±2.38	**0.008**
MSHQ-ejaculation function score Mean ± SD	5.71±2.68	9.28±4.82	**0.014**
MSHQ-ejaculation bother score Mean ± SD	2.33±1.55	2.57±1.98	0.275
IIEFQ score mean ± SD	24.65±5.07	27.54±4.50	0.185

SD: Standard deviation, FIS: Fatigue impact scale, MSHQ: Male sexuel healt questinore, IIEF: International index of erectile function

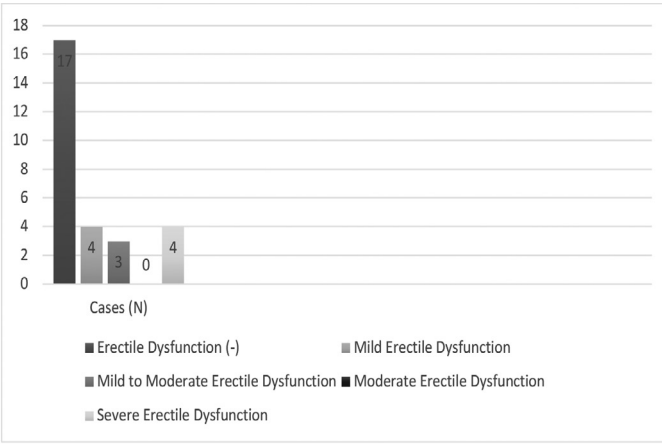

Figure 1. Erectile dysfunction status of the study group according to the IIEFQ

IIEF: International index of erectile function

test times were significantly longer (p=0.008, p=0.008, and p=0.026) (Table 3).

The healthy control group exhibited a negative correlation between FSH and testosterone (r=-0.783) and a positive correlation between FSH and AMH (r=0.400). A negative correlation was observed between AMH and testosterone (r=-0.500, p=0.004). Serum testosterone levels were well negatively correlated with SDMT scores and were well positively correlated with trail-making test times (A-B) [r=-0.582 (p=0.025), r=0.567 (p=0.017), and r=0.683 (p=0.036)]. The patient group exhibited a negative correlation between age and BVMT and SDMT [r=-0.461 (p=0.015), and r=-0.436 (p=0.026)]. A moderate negative correlation was also observed between serum total testosterone levels and SDMT scores (r=-0.498; p=0.034). Evaluation of erectile function in the MS group revealed a negative correlation between the IIEF and EDSS (r=-0.415, p=0.048), a positive correlation with the CVLT, one of the cognitive tests (r=0.503, p=0.011), and a negative correlation with trail-making test time (B form) (r=-0.521, p=0.015).

Table 3. Cognitive- fatigue-depression scores and sex hormones of all study groups

	ED (+)	ED (-)	p-value
Age (years) Mean ± SD	45.60±12.88	39.00±10.07	0.191
Age of onset (years) Mean ± SD	36.00±8.71	31.75±8.85	0.27
Disease duration (years) Mean ± SD	9.6±8.00	7.5±4.31	0.082
EDSS score Mean ± SD	2.7±2.03	1.62±0.80	**0.001**
CVLT score Mean ± SD	41.60±14.04	52.50±13.75	**0.008**
BVMT-R score Mean ± SD	14±9.75	24.50±6.85	**0.008**
SDMT score Mean ± SD	28.55±13.83	37.83±14.40	0.15
Trail making test-A score Mean ± SD	66.01±41.80	45.26±35.55	0.234
Trail-making test-B score Mean ± SD	173.95±94.83	96.84±50.72	**0.026**
FIS-cognitive subscale Mean ± SD	4.43±3.82	9.64±7.47	0.101
FIS-physical subscale Mean ± SD	7.43±7.45	9.18±6.88	0.615
FIS-psychosocial subscale Mean ± SD	14.86±13.59	18.64±14.29	0.582
Depression score Mean ± SD	12.78±8.55	11.73±8.11	0.783
Total testosterone level Mean ± SD	4.77±0.91	3.75±1.46	0.07
Plasma AMH level Mean ± SD	10.32±6.08	8.35±5.12	0.59

SD: Standard deviation, AMH: Anti-Mullerian hormone, FIS: Fatigue impact scale, SDMT: Symbol digit modalities test, BVMT-R: Revised brief visuospatial memory test, EDSS: Expanded disability status scale

Discussion

FSH and LH released from the pituitary gland are gonadotropic hormones LH stimulates the production of testosterone by stimulating Leydig cells in the testicular tissue, while the target of FSH is Sertoli cells involved in spermatogenesis. Also, FSH functions with testosterone in regulating Sertoli cell functions. Although decreased Sertoli cells, sperm counts, and testis volumes are detected in some individuals, normal sexual development and fertilization can still occur. However, full germ cell maturation independently of testosterone is impossible. FSH, LH, and testosterone levels are parameters for determining the roles in both fertility and erectile functions (17). Both FSH and LH levels increase in primary testicular insufficiency in infertile men with testicular insufficiency. However, it should be remembered that FSH and LH levels are variable in infertile men (18,19).

While sex hormones are generally known for their roles in sexual development and maturation during adolescence, sex steroids can act as trophic factors affecting brain development and neuron plasticity, and because of this effect, they can stimulate neurite outgrowth, synapse numbers, and myelination with their direct effects on glial cells (20-22). Regarding its capability of crossing the blood-brain barrier and directly affecting neuronal cells, the neuroprotective impacts of testosterone have been described in many studies (21,22). The detection of lower testosterone levels at the onset of disease in male patients with autoimmune disease has hypothesized that low testosterone levels may be a risk factor for autoimmune diseases (23). Low testosterone values have previously been notified in men with MS (24,25). However, the fact that no comparison was made with healthy controls should be remembered as a limitation of this study and evaluated accordingly.

The prodromal stage of MS has recently attracted significant attention. This is when many subjective complaints, such as depression, anxiety, decreased academic performance, and dermatological symptoms, appear before the clinical onset of MS. One study reported that low testosterone may also be a prodromal marker (26). However, further studies involving more significant patient numbers and different clinical characteristics are needed on this subject. Mobile male MS patients not receiving pulse steroids for at least three months, not in the attack period, and without very high EDSS scores were evaluated in this study. The erectile functions of the patient group and the profiles of hormones capable of affecting these were compared with those of healthy controls. Serum glucose, TSH, FSH, LH, total testosterone, and PRL levels were normal in the patient and healthy control groups. A previous study determined central hypogonadism at a rate of 40% at all ages in patients with MS and reported that low testosterone values were related to increased EDSS values (6). However, no hypogonadism was detected in the MS group in this study, but serum testosterone levels were statistically significantly lower in the patient group compared with healthy controls. No significant correlation was observed between EDSS and serum total testosterone levels in this study. The absence of any association between EDSS and testosterone may be related to the low number of patients, the group having relatively low EDSS values, or other potential factors affecting testosterone levels. In addition, no abnormality was detected in FSH, LH, TSH, or PRL levels in the MS group, and there was no statistically significant difference between the groups. As expected, a statistically significant negative correlation showing negative feedback was observed between FSH and testosterone, indicating a normally functioning hypothalamic-pituitary-gonadal axis in the healthy group. However, there was no similar correlation in the MS group. Evaluated together with the relatively lower testosterone levels determined compared with the healthy group, this suggests that the hypothalamic-pituitary-gonadal axis may be affected at any level in the MS group. However, the data from this study were insufficient to pinpoint the effect.

AMH can inhibit aromatase in Sertoli cells and act locally in Leydig cells to control steroidogenesis (19,20). In mice with *AMH* gene overexpression, decreased Leydig cell functions have also been shown (21-23). Leydig cells regulate testosterone production in testicular cells. Since testosterone production decreases as the capacity of Leydig cells decreases with aging, serum testosterone levels decline (27). There was a positive correlation between FSH and AMH and a negative correlation between AMH and testosterone in the MS group in this study. Accordingly, we concluded that either testosterone decreased following inhibition in the Leydig cells line with increasing AMH or that a negative correlation at any level exists between AMH and testosterone. One study examining the effect of inhibin B and AMH on sperm determined high serum FSH and low inhibin B and AMH levels in subfertile males (28). The authors of that study also reported that this hormone may represent a valuable marker of spermatogenesis due to the broad overlap between the control and subfertile males. The decrease in AMH production indicates increased intratesticular androgen concentration, and low AMH levels have been reported in azoospermia. The previously shown negative relationship between testosterone and AMH was also been demonstrated in our study (9). There are few published data regarding the possible role of AMH in male fertilization and sexual function. Additionally, investigating the relationship between AMH, FSH, and testosterone in both healthy and sexually dysfunctional individuals may help clarify the issue. Also, AMH levels in the seminal fluid can yield more effective results. However, both collection and measurement entail technical problems (29).

The increased frequency of ED in neurodegenerative diseases of the central nervous system can be explained by both lesion localization and the global effect on the central nervous system. Past studies have demonstrated the presence of ED in patients with MS (30-32). ED was also detected at a rate of approximately 40% in the MS group in this study. When we evaluated sexual functions in the patient and healthy groups using the MSHQ, the ejaculatory function was statistically significantly poorer in the patient group by comparison with the healthy. Consistent with this study, a previous study also observed dysejaculation in patients with MS patients, although no comparison with healthy controls was performed (33). In this study, a negative correlation was shown between IIEF and EDSS. Because low IIEF scores indicate poor erectile function, we evaluated low IIEF scores in patients with high EDSS as compatible with the usual course of the disease. When individuals with and without ED in the patient group were compared, EDSS scores were statistically significantly higher in the ED group. Another study comparing the erectile functions of MS patients with those of healthy controls obtained similar findings to ours, with IIEF scores being significantly lower in patients with high EDSS scores (34).

There has been minimal investigation of the hypothalamus-pituitary-testis axis and sperm parameter activity in patients with MS (24). In-depth evaluation of inflammation is important since it can impact fertility by affecting hormone production. Whether or not sperm counts and characteristics in MS patients were affected by high-dose cortisone use over many years, drugs with immunosuppressive characteristics or drugs secondary to autoimmunity were assessed using semen analysis. There was no difference between the MS group and healthy controls in terms of sperm count and motility. Also, no significant difference was observed in the healthy control group regarding sperm parameters. The few studies on this subject have investigated the impact of disease-modifying therapies on sperm parameters and have reported no change in sperm parameters or the association between clinical and radiological variables (35). In conclusion, this study has shown that although erectile dysfunction and low testosterone levels are determined in patients with MS patients, fertility is not impaired.

The impairment of cognitive function is seen in approximately half of the people with MS, and numerous factors impact cognition, such as age, sex, and disease severity (36,37). Following a previous study, a negative correlation was shown between age and information processing speed and visuospatial memory scores in this study (38,39). Studies showing a relationship between cognitive tests and testosterone have found that high testosterone levels are correlated with better cognitive functions (6). Also, studies are reporting an improvement in cognition with testosterone therapies, or testosterone does not affect cognition (40-43). This study determined a negative correlation between information processing speed and testosterone in the healthy control group. Concurrently, a positive correlation was determined between executive function and testosterone levels. There was also a negative correlation between testosterone and information processing speed in the MS group. That is to say, a negative correlation, although weak, was observed between testosterone and cognition in both the healthy and MS groups. This observation of a negative connection between testosterone and cognition in both groups, unlike a previous study, may be associated with the low number of patients or suggests that the relationship between these two parameters is more complex than currently thought. Additionally, in a previous study, it was reported that testosterone may damage cognitive function (44). Some observational studies have suggested that testosterone is related to better verbal memory or higher mini-mental state examination scores (45,46).

Study Limitations

The low number of patients may be considered as the principal limitation of this study. However, sex hormones in male MS patients have been investigated in several previous studies, and we think that this study's results, which evaluated sexual function disorder, cognitive functions, and sperm characteristics, may contribute to illuminating the function of sex hormones in MS.

Conclusion

The effect of androgens on cognition remains unclear. Erectile function disturbance in the MS group was associated with low verbal memory scores and low executive functions. Cognitive scores (verbal memory, executive functions, and visuospatial memory) were statistically significantly weaker in the group with ED than in the non-ED group. Higher EDSS scores and cognitive impairment in patients with MS patients with ED were regarded as consistent with both cognitive impairment and erectile function disorder, indicating a poor prognosis for MS.

Ethics

Ethics Committee Approval: Ethical approval for this study was granted by the Zonguldak Bülent Ecevit University Clinical Research Ethics Committee (approved number: 2017-125-20/12, date: 31.01.2018).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.P.Ç., M.A., Ö.Ç., S.Ö., Design: B.P.Ç., Ö.Ç., S.Ö., Data Collection or Processing: B.P.Ç., M.A., Ö.Ç., U.Ç., S.Ç., E.A.D., H.T.A., Analysis or Interpretation: M.A., Ö.Ç., U.Ç., E.A.D., H.T.A.,

Literature Search: B.P.Ç., M.A., Ö.Ç., U.Ç., S.Ç., E.A.D., H.T.A., Writing: B.P.Ç., Ö.Ç., U.Ç., S.Ö.

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Comparison of Using Cold Knife and Holmium Laser in Urethral Stricture: Long-term Outcomes

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

Laser energy can be preferred as an alternative to the traditionally used cold knife for treating urethral stricture. The effectiveness of using different techniques on treatment outcomes is important. It is also important to question the side effects that occur. For this purpose, different types of lasers have been used for treating urethral strictures. The results of studies with holmium laser are positive. Our study compares the efficacy and complications of cold knife and holmium lasers used in urethral stricture. In terms of the number of patients included in the study, it constitutes one of the largest groups in the literature. According to the results of our study, the use of a laser is superior to the cold knife in terms of effectiveness. However, there was no difference between them in terms of side effects.

Abstract

Objective: In this study, the efficacy, complication rates, and treatment results of cold knife and holmium:yttrium aluminum garnet (Ho:YAG) laser for treating urethral stricture was compared.

Materials and Methods: A total of 364 cases were operated with the diagnosis of urethral stricture between 2010 and 2020. Of these patients, 176 were operated using a cold knife and 188 using a Ho:YAG laser. Preoperatively and postoperatively, uroflowmetry, post-voiding residue (PVR), International Prostate Symptom Score (IPSS), and IPSS/quality of life (IPSS/QoL) values were determined in all patients. Additionally, complication rates, operation times, and stricture recurrence rates were determined.

Results: The length of the stricture in all cases was less than 3 cm. The maximum flow rate (Q_{max}), average flow rate (Q_{ave}), PVR, IPSS and IPSS/QoL values of the patients were determined as 8.16/6.45 mL/s, 4.36/4.62 mL/s, 124.50/135.65 mL, 20.33/23.55, 5.25/5.40 in the preoperative period in group 1 and group 2, respectively. In the postoperative 12th months, it was determined as 25.43/27.48 mL/s, 21.32/23.08 mL/s, 25.50/19.04 mL, 7.08/6.06, and 1.36/1.23. Stricture recurrence rates were 29.54% (n=52) and 10.63% (n=20) in groups 1 and 2, respectively.

Conclusion: Long-term recurrence rates are lower with the use of Ho:YAG laser in urethral strictures compared to cold knife.

Keywords: Urethral stricture, Ho:YAG laser, cold knife

Introduction

If not treated urethral strictures that occur due to acquired or congenital causes, they may cause irreversible changes in the urinary system. Different methods such as simple urethral dilatation, visual internal urethrotomy, uroLume stent placement, and urethroplasty can be used in urethral strictures (1). Treated urethral strictures may recur. Sachse's internal urethrotomy applied for this purpose has been accepted since 1974, but high recurrence rates of 35-60% have been reported (2). Excision and primary anastomotic urethroplasty are the gold standard in traumatic urethral strictures; however, bleeding, impotence, infertility, recurrence, and failure rates are high (3).

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For this reason, alternative approaches have been evaluated in urethral strictures. The first use of a laser for treating urethral stricture was in 1979 (4). Different laser types such as diode, neodymium yttrium aluminum garnet (Nd:YAG), argon, and holmium: yttrium aluminum garnet (Ho:YAG) laser have been used for treating urethral strictures (5). The Ho:YAG laser cuts the tissue directly while vaporizing it with clearer vision and less bleeding, leaving minimal scarring in the urethra (6). In this study, we compared the treatment results of cold -knife urethrotomy and Ho:YAG laser use in patients with urethral stricture.

Materials and Methods

The Patient Evaluation

In this prospective randomized controlled study, the results of a total of 364 patients who underwent internal urethrotomy with cold knife or Ho:YAG laser for primary urethral stricture between September 2010 and April 2020 were evaluated. In the preoperative evaluation, the patients presented with complaints such as decreased urine flow rate, difficulty in urination, residual urine sensation, pollakiuria, dysuria, and nocturia. In the preoperative period, etiological factors that may cause urethral stricture such as trauma, urine infection, iatrogenic injury (instrumental or surgical), previous transurethral catheter placement history, and previous coroner angiography or bypass surgery history were determined. Genital examinations of all cases were performed, and conditions such as meatal stenosis and hypospadias that made urinary flow difficult were excluded. Uroflowmetry and post-voiding residue (PVR) measurements were performed in all cases. Additionally, the severity of the patient's symptoms was evaluated by applying the International Prostate Symptom Score (IPSS), and IPSS/quality of life (QoL) questionnaires. All cases were evaluated with complete urinalysis and urine culture, complete blood count, and kidney function tests. Patients with active urinary tract infections have been treated with antibiotics preoperatively. Cases that were multiple sites (>1), completely obliterated, or had stenosis longer than 3 cm were excluded from the study. Patients who underwent urological intervention due to urethral stricture and another concomitant cause (such as prostate cancer, benign prostatic hyperplasia, bladder tumor or stone, ureteral stone) were excluded from this study. Additionally, patients who had undergone previous endoscopic or open surgery due to urethral stricture were excluded from this study. Also, patients neurological diseases have been excluded from this study. The patients were divided into two as the cold knife group (group 1, n=176) and the Ho:YAG laser group (group 2, n=188). After the patients were informed about the laser and cold knife, the technique to be used was explained and their informed consent was obtained. Ciprofloxacin was administered to the patients 2 h before the operation and continued for 5 days postoperatively. The patients were discharged on the postoperative first day. The transurethral catheter was removed after an average of 5 (range 3 to 10 days) days. Perioperative and postoperative complications were noted. All patients were evaluated regularly at the 1st, 6th, and 12th months postoperatively. Patients who had no symptoms during their follow-up, who urinated at least 150 mL in uroflowmetry, had a maximum flow rate of more than 15 mL/s, had residual urine of less than 50 mL and an IPSS score between 0-7 were considered successful. In the presence of symptoms such as decreased urine flow, dysuria, difficulty urinating and urinary retention, patients were evaluated with uroflowmetry, PVR, IPSS, IPSS/QoL tests and cystoscopy was performed. A definitive diagnosis of recurrence for urethral stricture was made by performing cystoscopy. The study protocol was approved by the Ankara Atatürk Training and Research Hospital Ethics Committee, and all patients signed an informed consent agreement.

Surgical Technique

All cases were operated by a sinle surgeon experienced with endourethrotomy. The surgical procedure was performed under general or spinal anesthesia and in the lithotomy position. A 21-F rigid internal urethrotome and 0-degree optic (Karl STORZ® medical, Germany) were used in the operation. At the beginning of the operation, after entering the external urethral meatus, urethral stenosis was observed, and the guide wire (0.035 inch) was inserted and advanced beyond the stricture. Then, the cold knife was advanced through the stenosis segment and incisions were made at the 12 o'clock position. If necessary, another incisions were made into the scar tissue at the 5 and/or 7 o'clock position. This procedure was repeated until the 21-F internal urethrotome passes comfortably through the urethra, and a sufficient caliber opening was obtained in the urethra. Then, diagnostic cystoscopy was performed and the procedure was terminated by placing a 18-F silicone catheter transurethrally. Patients in group 2 were being seen urethral stricture using 21-F internal urethrotome and 0-degree optics (Karl STORZ® medical, Germany), and the guide wire (0.035 inch) was inserted and advanced beyond the stricture. Then, using Ho:YAG laser (SPHINX®, Germany) energy, the stricture segment was enlarged until an opening was obtained for the internal urethrotome to pass easily. All the scarred tissues in the stricture area were coagulated and preserved the healthy mucosa. A 550-nm Ho:YAG end firing laser fiber was used and the energy of the Ho:YAG laser was set to 2 Joules and its frequency to 30 Hz. This energy and frequency setting was chosen because it results in a satisfactory compromise of low tissue penetration

depth and low coagulation effect. It was observed that the 21-F internal urethrotome passed easily through the opening and procedure was terminated by inserting a 18-F silicone catheter transurethrally after diagnostic cystoscopy.

Statistical Analysis

All data were expressed as mean ± standard deviation. Statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). Parametric variables were assessed using a One-Sample t-test. Numerical variables, such as demographic data, and peroperative and postoperative complications were assessed using the Mann-Whitney U test. A p-value less than 0.05 was considered as statistically significant.

Results

The mean age was determined as 59.5 (20-79) years in group 1 and 61.3 (18-82) years in group 2. No significant difference was observed between the two groups in terms of etiological factors (Table 1). Iatrogenic factors were the most common etiologic factors in both groups. The length of the stricture in all cases included in the study was determined to be less than 3 cm. When the operation times were compared, it was found that it was significantly shorter in the cold -knife group compared with the Ho-Laser group. The mean operation time (time between entry and exit of the urethrotome into the urethra) was 11.50±5.42 minutes in group 1 and 23.40±13.24 minutes in group 2. Mean Q_{max}, Q_{ave}, PVR, IPSS, and IPSS/QoL values were preoperatively 8.16±1.12 mL/s, 4.36±1.06 mL/s, 124.50±45.30 mL, 20.33±4.16, and 5.25±0.94 in group 1 and 6.45±1.19 mL/s, 4.62±1.03 mL/s, 135.65±54.35 mL, 23.55±5.18, and 5.40±0.88 in group 2, respectively. The same values were 25.43±4.38 mL/s, 21.32±3.18 mL/s, 25.50±5.75 mL, 7.08±2.08, and 1.36±0.16 in group 1 and 27.48±5.81 mL/s, 23.08±2.36 mL/s, 19.04±8.45 mL, 6.06±2.04 and 1.23±0.21 in group 2, respectively, in the last postoperative control (Tablo 2). Recurrence rates were determined as 29.54% (n=52) and 10.63% (n=20) in groups 1 and 2, respectively ($p<0.05$ for all comparisons). The mean stricture development time was found to be 6.4 months in groups 1 and 9.3 months in group 2. The most common postoperative complications were urinary tract infection and dysuria. However, there was no statistically significant difference between the two groups in terms of intraoperative and postoperative complications (Table 3).

Discussion

Ho-YAG Laser can be used for treating urological diseases such as urolithiasis (7), benign prostatic hyperplasia (8), urethral strictures (9), bladder tumors (10), and external genital lesions

Table 1. Etiologic factors of the patients with urethral stricture

	Group 1 (n=176)	Group 2 (n=188)	p
Idiopatic	55 (31.25%)	63 (33.51%)	0.765
Transurethral catheterisation	13 (7.38%)	11 (5.85%)	0.801
Coronary heart disease	23 (13.06%)	18 (9.57%)	0.697
Urethritis/recurrent UTI	10 (5.68%)	17 (9.04%)	0.635
Perineal trauma	2 (1.13%)	1 (0.53%)	0.631
Iatrogenic factors	73 (41.47%)	78 (41.48%)	0.843

UTI: Uriner tract infection. Etiological factors were assessed by using Mann-Whitney U test ($p<0.05$: Statistically significant)

Table 2. Preoperative and postoperative uroflowmetry, ultrasonography and IPSS values

	Preoperative Group 1/2	Postoperative 1st month Group 1/2	Postoperative 6th month Group 1/2	Postoperative 12th month Group 1/2	p
*Q_{max} (mL/s)	8.16±1.12 6.45±1.19	27.17±4.85 31.11±5.35	25.98±3.85 28.45±4.96	25.43±4.38 27.48±5.81	0.794
*Q_{ave} (mL/s)	4.36±1.06 4.62±1.03	23.16±2.14 25.32±3.56	21.50±3.05 24.36±2.65	21.32±3.18 23.08±2.36	0.826
*PVR (mL)	124.50±45.30 135.65±54.35	23.35±5.43 26.05±5.28	25.45±6.21 23.50±6.65	25.50±5.75 19.04±8.45	0.693
*IPSS	20.33±4.16 23.55±5.18	4.36±1.65 4.09±1.35	6.80±1.56 4.92±1.34	7.08±2.08 6.06±2.04	0.687
*IPSS/QoL	5.25±0.94 5.40±0.88	1.16±0.18 1.05±0.14	1.12±0.21 1.02±0.11	1.36±0.16 1.23±0.21	0.774

Q_{max}: Maximum flow rate, Q_{ave}: Average flow rate, PVR: Post voiding residue, IPSS/QoL: International Index of Prostate Symptom Score/quality of life. *Parametric variables were assessed by using One-Sample t-test ($p<0.05$: Statistically significant)

Table 3. Peroperative and postoperative complications			
	Group 1, n=176	Group 2, n=188	p
Hematuria	3 (1.70%)	-	0.865
Urinary extravasation	4 (2.27%)	1 (0.53%)	0.722
UTI	16 (9.09%)	13 (6.91%)	0.757
Dysuria	12 (6.81%)	7 (3.72%)	0.828
Urinary incontinence	4 (2.27%)	1 (0.53%)	0.653
Urinary retantion	-	-	-
Urinary fistula	-	-	-
Epididymoorchitis	9 (5.11%)	7 (3.72%)	0.846
Erectile dysfunction	-	-	-
Penile or scrotal edema	4 (2.27%)	1 (0.53%)	0.663
UTI: Uriner tract infection. Peroperative and postoperative complications were assessed by using Mann-Whitney U test (p<0.05: Statistically significant)			

(11). The management of urethral strictures has often been a challenge for urologists. Its incidence in men was approximately 0.6% (12). Although the symptoms are different, dysuria, urinary retention, urinary incontinence, and urinary obstruction can be observed (13). Although it is generally associated with trauma, transurethral interventions, and infections, it can also be seen idiopathically. Stricture occurs because of mucosal laceration, infection, and scar tissue formation (14). Important risk factors that play a role in recurrence are the length of the stricture, the depth of the scar tissue, the etiology, the location of the stricture, and the severity, which is characterized by spongiofibrosis (14,15). The treatment method to be chosen can be determined depending on the location of the stricture, its length, and the experience of the surgeon (13).

A laser was first used in 1979 for treating urethral strictures (4). The Ho:YAG is a solid laser at a wavelength of 2.140 nm and emits pulse-like energy. Tissue absorption is non-selective but uniform, with a penetration depth of only 0.4 mm. The emission time is as short as 0.25 millisecond, and it applies a transient power of no more than 10 kilowatt. Laser energy acts by vaporizing its target with minimal thermal effect in tissues such as stones and scars (16). Endouretrotomy with Ho:YAG laser is a minimally invasive, effective, and reliable method and compared to other methods such as electrical resection and laser incision, it removes scar tissue through evaporation and thermal damage to neighboring urogenital tissues is minimal. Additionally, the scar formed after urethrotomy is insignificant (17). Ho:YAG laser has advantages such as less bleeding, a clear vision, more precise incision, and ablation in the scar tissue.

There is no consensus on the long-term results of the use of cold knives and lasers in urethral strictures. In addition to the publications reporting that laser use is superior (18,19), studies (20-22) showing that laser is not superior to a cold knife have been published. Because of the 12-month follow-up of 138 patients who were operated using Ho-YAG laser, the recurrence of stricture was reported in 26.8% cases. Recurrens have been reported to be at the site of the old stricture and milder than previous strictures. Additionally, the authors have been stated that these recurrences were mostly seen in the bulbar region, occurring in patients with strictures longer than 2 cm and with a history of trauma (23). In a study comparing Ho-YAG laser and cold knife, it has been reported that the recurrence rate was 20.7% in the cold knife group and 32.4% in the Ho-YAG group because of a 12-month follow-up. Although there was no difference between the two groups in terms of Q_{max} and postoperative complications, it was stated that the operation time was longer in the laser arm (24). In another study comparing Ho-YAG laser and cold knife, including 80 patients, recurrence of urethral stricture was reported at a rate of 20% in the cold knife group and 10% in the laser group after a 1-year follow-up. In this study, which included cases with strictures shorter than 1.5 cm, it was stated that there was no difference between the groups in terms of postoperative complications, but the operation time was significantly longer in the laser group (9). Additionally, it has been reported that holmium laser can be used effectively and safely for treating urethral strictures in children, and the success rate is higher (76.2% vs. 47.61%) compared with the use of cold knife (25). In a study of 78 patients who underwent Ho:YAG laser, in 31 patients (40%) who were completely obliterated and had a stricture longer than 1.5 cm reported recurrence of the stricture. It was also stated that these patients had undergone an intervention before. It has been emphasized that they get better results in short bulbar strictures (6). Choi et al. (17) used Ho:YAG laser in 14 patients with stenosis less than 2 cm and developed secondary to trauma or inflammation and reported that this method is minimally invasive, safe and effective. In a prospective randomized clinical study involving 51 patients in which the use of Ho:YAG laser and cold knife was compared, it was reported that the Ho:YAG laser provided a lower recurrence rate and shorter operative time without a significant difference in Q_{max} (26). In a study of 190 patients, it was reported that the use of Ho:YAG laser in long urethral strictures was a safe and minimally invasive technique providing high success rates (27). Success rates of 60-85% have also been reported in other studies using Ho:YAG laser (28).

Using the Ho:YAG laser is a process that requires experience. In cases where the stricture is close to the external urethral sphincter, pubis, rectum, pelvic vessels, and nerves, complications such as urinary incontinence and rectal fistula may occur because of incidental damage (29). Apart from these, internal urethrotomy has complications such as bleeding, urinary tract infection, urosepsis, extravasation, impotence, and recurrence of stricture (6). Using the necessary antibiotherapy for patients with uriner tract infection in the preoperative period and paying

attention not to damage the sphincter during the operation can reduce complications. In our study, Ho:YAG laser was used in 188 patients and a cold knife was used in 176 patients, whereas the success rate (no recurrence) was 70.46% in cases treated with cold knife, whereas the success rate was 89.37% in cases treated with Ho:YAG laser. The fact that the patient follow-up period is 12 months, similar to the literature, can be considered a factor limiting the study. However, it can be considered the advantage of this study that it is prospective, comparative, and includes a large number of patients. We believe that conducting other studies with longer follow-up periods will guide the determination of the importance of the use of Ho-YAG laser in urethral strictures.

Conclusion

According to the results of our study, in Ho:YAG laser urethrotomy, the stricture is less likely to recur compared with cold knife urethrotomy, and holmium laser urethrotomy can be considered a minimally invasive and effective method that can be used safely for treating urethral strictures.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ankara Atatürk Training and Research Ethics Committee.

Informed Consent: All patients signed an informed consent agreement.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Ureteral Stricture Outcomes Using Small Ureteral Access Sheath During Retrograde Intrarenal Surgery

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

Ureteral access sheath (UAS) is one of the most important instruments used during retrograde intrarenal surgery. Ureteral trauma due to UAS is an important complication causing serious morbidity in the long-term period. Using the smallest diameter UAS is effective and safe to avoid ureteral trauma. Therefore we emphasise that the most atraumatic instruments should be chosen.

Abstract

Objective: This study evaluated ureteral injury and long-term stricture progression after the smallest ureteral access sheath (UAS) application during retrograde intrarenal surgery.

Materials and Methods: A total of 154 patients who had undergone retrograde intrarenal surgery procedures and applied a 9.5/11.5-F UAS for kidney stones between September 2016 and March 2019 were prospectively included, and intraoperative, postoperative, and late complications were evaluated. Ureteral injuries were visualized using flexible and semi-rigid ureterorenoscopy, and ureteral stricture was assessed by computed tomographic urography at one-year controls.

Results: 56% (n=86) of the patients were males, and %45 (n=68) the mean age was 47±15 years, stone size was 17.1±8 mm, operative time was 56±23 minutes, 80% had ureter wall injury, and 39% and 41% had grade 0 and grade 1 lesions, respectively. Minor complications were developed in 3%, and major complications were seen in 2% of cases. The ureteral stricture was not observed in 1st-year controls.

Conclusion: The routine application of 9.5/11.5-F UAS is safe to use in flexible ureteroscopy without any long-term adverse effects.

Keywords: Ureteral injury, ureteral stricture, ureteral access sheath, long-term complications, patient outcomes

Introduction

In the last few decades, kidney stone surgery has undergone many technological developments, and retrograde intrarenal surgery (RIRS) has become one of the standard treatments for patients with renal stones. The ureteral access sheath (UAS) was developed in 1974 by Takayasu and Aso (1). It is often used during RIRS to facilitate the entry of a flexible ureterorenoscopy (URS) into the renal collecting system. Additionally, it enables easy re-entry into the collecting system, consequently shortening the operating time, improving vision, decreasing intrapelvic pressure, and increasing the flexible ureteroscope's life span (2-5). Currently, UAS are produced with numerous characteristics, including different materials, lengths, tip formation, diameters, stiffness, and radiopaque markers (6). The selection of the UAS among the choices of manufacturers and models typically depends on surgeon choice, cost, and ureteroscope size.

Despite their advantages, there are some critical misgivings concerning UAS use. UAS usage entails a risk of ureteral damage, including the smooth muscle layer after insertion (7). Additionally, the over-distention created by a UAS may decrease blood flow of the ureteral wall and theoretically cause long-

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term ureteral stricture formation (8). Moreover, large-sized UASs have been reported to affect ureteral blood flow more (9). Thus, UASs with small outer and large inner diameters are clinically more practical.

To the best of our knowledge, no prospective study in the international literature has evaluated the effect of UAS -related ureteral injury and possible ischemia on the development of urethral stricture. This study analyzed intraoperative, postoperative complications and the incidence of ureteral injury by using the smallest diameter UAS on the market and the effect of injuries and possible ischemia/inflammatory changes on the risk of ureteral stricture development in the long term.

Materials and Methods

A total of 154 RIRSs for renal stones that a UAS was administered between September/2016 to March/2019 were prospectively included in the study. Patients who were not previously stented were undergone a complete physical, laboratory, and radiological assessment. In the case of urine culture positivity, patients were treated with appropriate antibiotics preoperatively. Exclusion criteria were:

- Previous urinary or stone surgery,
- Any urinary system abnormality including ectopic, horseshoe, or malrotated kidney(s), calyceal diverticulum stones, duplicated collective system,
- Ureteral dilatation,
- Prior unsuccessful sheath administration.

A 9.5/11.5 F UAS (Cook™, Cook Medical, Dublin, Ireland) (length: 35 cm for females and 45 cm for males) were used in surgeries under general anesthesia. A9.5-F semi-rigid ureteroscope (Karl Storz™, Karl Storz, Tuttlingen, Germany) was used routinely for URS to diagnose ureteral stone or stricture before RIRS and for placing a hydrophilic guidewire for the optical dilatation. After the passive dilatation by a semirigid ureterorenoscope, a UAS was inserted over the guidewire under fluoroscopic guidance. Next, inserted a 7.5-F flexible ureteroscope (Karl Storz Flex-X2™, Karl Storz, Tuttlingen, Germany) through the sheath. A 30W Holmium YAG laser (SphinxX™, Lisa, Katlenburg-Lindau, Germany) was used to fragment kidney stones, but the residual fragments were not routinely extracted. The procedure was terminated after inspecting the whole ureteral wall using a 9.5-F semi-rigid URS. JJ stent was removed at 2nd to 4th weeks postoperative if placed during surgery.

Intra-operative ureteral lesion grades were classified, ranging from 0 to 4, according to Traxer and Thomas (7). Additionally, postoperative complications were reported using the modified Clavien-Dindo classification (10).

Residual stones ≤3 mm was accepted as stone-free one month after the procedure. Patients were evaluated by computed tomographic urography in the postoperatively first year. A fixed narrowing ureter with proximal dilatation was considered stricture (11).

This study was reviewed and approved by the Institutional Review Board (University of Health Sciences Turkiye, Ankara Numune Training and Research Hospital - approval number: ANEAH-E-1762, date: 2019). The study was performed in accordance with the most recent version of the Declaration of Helsinki.

Results

A total of 154 patients with a mean age of 47±15 (range: 12-81) years, and 56% (n=86) were males were included in the analyses. The mean surgery time was 56±23 (range: 30-120) minutes, and the mean stone size was 17.1±8 (7-40) mm. The analysis of the ureteral injury revealed that 79.9% of the patients had an injury that was non-significant (grade 0) in 39% and grade 1 in 40.9% of patients. None of the patients had injuries equal to or higher than grade 2. Five patients (3.2%) had Clavien I and II complications in the postoperative period, including hematuria and fever. Grade IV complications developed in 3 patients (1.9%) (sepsis requiring intermediate care/intensive care unit management) (Table 1).

After the 1st-year follow-up controls, none of the patients had a ureteral stricture. In the first session, 118 patients (76.6%) were stone-free, and 30 patients with residual stones underwent a second RIRS session, which revealed an overall stone-free rate of 90.3% (n=139) (Table 2). When a total of 62 patients with grade 0-1 lesions were evaluated, the stone-free rate was found to be 71.2% and it was similar to the total first session stone-free rate (p=0.124).

Discussion

The use of a UAS during RIRS, despite having a few advantages over RIRS without a UAS, also remains controversial equipment

Table 1. Five-point grading system for ureteral injury (7)

Grade	Description
0	No ureteral lesion or only mucosal petechiae
1	Mucosal erosion or a mucosal flap without smooth muscle injury
2	Damage to the mucosa and smooth muscle but no adventitia, with no retroperitoneal tissue visible
3	Injury indicating ureteral perforation involving the full thickness of the ureteral wall, including the adventitia
4	Total ureteral avulsion

in endourological surgery owing to an increased risk of ureteral damage. The normal ureteral lumen is narrower than any UAS in the market (12). The insertion of a UAS dilates the ureteral wall and thus has the risk of causing ureteral injury (mucosal and submucosal edema, hematoma, variable degree mucosal erosions); additionally, the placement of reinforced UAS may produce partial or even complete ureteral transection (13). Another concern about UAS is its effect on ureteral blood flow. Lallas et al. (9) investigated the possible acute ischemic effects of varying diameters UAS using a swine model. Blood flow to the ureteral segment was measured using laser Doppler flowmetry, and UAS remained in the ureter about 70 min. The authors revealed that decreases in ureteral blood flow using a 10/12-F UAS (average; 12%) was minimal compared with an up to 64.5% decrease with larger UAS. The authors reached the nadir blood flow averaging 20.0 to 30.0 min. They concluded that despite its findings safety concerning acute ischemic effect, one should continue to proceed with precautions when selecting the proper-size UAS, as chronic effects remain in controversial. However, there perfusion that occurs after remove of the UAS can reveal the ureteral wall to free radicals and subsequent tissue injury (7). Lildal et al. (14) evaluated the acute inflammatory cytokine expression for cyclooxygenase-2 and tumor necrosis factor-alpha in ureteral tissue and reported significant upregulation after 2 min of UAS deployment, which were 6.5-fold and 8-fold, respectively (14).

First, Traxer and Thomas (7) prospectively assessed the incidence and severity of UAS-related ureteral wall damage, and they generated a classification system in 2013. Their study included 359 patients who underwent RIRS for renal stones, and 12/14-F UAS was used to permit the digital URS. Patients were divided into two groups, including low-grade damage (0 or 1 grade) and high - grade damage (2 to 4 grade), which included smooth muscle layers of the ureter. Low-grade damages were found in 86.6% of patients, grade 2 injuries observed in 10.1% of patients, and grade 3 injuries in 3.3%. They did not report a grade 4 injury. The incidence of postoperative complications was 7%. In a novel study by Loftus et al. (13), 95 patients were randomized to two the same sizes (12/14-F) of different brands of UAS, and they analyzed the incidence of UAS-related ureteral injury. The authors used the same classification system as we used (7), and they validated this 5-point classification system. The end of the study, they found grade 1, 2, 3 and 4 injuries in 47.8%, 13.4%, 10.4% and 0.0% of patients, respectively. The authors concluded that ureteral trauma could be easily assessed using a standardized 5-point scale with good inter-rater reliability. Also, they concluded that not pushing if there is a resistance and switching to a smaller diameter sheath in prolonged applications should be prevent high-grade injuries. In our series, the grade 1 injury rate of 40.9% is also similar to the results with two studies as mentioned above. Unlike the other two studies, we did not observe grade 2 and higher injuries. This is presumably related to our use of a smaller size of UAS. Because pushing against large-size UAS into the narrow ureter during placement, possibly causes high-grade ureteral trauma. Another reason may be a mismatch in the UAS and ureteral tone. Using a larger UAS may require more force during insertion, and a higher pressure would refer to a higher risk of ureteral damage. Koo et al. (15) found that high-grade ureteral damage did not occur in patients in which the UAS force of insertion was <600 G (600 G=5.88 N).

Table 2. Demographic data of the patients

Age, Mean ± SD (min-max) years	47±15 (12-81)
Gender	
Male	86 (55%)
Female	68 (45%)
Stone size, Mean ± SD (min-max) mm	17.1±8 (7-40)
Operative time Mean ± SD (min-max) minutes	56±23 (30-120)
Stone-free rate	
Immediate	76.6% (n=118)
Overall	90.3% (n=139)
Ureteral injury	
Overall	79%
Grade 0	39%
Grade 1	40.9%
Complications	
Clavien I-II	5 (3.2%)
Clavien IV	3 (1.9%)

SD: Standard deviation, min: Minimum, max: Maximum

We know that ureteric strictures can develop even after seemingly uncomplicated or complicated endoscopic treatment of urolithiasis (16,17). Also, decreased blood flow related to the usage of UAS theoretically increases the risk of ureteral stricture. Recent literature findings also suggest limiting the duration of ureterorenoscopic surgeries to prevent complications, as complications and stricture risk increase when operative time is prolonged. Loftus et al. (13) suggested that the correlation between ureteral stricture and ureteral injury emphasizes the clinical significance of these injuries. Delvecchio et al. (8) retrospectively evaluated 62 cases who underwent 71 ureterorenoscopic surgeries using UAS and complete follow-up longer than three months. The authors found only one stricture (1.4%) in the left ureteropelvic junction. However, this patient had undergone multiple endoscopic surgeries because of recurrent struvite calculi.

In a recent study, Huang et al. (18) shared their data on ureteral stenosis, in which they evaluated the results of RIRS performed for kidney stones of 2 cm and larger. The authors reported

that through the 6-month follow-up, no ureteric stricture was detected. Unlike our study, Huang et al. (18) used 13/15F UASs during the operation, and the follow-up times were shorter than our study. In another recent study, Sari et al. (19) evaluated the efficacy and safety of RIRS in 1489 patients using UAS. The authors reported that they detected ureteral stenosis in 3 patients. In this study, two different sizes of UAS (9.5/11.5 F or 11/13 F) were used, and the patients were evaluated retrospectively. The major difference in our study is that it has a prospective design, and we used the UAS with the smallest diameter in all patients.

In this study, we prospectively evaluated 154 consecutive RIRS procedures with adjunctive use of a UAS after a 1-year follow-up, and we did not detect any ureteral stricture. even though grade 2 or higher ureteral lesions may cause ureteral stricture, we do not detect high-grade injury in our cohort. We speculate that using larger diameter UAS may lead to more frequent ureteral injury, more ureteral ischemia, and more ureteral stricture. Using the smallest diameter, UAS has high protection in terms of all these parameters.

Study Limitations

There are a few limitations to our study. First, as we are aware that the number of patients in our study is low. We think that our research can shed light on higher-volume studies. Latter, the study is of a cohort design. Comparative studies with different sizes of UAS can provide further contribution and information. In parallel with the developments in laser technologies, RIRS is becoming more common for larger stones. Therefore, we can say that the stone size is slightly high in our study.

Conclusion

The results of our study indicate that the 9.5/11.5-F UAS is safe for routine use to ease flexible URS and no cause complications in the long-term periods. However, awareness of the potential ureteral wall damage and the ischemic effects of using unnecessarily larger UAS for long -term periods in patients at risk of damage should be keep in mind.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Institutional Review Board (University of Health Sciences Turkiye, Ankara Numune Training and Research Hospital - approval number: ANEAH-E-1762, date: 2019). The study was performed in accordance with the most recent version of the Declaration of Helsinki.

Informed Consent: All patients provided informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH
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Safety and Efficacy of Selective Renal Artery Embolization in the Management of Postprocedural Acute Renal Bleeding: Experience of A Tertiary Care Center

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

Any intervention on the kidney may cause disruption of arteriovenous system and pose acute renal bleeding. In the present study we evaluated selective renal artery embolization. The study shows that selective renal artery embolization is a safe and highly effective method to control postprocedural acute renal bleeding.

Abstract

Objective: Our objective was to evaluate the safety and efficacy of selective renal artery embolization in the management of post-procedural acute renal bleeding.

Materials and Methods: This was a prospective observational study that included all patients who presented to us with acute renal bleeding the following kidney procedures. Demographic, radiological, and invasive angiographic data of patients were recorded. Selective renal artery embolization was performed by an interventional radiologist, and patients were observed for any complications.

Results: We received 20 patients with an average age of 46.2±13.18 years having bleeding following procedures done on the kidney. Fifteen (75%) patients had undergone procedure for renal stone disease, 3 (15%) had bleeding following nephron-sparing surgery (NSS), 1 (5%) patient had undergone percutaneous nephrostomy tube placement, while another patient had undergone biopsy of renal allograft. The average drop in hemoglobin recorded before the embolization was 2.45±0.69 mg/dL in percutaneous nephrolithotomy patients, 3.05±1.28 mg/dL in nephrolithotomy patients and 3.32±0.82 mg/dL following NSS. Renal pseudoaneurysm was the most common vascular lesion identified on angiography in 50% of patients, followed by arteriovenous fistula (AVF) in 30% of patients. A combination of pseudoaneurysm and AVF was seen in 10% of patients, and 10% of patients had active extravasation from injured vessels. One (5%) patient required emergency nephrectomy after two failed attempts of angioembolization. There were no major complications recorded except for urosepsis in 2 (10%) patients and acute kidney injury in 1 (5%) patient.

Conclusion: Transarterial selective renal artery embolization is a safe and highly effective method to control postprocedural acute renal bleeding.

Keywords: Arteriovenous fistula, nephron sparing surgery, percutaneous nephrolithotomy, renal pseudoaneurysm, selective renal artery embolization

Introduction

Kidneys are highly vascular organs that receive 20% of the cardiac output. This blood flow is mainly distributed in the high-flow arteriovenous system found in close proximity to the renal collecting system. Any intervention done on the kidney, such as open renal surgeries, percutaneous nephrolithotomy (PCNL), or renal biopsy, which causes disruption of this arteriovenous system poses a potential risk of post-procedural acute renal bleeding. The most dreaded complication following PCNL is bleeding occurring in 14-24% of cases. Conservative management with supportive care and blood

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transfusion is usually sufficient in most of the cases; however uncontrolled and life-threatening bleeding may warrant urgent angioembolization or renal exploration in 0.8% of cases (1,2). With widespread use of imaging modalities, small renal tumors are usually diagnosed incidentally. Nephron-sparing surgery (NSS) is now considered as standard treatment for renal tumors up to the size of 7 cm when technically feasible (3). Postoperative hemorrhage occurs in 3-10% of cases following NSS and typically presents 7-14 days postoperatively. These bleeding are usually attributed to pseudoaneurysms and arteriovenous fistulas (AVF). Re-exploration or selective renal artery embolization is often required to control bleeding in such cases (4). Re-exploration usually ends with nephrectomy in most of these cases. Open nephrolithotomy is still being practiced in developing countries for the management of renal calculi and is sometimes associated with life-threatening secondary hemorrhage requiring emergency nephrectomy. Transarterial angioembolization is a minimally invasive procedure that precisely controls bleeding, salvage renal function, and avoids the more invasive and morbid renal exploration in such cases.

In this study, we evaluated the safety and efficacy of selective renal artery embolization (RAE) in the management of postprocedural acute renal bleeding.

Materials and Methods

The current study was conducted at our institute, which is a tertiary care referral center that receives patients from different parts of the state. It is a prospective observational study over a period of 3 years from August 2019 to August 2022 and included all patients who presented to us with continuous bleeding of renal origin following various open or percutaneous surgical procedures performed on the kidney and were managed with selective transarterial renal angioembolization. Written informed consent was obtained from each patient, and the study was approved by the Sher-i-Kashmir Institute of Medical Sciences Institutional Ethics Committee with protocol no. IEC/SKIMS protocol #245E/2022. As our hospital is one of the few centers in the region where the facility of angioembolization is available, the study included patients in whom the procedures had been performed in our hospital as well as patients referred from other hospitals. The demographic, clinical and radiological data of the patients at the time of primary procedure were recorded (Table 1). Standard PCNL was defined as tract circumference of more than 20-Fr, while mini-PCNL was defined as tract circumference of less or equal to 20-Fr. All patients underwent computed tomographic angiography (CTA) to identify the source of bleeding and the dimensions of the affected vessel. Clinical, radiological, and invasive angiographic findings that included the site of the bleeding vessel, size, and number of bleeding pathologies (pseudoureurysm/AVF) were recorded (Table 2).

Angioembolization was performed by a single interventional radiologist after obtaining written informed consent from all patients. All procedures were performed in the intervention radiology suite under local anesthesia. After placement of the femoral arterial access sheath, a renal double curve (RDC) 5-Fr angiographic catheter was navigated into the main renal artery over the hydrophilic guide wire (Terumo guide wire) under fluoroscopic guidance. Angiographic films were recorded to identify the bleeding vessel. A 2.9-Fr vascular microcatheter was navigated through the RDC into the bleeding vessel under fluoroscopic guidance. Repeated angiographic films were taken to positively identify the bleeding vessel that was selectively embolized with platinum embolization coils. The size and number of coils to be deployed was determined by the size of the vessel affected by pseudoaneurysm or AVF. Subsequent angiographic films were taken to confirm the sealing of the bleeding vessel. Patients were observed in the ward for the next 24-48 h for any post-procedure complications. A final Doppler study was conducted 24 h after embolization to confirm the resolution of pseudoaneurysm/AVF.

Results

In this prospective study, 20 patients presented to us with severe bleeding of renal origin the following kidney procedures. There were 75% male and 25% female patients with an average age of 46.2±13.18 years (range 28-75 years). Diabetes with hypertension was recorded as a comorbidity in 10% of patients; hypertension alone was reported as a comorbidity in 20% of patients and 5% of patients had chronic kidney disease with hypertension. Renal stone disease was the primary pathology in 75% of patients admitted for angioembolization, among which 80% had undergone PCNL and 20% underwent open nephrolithotomy. The average stone size was 5.06±2.8 cm^2 and 13.5±3.9 cm^2 in the PCNL and the open nephrolithotomy group, respectively. Among the renal stone patients, 60% had undergone standard PCNL with more than one tract dilated in 3 (33.4%) patients and 20% had undergone mini PCNL. 15% of patients with renal bleeding had undergone NSS with an average tumor size of 13.16±5.96 cm^2. One (5%) patient had developed pseudoaneurysm in the graft kidney following renal biopsy and another patient had renal bleeding following percutaneous nephrostomy (PCN) placement for obstructive uropathy. Bleeding in the form of hematuria was reported on an average postoperative day 7 in PCNL patients, 3rd day of nephrolithotomy, 8th day of NSS, 3rd day of graft biopsy, and 13th day of PCN.

The average drop in hemoglobin recorded before the embolization was 2.45±0.69 mg/dL in PCNL patients, 3.05±1.28 mg/dL in nephrolithotomy patients and 3.32±0.82 mg/dL following NSS. The average number of blood transfusions required in our study was 0.8±0.83 units per patient. Blood transfusion was predominantly required in patients following NSS (1.67±057 units/patient). In post-PCNL patients, pseudoaneurysm was the most common vascular pathology noted in 6 (50%) patients (Figure 1), while AVF was identified in 3 (25%) patients. One (8.3%) patient had pseudoaneurysm with AVF and 2 (16.7%) patients had active extravasation demonstrated on angiography (Figure 2a, b). Renal angiography of post-nephrolithotomy patients revealed double pseudoaneurysm in 1 (33.4%) patient, solitary pseudoaneurysm in 1 (33.4%) patient and pseudoaneurysm with AVF in another (33.4%) patient (Figure 3a, b). The predominant bleeding source identified in NSS was AVF in 2 (66.7%) patients and double pseudoaneurysm in another (33.3%) patient. Post renal biopsy patient had a bleeding pseudoaneurysm in the territory of the lower segmental artery of the allograft.

Embolization was done using soft platinum embolization microcoils (0.018 inch core diameter). Embolization in post PCNL bleeding required a single 3 mm coil in 4 (33.4%) patients, double 3 mm coils in 4 (33.4%) patients, single 5 mm coil in 2 (16.7%) patients, and double 5 mm coils in 2 (16.7%) patients.

Table 1. The demographic, clinical and radiological data of the patients at the time of primary procedure done on kidney

S no.	Age (years)	Sex M/F	Comorbidity	Primary pathology	Primary procedure	Time of presentation
1.	32	M	Nil	3×2 cm lower calyceal calculus	Standard PCNL Two tract dilatation	4th day
2.	41	F	Nil	1×1.5 cm lower pole calculus	Mini PCNL	10th day
3.	50	M	Hypertension	3×3.5 cm partial Staghorn calculus	Nephrolithotomy	3rd day
4.	28	M	Nil	1.5×1.3 cm upper pole renal calculus	Mini PCNL	12th day
5.	61	M	Diabetes & hypertension	3×3.5 cm mid pole renal mass, predominantly endophytic	Nephron spring surgery	8th day
6.	43	F	Nil	4×3 cm Staghorn calculus	Nephrolithotomy	5th day
7.	36	M	Nil	1.5×1.9 cm upper calyceal calculus	Standard PCNL	8th day
8.	51	M	Nil	3×3 cm Staghorn calculus	Standard PCNL Two tract dilatation	1st
9.	55	F	Hypertension	2×3 cm renal calculus	Standard PCNL	13th day
10.	33	M	Nil	2×2.2 cm lower calyceal calculus	Standard PCNL	4th day
11.	72	M	Hypertension	4×5 cm upper pole renal mass	Nephron sparing surgery	5th day
12.	38	M	Nil	2×2.8 cm renal pelvic calculus	Standard PCNL	13th day
13.	56	F	Diabetes & hypertension	Renal tumor-upper pole 3×3 cm mid pole predominantly endophytic	Nephron sparing surgery	11th day
14.	75	M	Hypertension	2.5×2.8 cm renal calculus	Standard PCNL	1st
15.	48	F	Nil	3×3.5 cm staghorn calculus	Standard PCNL Two tract dilatation	9th day
16.	29	M	Nil	1×1.6 cm mid calyceal calculus	Mini PCNL	6th day
17.	52	M	Nil	2×2.2 cm upper calyx calculus	Standard PCNL	6th day
18.	44	M	Nil	4×4.5 cm Staghorn calculus	Nephrolithotomy	1st
19.	45	M	Hypertension with chronic kidney disease	Post renal transplant rejection	Graft kidney biopsy	3rd day
20.	35	M	Nil	Carcinoma rectum with obstructive uropathy	Percutaneous nephrostomy	13th day

M: Male, F: Female, PCNL: Percutaneous nephrolithotomy

Table 2. Clinical, radiological and invasive angiographic findings at the time of transarterial angioembolization

S. no	Drop in hemoglobin	Blood transfusion required	Angiographic findings	Size (coiled embolus diameter) & number of coils deployed	Ancillary procedures required	Outcome and complications
1.	1.52 mg/dL	0	Pseudoaneurysm in lower segmental artery territory	3 mm/1 coil	Nil	Hemostasis secured without any complication
2.	2.2 mg/dL	0	Pseudoaneurysm in apical segmental artery territory	3 mm/1 coil	Nil	Hemostasis secured, post embolisation syndrome
3.	2.12 mg/dL	1	Two pseudoaneurysms in posterior segmental artery territory	3 mm/1 coil 5 mm/1 coil	Percutaneous nephrostomy	Hemostasis secured, urosepsis managed with antibiotics
4.	1.92 mg/dL	0	Arteriovenous fistula in upper segmental artery territory	3 mm/2 coils	Nil	Hemostasis secured, post embolisation syndrome
5.	3.22 mg/dL	2	Pseudoaneurysm with AVF in lower segmental artery territory	5 mm/1 coil	Clot evacuation	Hemostasis secured without any complication
6.	2.52 mg/dL	1	Pseudoaneurysm in middle segmental artery territory	3 mm/2 coils	DJ stenting	Hemostasis secured, urosepsis managed with antibiotics
7.	2.72 mg/dL	0	Pseudoaneurysm with AVF in upper segmental artery territory	5 mm/1 coil	Nil	Hemostasis secured without any complication
8.	4.12 mg/dL	3	Active bleeding from posterior segmental artery territory	5 mm/2 coils	Clot evacuation	Hemostasis secured, post embolisation syndrome
9.	2.72 mg/dL	0	Arteriovenous fistula in middle segmental artery territory	3 mm/2 coils	Nil	Hemostasis secured without any complication
10.	2.62 mg/dL	0	Pseudoaneurysm in lower segmental artery territory	3 mm/1 coil	Nil	Hemostasis secured without any complication
11.	3.12 mg/dL	1	Two pseudoaneurysm in upper segmental artery territory	3 mm/1 coil 5 mm/1 coil	Nil	Hemostasis secured without any complication
12.	2.22 mg/dL	0	Pseudoaneurysm in middle segmental artery territory	3 mm/2 coils	Nil	Hemostasis secured without any complication
13.	3.62 mg/dL	2	Pseudoaneurysm with AVF in upper segmental artery territory	5 mm/2 coils	Clot evacuation	Hemostasis secured, post embolisation syndrome
14.	3.2 mg/dL	2	Active bleeding from posterior segmental artery territory	5 mm/2 coils	Clot evacuation, hemodialysis	Urosepsis with acute kidney injury managed & patient discharged with normal creatinine
15.	2.22 mg/dL	0	Arteriovenous fistula in posterior segmental artery territory	3 mm/2 coils	Nil	Hemostasis secured without any complication
16.	1.82 mg/dL	0	Pseudoaneurysm in middle segmental artery territory	5 mm/1 coil	Nil	Hemostasis secured without any complication
17.	2.12 mg/dL	0	Pseudoaneurysm in apical segmental artery territory	3 mm/1 coil	Nil	Hemostasis secured, post embolisation syndrome
18.	4.52 mg/dL	3	Pseudoaneurysm with Arteriovenous fistula in posterior segmental artery territory	5 mm/2 coils	Clot evacuation with repeat embolisation	Failed to achieve hemostasis, nephrectomy done
19.	2.32 mg/dL	1	Pseudoaneurysm in lower segmental artery territory	3 mm/2 coils	Nil	Hemostasis secured without any complication
20.	2 mg/dL	0	Arteriovenous fistula in posterior segmental artery territory	5 mm/1 coil	Nil	Hemostasis secured, post embolisation syndrome

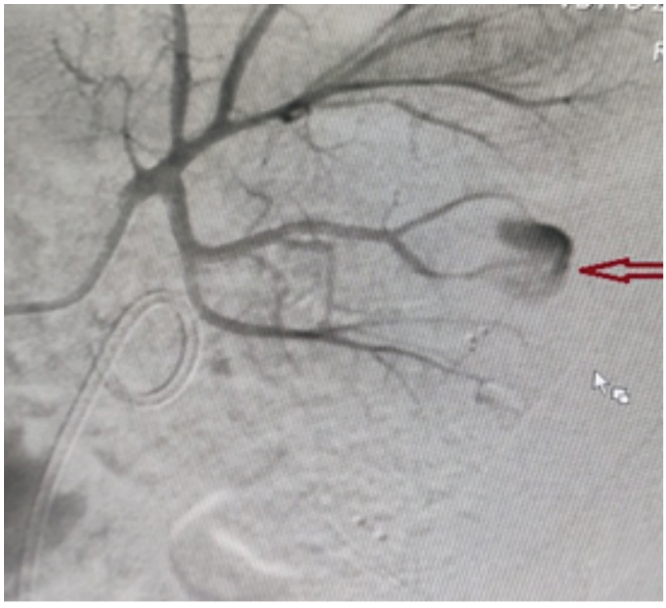

Figure 1. Post percutaneous nephrolithotomy solitary pseudoaneurysm (red arrow) in middle segmental artery

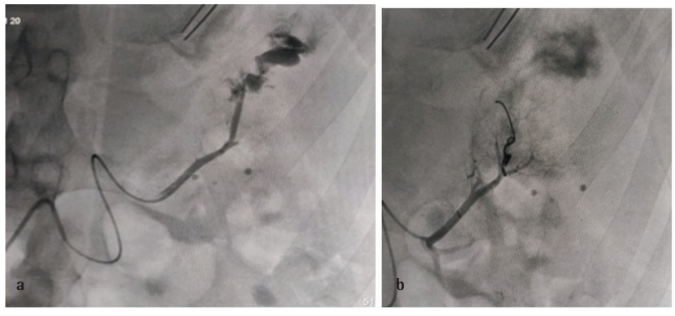

Figure 2. a, b. Active extravasation in apical segmental artery (a) and sealing of bleeding vessel by embolization coil (b)

Post-nephrolithotomy angioembolization required two 3 mm coils in 1 (33.4%) patient, a single 5 mm coil in 1 (33.4%) patient and two coils (3 mm/5 mm) in another (33.4%) patient. NSS patients required a single 5 mm coil in 1 (33.4%) patient, double 5 mm coils in one (33.4%) patient (Figure 4) and 2 coils (3 mm/5 mm) in 1 (33.4%) patient. Post renal biopsy patient required two 3 mm coils while post PCN patient required single 5 mm coil. The ancillary procedures required post embolization were cystoscopic clot evacuation in 25% of patients, PCN in 5% of patients, and Double J (DJ) stenting in 5% of patients. One patent received two sessions of hemodialysis to treat acute kidney injury (AKI).

The hemostasis was secured in all patients for 1 (5%) patient who underwent two unsuccessful attempts of angioembolization. Emergency nephrectomy was done to control bleeding. Post embolization syndrome consist of mild fever and flank pain

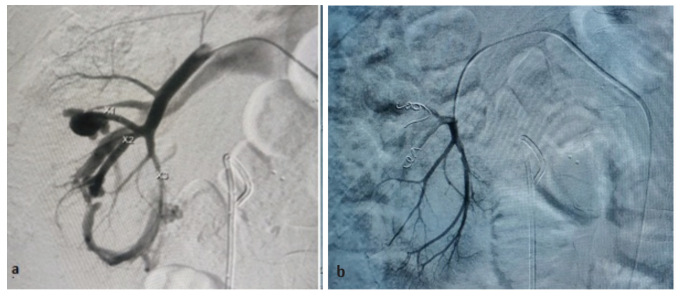

Figure 3. a, b. Double pseudoaneurysm with arteriovenous fistulas (a) and post coiling closure of double pseudoaneurysm (b)

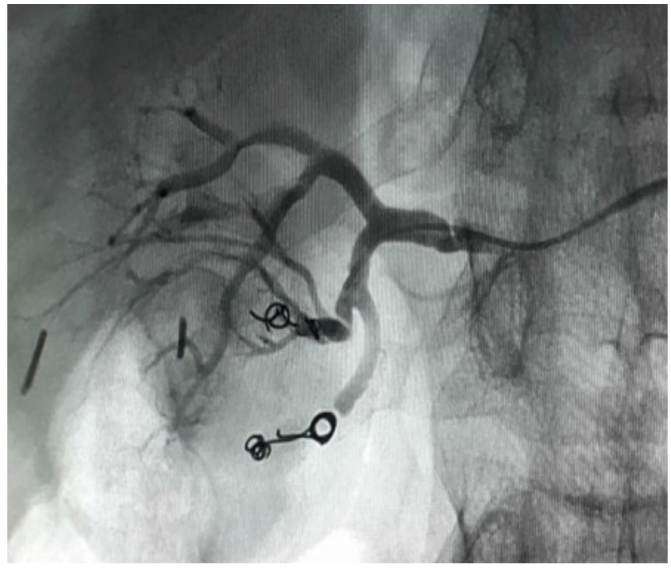

Figure 4. Post coiling sealing of double pseudoaneurysm in nephron sparing surgery

with tachycardia were reported in 30% of patients. There were no major complications except for urosepsis in 10% of patients that was managed by PCN tube placement in one patient and stenting with antibiotics in another patient. One (5%) patient had AKI with urosepsis requiring two sessions of hemodialysis and the patient was discharged in stable condition with normal serum creatinine level.

Discussion

Bleeding represents a common complication of the following procedures performed on the kidney such as PCNL, nephrolithotomy, and NSS. Bleeding may occur during or immediately after the procedure, or the patient may present in a delayed manner usually after an interval of few days, which is commonly secondary to formation of a pseudoaneurysm or AVF (5). Most of the patients in our study had bleeding following PCNL because nephrolithiasis is predominant in our region

and PCNL is performed very frequently. Multiple factors have been attributed to increased risk of bleeding following PCNL, including large stone size, multiple tract dilatations, prolonged operative time, hypertension, and presence of diabetes mellitus (6). Isolated hypertension as a comorbidity was reported in 20% of patients and hypertension with diabetes was present in 10% of patients in our study. The increased risk of renal bleeding in diabetes has been related to its association with atherosclerosis and microangiopathies. Kukreja et al. (7) attributed the increased risk of renal bleeding in hypertension to atherosclerosis. Most post PCNL bleeding was recorded in patients who underwent standard PCNL (tract circumference >20 Fr). Deng et al. (8) reported an increased risk of bleeding in standard PCNL compared to mini PCNL. Postoperative bleeding following NSS remains the most serious complication with an incidence of about 6%. Large tumor size, centrally located tumor, and hypertension have been associated with increased risk of bleeding following NSS (9). Among patients with post NSS bleeding in our study, 66.7% had predominantly endophytic tumors located at the mid pole. Image-guided needle biopsy of the allograft kidney is usually safe with a low incidence of symptomatic AVF of about 0.4% (10). 5% of patients in our study had AVF following renal allograft biopsy. PCN is associated with serious vascular complications in 1-2% of cases. We had only 5% patients with pseudoaneurysm following PCN tube placement.

Bleeding the following kidney procedures is conservatively managed in most cases. Most severe cases of bleeding are those of intrarenal arterial origin with pseudoaneurysm, AVF, or an injured segmental artery demonstrated on imaging studies. These cases usually present 4-15 days after the procedure (11). Our patients presented on average 7 days following PCNL, 3 days following nephrolithotomy, and 8 days following NSS. The average drop in hemoglobin in our patients was 2.45±0.69 mg/dL following PCNL, 3.05±1.28 mg/dL following nephrolithotomy and 3.32±0.82 mg/dL following NSS. The transfusion rate after PCNL is reported to range from 3% to 23% (12). The average transfusion required in our study was 0.8 units/patient. The clinical diagnosis of pseudoaneurysm or AVF should be confirmed by non-invasive imaging modalities. CTA is a sensitive noninvasive imaging modality for the diagnosis of renal bleeding and is recommended as a roadmap for managing these patients (13). All of our patients underwent initial CTA to diagnose the cause of bleeding.

Significant bleeding the following procedures on the kidney usually intrarenal in origin. This complication is the result of AVF or intrarenal pseudoaneurysm formation and usually presents after weeks from the primary procedure (14). In most cases, bleeding can be managed conservatively. However, for severe and persistent bleeding, selective RAE is required to stop bleeding and salvage renal function (15). All of our patients underwent selective RAE in the interventional radiology suite. Since 1970s when RAE was first introduced, the technique has been refined with better embolic agents, smaller delivery catheters allowing precise cannulation of smaller vessels, and better fluoroscopic equipment. Though invasive compared to CT angiography, it provides a more detailed anatomy of the bleeding vessels with the provision to control bleeding at the same time (16). Renal pseudoaneurysm are the most common vascular lesion identified on angiography in these patients. They are formed as a result of arterial injury with contained hemorrhage within the kidney. The associated hematoma is surrounded by the fibrous inflammatory tissue that is very unstable and prone to rupture, leading to massive bleeding. They may occur isolated or in association with AVF (11). Pseudoaneurysm was the most common vascular lesion identified in our study occurring in 50% of post PCNL bleeding patients, 66.7% of post nephrolithotomy patients, 33.4% of post NSS bleeding patients. AVF is a rare pathological communication between renal arteries and veins without interconnecting capillaries that is seen as a source of renal bleeding. They are fragile communications that open under high arterial pressure leading to torrential bleeding (17). Isolated AVF were recorded in 25% of post-PCNL bleeding cases and 66.7% of post-NSS bleeding cases. Pseudoaneurysm with AVF were recorded in 10% of our patients. Active bleeding of the segmental artery without the formation of pseudoaneurysm or AVF were recorded in 10% of our patients.

The success rate of endovascular treatment of renal pseudoaneurysm ranges from 71-100% (18). The success rate in our study was 95%, with a single patient failing two attempts of embolization required emergency nephrectomy. The rate of nephrectomy after PCNL is extremely low (0.2%) because of the high success rate of angioembolization (14). Super selective embolization of a vessel as distal as possible, at least at the interlobar arteries, is mandatory to preserve the renal parenchyma and minimize complications. This can usually be achieved by using microcatheters as delivery devices and microcoils as embolic agents (18). We used microcatheter for the deployment of platinum embolization microcoils (0.018 inch) in our patients. Impaired renal function, difficult vascular anatomy, and stenosis of the main renal artery are some limitations and technical challenges for angioembolization. In one of our patients embolization failed because of the difficult tortuous anatomy of the renal vessels.

Selective RAE is a safe procedure with minimal complications. It precisely seals bleeding vessels without collateral damage to the rest of the renal parenchyma. Chatziioannou et al. (19) reported that selective RAE leads to permanent cessation of bleeding and prevents serious renal parenchymal infarction.

None of our patients had permanent renal impairment following embolization, indicating the limited loss of renal parenchyma. Post embolization syndrome consisting of fever, flank pain, vomiting, and leukocytosis has been reported in over 90% of patients following angioembolization. 30% of our patients had transient fever and flank pain following renal artery embolisation. Treatment consists of analgesics, antipyretics, and antiemetics until symptoms resolve (20). More serious complications reported in RAE are coil migration and inadvertent non-target embolization leading to spine, bowel and limb infarction (21). None of these serious complications was reported in our study.

Study Limitations

The limitations of our study are that it is a single-center study with a relatively small sample size.

Conclusion

Severe and persistent hemorrhage is the most feared complication that can occur following kidney procedures. Selective RAE is safe and highly effective in the control of renal origin bleeding. The procedure is associated with minimal complications; it salvages renal function and avoids more invasive renal exploration or nephrectomy.

Ethics

Ethics Committee Approval: The study was approved by the Sher-i-Kashmir Institute of Medical Sciences Institutional Ethics Committee with protocol no. IEC/SKIMS protocol #245E/2022.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A., Concept: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A., Design: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A., Data Collection or Processing: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A., Analysis or Interpretation: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A., Literature Search: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A., Writing: S.A.P., S.M., S.M., S.W., A.B., N.C., S.L., F.A.

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ORIGINAL RESEARCH
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Minimally Invasive Treatment of Female Stress Urinary Incontinence with Polyacrylamide Hydrogel (Bulkamid®): Outcomes of a Contemporary Turkish Cohort Including Cases with Mixed Urinary Incontinence and Previously Failed Prior Surgery

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

Heightened concerns about the safety of mesh-based surgery for treating female stress urinary incontinence following reports from various organizations worldwide have boosted the interest in alternative management options. Urethral bulking agents have regained popularity within this context owing to their minimally invasive nature and favorable safety profile. Our study showed that polyacrylamide hydrogel injection appears to be a safe and effective minimally invasive surgical treatment option for women with pure stress urinary incontinence and stress-predominant mixed urinary incontinence in both primary and secondary settings in a Turkish cohort.

Abstract

Objective: We aimed to describe the outcomes and patient satisfaction (PS) rates of transurethral polyacrylamide hydrogel (PAHG) (Bulkamid®) injection for the treatment of female stress urinary incontinence (SUI) in a Turkish cohort.

Materials and Methods: Twenty-two patients who underwent injection primarily or secondarily between December 2019 and March 2023 due to SUI or stress-predominant mixed urinary incontinence (MUI) were retrospectively evaluated. All patients underwent an invasive urodynamic study (UDS) before the procedure. The primary outcome was treatment success (TS), defined as no pad use, negative International Continence Society (ICS) uniform cough stress test (CST), and no SUI on International Consultation on Incontinence Questionnaire-Short Form question 6. The secondary outcome was PS.

Results: The median age was 61.5 (41-84) years. Six patients had stress-predominant MUI and 15 had SUI. PAHG injection was the primary and secondary treatment in 17 and 4 patients, respectively. ICS uniform CST was positive in all patients. In 8 patients, intrinsic sphincter deficiency (ISD) was detected during UDS. One patient developed transient urinary retention after surgery. At a median follow-up of 17 (1-38) months, the overall TS rate was 85.7%. Success rates in primary vs. secondary setting and pure SUI vs. MUI were 88.2% vs. 75% and 80% vs. 100%, respectively. The overall PS rate was 90%. Satisfaction rates in the primary vs. secondary setting and pure SUI vs. MUI were 93.6% vs. 75% and 85.7% vs. 100%, respectively. TS and PS rates were 100% in all patients with ISD.

Conclusion: PAHG injection proved to be a safe and effective minimally invasive treatment for pure stress and stress-predominant MUI in both primary and secondary settings.

Keywords: Bulkamid, injection, polyacrylamide hydrogel, stress, urinary incontinence

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Introduction

Heightened concerns about the safety of mesh-based surgery for treating female stress urinary incontinence (SUI) following reports from various organizations worldwide have boosted the interest in alternative management options (1). Urethral bulking agents have regained popularity within this context owing to their minimally invasive nature and favorable safety profile.

Bulking agents are divided into two groups: particulate agents (composed of solid microparticles in an absorbable liquid or gel carrier) and non-particulate agents (comprising a homogenous gel resistant to absorption). Carbon-coated zirconium oxide (Durasphere®), calcium hydroxylapatite (Coaptite®), and polydimethylsiloxane are particulate products in the market. Polyacrylamide hydrogel (PAHG) (Bulkamid®) is the only non-particulate product that gained FDA approval in 2006 for female SUI treatment. PAHG is a polymer gel consisting of 2.5% cross-linked polyacrylamide and 97.5% water for injection. It is resistant to degradation. PAHG has been used in aesthetic, plastic, and reconstructive surgery in Europe for many years, and long-term as well as experimental studies have shown that the gel is gradually integrated into host tissue through a fine network of vessel-bearing connective tissue, without capsular fibrosis or calcification (2-4). PAHG entered the market in Turkiye by the end of 2019. Our cohort also included the first patient who underwent PAHG injection on December 9th, 2019 in Turkiye.

The primary aim of this study was to describe the treatment outcomes and patient satisfaction rates of PAHG injection for the treatment of female SUI in a Turkish cohort.

Materials and Methods

After ethical approval obtained from the Institutional Review Board of Koc University (2023.068.IRB1.020) on 27.02.2023, the data of all female patients who underwent transurethral PAHG injection as a primary or secondary treatment between December 2019 and March 2023 due to SUI or stress-predominant mixed urinary incontinence (MUI) were retrospectively evaluated. A total of 22 PAHG injection procedures were performed. One patient who underwent oncological pelvic surgery (due to endometrium cancer) complicated by bladder perforation and who received adjuvant pelvic radiotherapy, brachytherapy, and chemotherapy was excluded (Figures 1 and 2). The indications for PAHG injection were detection of intrinsic sphincter deficiency (ISD) on invasive urodynamic study (UDS), failure of previous SUI surgery, and patient preference toward minimally invasive treatment. ISD was defined as a Valsalva leak point pressure below 60 cmH_2O (5). All injections were performed by the same surgeon, who had more than 30 years of experience in functional, female, and reconstructive urology and in injection treatment for various urological indications such as vesicoureteral reflux and post-prostatectomy UI as well as female SUI. Age, duration of complaints, pelvic examination findings, frequency of micturition, postvoid residual urine volume, and invasive UDS results were recorded.

Pelvic examination included the International Continence Society (ICS) uniform cough stress test (CST) (6). As defined by the Q-tip test, the degree of displacement of the intraurethral cotton swab on the horizontal plane upon increased intraabdominal pressure was used to assess urethral mobility (7). 0° immobile urethra, 0-30° decreased urethral mobility, >30° hypermobile urethra (8).

All patients underwent invasive UDS preoperatively according to the ICS standards (9).

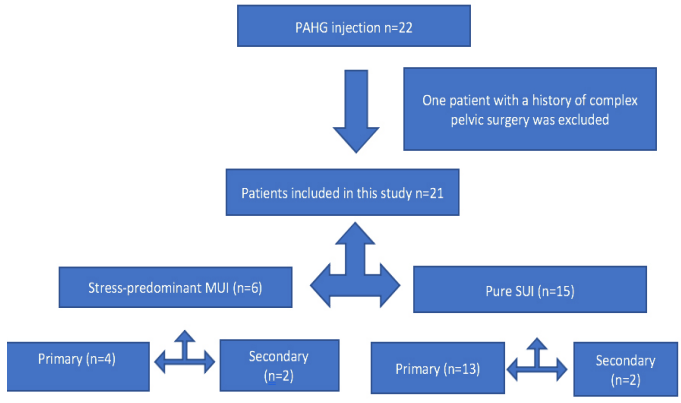

Figure 1. Flowchart showing the methodology and patient distribution with regards to type of urinary incontinence

PAHG: Polyacrylamide hydrogel, MUI: Mixed urinary incontinence, SUI: Stress urinary incontinence

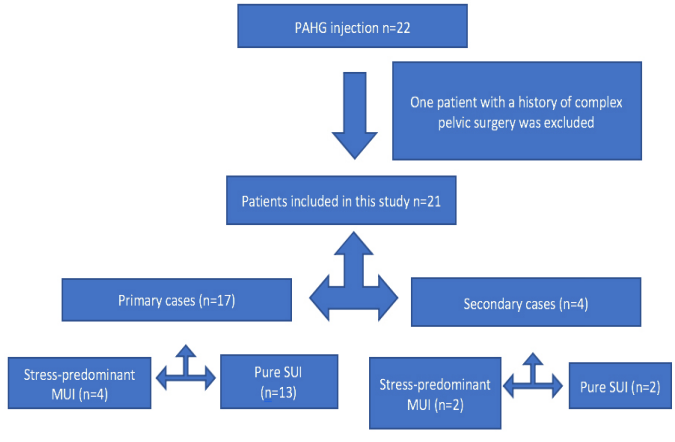

Figure 2. Flowchart showing the methodology and patient distribution with regards to history of previous SUI surgery

PAHG: Polyacrylamide hydrogel, MUI: Mixed urinary incontinence, SUI: Stress urinary incontinence

All procedures were performed on an outpatient basis under general anesthesia in the lithotomy position with a proprietary delivery system and a 23-G injection needle. After completing the cystoscopic evaluation, 2 cc PAHG was injected at 4 different sites on the bladder neck-urethral junction (Figure 3) (10). The bladder was emptied with an 8-Fr feeding tube at the completion of the procedure.

ICS uniform CST was repeated at follow-up visits. The number of pads per day and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) scores related to SUI (item #6) were questioned during a phone interview (11). Additionally, patients were asked to weigh the change in their continence status as "cured", "improved", "not changed" or "worsened". Patients were asked whether they would recommend PAHG injection to a friend. Additional treatment for SUI following PAHG injection was also questioned.

The primary outcome measure was treatment success, which was defined as no pad use, negative ICS uniform CST, and declaration of no SUI on ICIQ-SF question 6.

The secondary outcome measure was satisfaction with treatment outcome. Defining post-injection continence status as "cured" and recommending PAHG injection to a friend were accepted as satisfaction criteria.

Patients with a history of complex pelvic surgery were excluded. Patients who received invasive SUI treatments after PAHG injection were excluded from the satisfaction evaluation.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0. Continuous variables are reported as medians with ranges.

Results

The median age of the patients was 61.5 (41-84) years. Six patients had stress-predominant MUI, whereas 15 had pure SUI. PAHG injection was the primary treatment in 17 patients, whereas 4 had previous SUI surgeries. The median duration of symptoms was 24 (6-100) months. The median urinary incontinence frequency was 3/day (2-8).

None had grade 3 or higher pelvic organ prolapse. ICS uniform CST was positive in all patients. Eight (38%) of 21 patients had increased urethral mobility. Three patients had decreased urethral mobility and 10 had immobile urethra.

The median pre-injection maximum urine flow rate, average urine flow rate, voided volume (VV), and postvoid residual urine volume (PVR) were 20.8 (10-39) mL/s, 9 (2-19) mL/s, 407.5 (120-840) mL, and 10 (10-30) mL, respectively. Invasive UDS revealed urodynamic SUI in all patients and ISD in 8 patients. In 5 patients, pressure-flow studies could not be completed because of catheter dislodgement or inability to void with a urethral catheter. Table 1 summarizes the invasive UDS results.

Seventeen patients (80.9%) had no previous SUI surgery. Two patients previously underwent transurethral injection with another bulking agent (dextranomer/hyaluronic acid copolymer, Deflux®) and 4 had mid-urethral sling (MUS) surgery at other institutions [3 transobturator tape (TOT), 1 transvaginal tape (TVT)]. Another patient had a history of deflux injection and TOT insertion. Among those with a history of MUS surgery, 2 underwent tape cutting due to mesh erosion before PAHG injection.

The median operative duration was 15 (10-30) minutes. The mean cystoscopic bladder capacity was 700 (100-1000) mL. One patient developed urinary retention early after surgery, which subsided spontaneously following drainage of the bladder with a feeding tube.

At a median follow-up of 17 (1-38) months, the median post-injection maximum urine flow rate, average urine flow rate, VV, and PVR were 32 (12-48) mL/sec, 13 (6-19) mL/sec, 400 (210-840) mL and 10 (0-40) mL, respectively.

The success rate was 85.7% (18/21). In 1 patient, TOT was performed 3 months after PAHG injection because of persistent SUI. In another patient who previously underwent TOT, duloxetine treatment was initiated (Table 1).

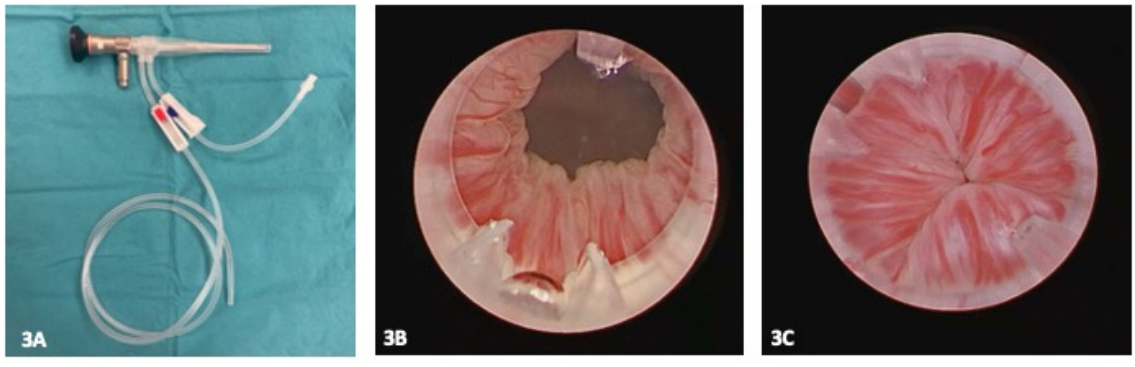

Figure 3. Proprietary system, bladder neck before and after hydrogel injection. 3A. Proprietary system, 3B. Pre-injection, 3C. Post-injection

Table 1. Demographical, clinical, operative and follow-up data including all patients

Patient	Age	Follow-up (months)	Type of UI	Primary/ Secondary	Previous SUI treatment	Urethral mobility	ALPP	DOA	Bladder compliance	Maximum cytometric capacity	Pdet @Q_{max}	Pads/ day (preop)	Pads /day (postop)	ICS uniform CST (postop)	ICIQ-SF SUI Score (postop)	Patient reported satisfaction	Additional Treatment	Suggest this procedure to a friend?	Treatment success	Patient satisfaction
1	63	38	S	P	-	IM	51	None	>40	560	3	3	0	Negative	0	Cured	No	Yes	Yes	Yes
2	79	38	M	P	-	IM	56	Yes	15	362	13	3	0	Negative	8	Cured	OAM	Yes	Yes	Yes
3	56	35	S	S	TOT Deflux Tape cut	DM	11	None	>40	170	13	NA	0	Negative	0	Cured	No	Yes	Yes	Yes
4	57	32	M	P	-	IM	90	None	>40	510	41	1	0	Negative	0	Cured	No	Yes	Yes	Yes
5	51	32	S	P	-	HM	100	None	>40	547	10	NA	0	Negative	0	Cured	No	Yes	Yes	Yes
6	76	21	S	P	-	DM	155	None	>40	312	-	3	3	Negative	21	Not changed	No	No	No	No
7	46	21	S	S	TOT	IM	80	None	>40	340	27	2	1	Negative	10	Improved	Duloxetine	No	No	No
8	60	38	M	P	-	IM	97	None	>40	350	25	NA	0	Negative	0	Cured	No	Yes	Yes	Yes
9*	72	15	M	S	Deflux	HM	94	None	26	400	-	NA*	NA*	Negative	NA*	NA*	Botulinum toxin injection	NA*	NA*	NA*
10	72	17	S	P	-	IM	45	None	>40	409	-	3	0	Negative	0	Cured	No	Yes	Yes	Yes
11	46	17	S	P	-	HM	34	None	>40	509	10	2	0	Negative	0	Cured	No	Yes	Yes	Yes
12	84	10	S	P	-	IM	40	None	>40	314	-	4	0	Negative	0	Cured	No	Yes	Yes	Yes
13	46	10	S	P	-	HM	130	None	>40	582	-	1	0	Negative	0	Cured	No	Yes	Yes	Yes
14	43	10	S	P	-	HM	120	None	>40	520	33	2	0	Negative	0	Cured	No	Yes	Yes	Yes
15	76	10	S	P	-	IM	80	None	>40	360	32	NA	0	Negative	0	Cured	No	Yes	Yes	Yes
16	58	7	M	P	-	HM	133	None	>40	563	7	3	0	Negative	0	Cured	No	Yes	Yes	Yes
17	72	6	M	S	TVT Tape cut	IM	115	Yes	9	110	19	4	0	Negative	0	Cured	No	Yes	Yes	Yes
18	71	4	M	S	TOT	IM	25	None	>40	428	8	NA	0	Negative	0	Cured	OAM	Yes	Yes	Yes
19	60	35	S	P	-	HM	98	None	>40	506	30	NA	0	Negative	0	NA**	TOT	NA**	No	NA**
20	70	2	S	P	-	HM	182	None	>40	350	0	2	0	Negative	0	Cured	No	Yes	Yes	Yes
21	62	1	S	P	-	DM	56	None	>40	536	0	1	0	Negative	0	Cured	No	Yes	Yes	Yes
22	41	1	S	P	-	HM	100	None	>40	646	3	1	0	Negative	0	Cured	No	Yes	Yes	Yes

* The patient who underwent oncological pelvic surgery (endometrium cancer) and had adjuvant pelvic radiotherapy, brachytherapy and chemotherapy complicated by bladder perforation was excluded.
**Patient excluded from satisfaction evaluation due to undergoing TOT 3 months after PAHG injection, UI: Urinary incontinence, SUI: Stress urinary incontinence, ALPP: Abdominal leak point pressure, DOA: Detrusor overactivity, Pdet@Q_{max}: Detrusor pressure recorded at the maximum urine flow rate during pressure-flow study, CST: Cough stress test, IM: Immobile urethra, DM: Decreased mobility, HM: Hypermobile urethra, TOT: Transobturator tape, TVT: Transvaginal tape, NA: Not available, OAM: Oral antimuscarinic treatment, ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form

Table 2. Treatment success and patient satisfaction rates for primary, secondary, pure stress urinary incontinence and stress-predominant mixed urinary incontinence

Total	Treatment success* (n, %)	Patient satisfaction** (n, %)
	18/21, 85.7	**18/20, 90**
Urethral mobility		
Hypermobile	7/8, 87.5	7/7, 100%
Decreased mobility	2/3, 66	2/3, 66%
Immobile	9/10, 90	9/10, 90
ALPP <60 cmH_20	8/8, 100	8/8, 100%
Immobile urethra + ALPP <60 cmH_20	5/5, 100	5/5, 100
Primary	15/17, 88.2	15/16, 93.6
Secondary	3/4, 75	3/4, 75
Pure SUI	12/15, 80	12/14, 85.7
Stress-predominant MUI	6/6, 100	6/6, 100
Primary	15/17, 88.2	15/16, 93.6
Pure SUI	11/13, 84.6	11/12, 91.6
Urethral mobility		
Hypermobile	6/7, 85.7	6/6, 100
Decreased mobility	1/2, 50	1/2, 50
Immobile	4/4, 100	4/4, 100
ALPP <60 cmH_20	5/5, 100%	5/5, 100%
Stress-predominant MUI	4/4, 100	4/4, 100
Urethral Mobility		
Hypermobile	1/1, 100	1/1, 100
Decreased mobility	-	-
Immobile	3/3, 100	3/3, 100
ALPP <60 cmH_20	1/1, 100	1/1, 100
Secondary	3/4, 75	3/4, 75
Pure SUI	1/2, 50	1/2, 50
Urethral mobility		
Hypermobile	-	-
Decreased mobility	1/1, 100	1/1, 100
Immobile	0/1, 0	0/1, 0
ALPP <60 cmH_20	1/1, 100	1/1, 100
Stress-predominant MUI	2/2, 100	2/2, 100
Urethral mobility		
Hypermobile	-	-
Decreased mobility	-	-
Immobile	2/2, 100	2/2, 100
ALPP <60 cmH_20	1/1, 100	1/1, 100

*Defined as: Negative ICS uniform CST, no pad use after injection, ICIQ-SF Q6 score of 0
**Defined as: Self-defined as "cured" after PAHG injection and recommending the procedure to a friend. One patient excluded from satisfaction evaluation due to undergoing TOT 3 months after PAHG injection, PAHG: Polyacrylamide hydrogel, MUI: Mixed urinary incontinence, SUI: Stress urinary incontinence, ALPP: Abdominal leak point pressure, ICS: International Continence Society, CST: Cough stress test, ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form

The patient satisfaction rate was 90% (18/20). None of the patients defined post-injection continence status as "worsened". Eighteen patients defined their new status as "cured" and all declared that they would recommend PAHG injection to a friend. One patient defined post-injection continence status as "not changed" and another as "improved". The patient who underwent TOT procedure following PAHG injection was excluded from this assessment, despite achieving "improved" status.

Among 6 patients who had stress-predominant MUI preoperatively, 2 (33.3%) continued anticholinergic oral pharmacotherapy.

Treatment success and patient satisfaction rates for primary and secondary SUI as well as pure SUI and stress-predominant mixed UI are summarized in Table 2.

Discussion

With increasing awareness of complications related to mesh use in sling surgery, injection of urethral bulking agents has started to occupy a larger space in our armamentarium as a minimally invasive surgical treatment option for female SUI not only in the primary setting but also for cases with persistent leakage despite previous surgery (12,13). According to the American Urological Association and the National Institute for Health and Clinical Excellence guidelines, the indications of urethral bulking agents could be listed as being surgically unfit for a procedure under general anesthesia, patient's desire to undergo a minimally invasive intervention, decreased urethral mobility, and history of failed SUI surgery (12,14). In our study, 61.9% (13/21) of the patients had decreased urethral mobility, 4 of 21 (19%) reported persistent SUI despite previous surgeries, and the majority expressed their willingness to undergo a minimally invasive procedure to treat their incontinence.

An ideal bulking agent should be non-immunogenic, biocompatible, and trigger minimal inflammatory and fibrotic responses (15). Polyacrylamide hydrogel (Bulkamid®) is the only FDA-approved non-particulate bulking agent in the market. PAHG's bulking effect occurs as a result of host cells' entrance into the hydrogel and building a long-lasting network that stabilizes the gel *in situ* (4). In addition, the endoscope used for PAHG injection has a rotatable sheath with inflow/outflow apertures, and its working channel can accommodate a needle of 23-G caliber and 12 cm length. These instrumental nuances served well for the standardization and replicability of PAHG injection (16). Owing to these structural and technical advantages, PAHG was introduced as a potentially safer and more effective option than other bulking agents.

The reported success rates of PAHG injection show significant variation due to non-standardized outcome assessment. Studies have shown treatment success rates ranging between 42 % and 70% (17-21). The most commonly used success criteria were improvement in the ICIQ-SF and visual analog scale scores, the number of incontinence episodes, pad weight tests, and negative ICS uniform CST (21). Our overall treatment success rate, which was defined as no pad use, negative ICS uniform CST, and declaration of no SUI on ICIQ-SF question 6, was 85.7%. The follow-up duration and re-injection ("top-up") rates of the studies involving patients who underwent PAHG injection ranged between 3 to 96 months and 7-70%, respectively (21). None of the patients in our study underwent repeat injection at a mean follow-up duration of 19.8 months.

Our subjective success rate was 90% as determined by post-injection continence status being defined as "cured" and feeling confident enough to recommend PAHG injection to a friend. This is at the upper end of the success range (61-95%) reported in relevant studies (16,22-24). This might be a result of the heterogeneity of the outcome assessment tools, such as the visual analog scale, Likert scale, ICIQ-SF, Patient Global Improvement Questionnaire, Incontinence Impact Questionnaire, and patients' definitions of their new conditions on a scale from worsened to improved (25).

In a recent review, Braga et al. (20) reported subjective and objective cure rates of PAHG injection in recurrent SUI ranging between 11.8% to 83%. Our results demonstrated 75% cure rate in patients with SUI despite previous surgery, which is compatible with the literature.

Only a few studies have compared the outcomes of PAHG injection in patients with pure SUI vs. stress-predominant MUI and reported better outcomes in pure SUI (16,23). In contrast, we detected higher objective and subjective cure rates in stress-predominant MUI. This might be a reflection of the small sample size (13 pure SUI vs 8 MUI). Eight patients had ALPPs below 60 cmH_2O on pre-operative invasive UDS. Regardless of being in the primary or secondary setting or having pure SUI or stress-predominant MUI, treatment success was 100% in these women with ISD. Supporting this data with a larger sample size might better reveal the value of ISD in predicting the outcome of urethral bulking treatment.

Various studies comparing the safety profile of bulking agents revealed that PAHG had the lowest rate of adverse events (26). The most common adverse events related to PAHG injection were urinary retention (0-73.1%), dysuria (0-46.2%), urgency (0-24.7%), and urinary tract infection (0-23.8%). Hematuria (0-7.7%), pain (0-2.5%), and complications related to the injection site are relatively rare (21,27). In our series, transient urinary retention was the only recorded complication (n=1, 4.7%). The low complication rates in our study might be related to the expertise level of the operating surgeon (over 500 injections during his career), small sample size, and limited follow-up duration. Hansen et al. (28) showed that performing >75 injections/surgical career and more than 15 injections/year increased the chance of cure and decreased the readmission rates after treatment.

To the best of our knowledge, this is the first study to present the outcomes of PAHG injection for the treatment of female SUI in Turkiye. Reflecting the experience of a single surgeon who is highly experienced in the field of female and functional urology adds uniformity to patient evaluation, surgical technique, and outcome assessment. Another study strength was the use of standardized diagnostic methods such as ICS uniform CST, Q-tip test, and invasive UDS in all patients. In addition, the results of this study add to the growing body of evidence that supports the use of PAHG injection for female SUI and provide a local snapshot regarding its safety and efficacy.

Study Limitations

This study is not without drawbacks. A retrospective design with inherent selection biases, small population size, and relatively short follow-up duration are the main limitations. Future studies, including larger populations and comparison groups, will improve the data that our study provided.

Conclusion

With its high success and patient-reported satisfaction rates together with low likelihood of injection-related adverse events, as demonstrated in this Turkish cohort, PAHG injection appears to be a safe and effective minimally invasive surgical treatment option for women with pure SUI and stress-predominant mixed UI in both primary and secondary settings.

Ethics

Ethics Committee Approval: Ethical approval obtained from Koç University Institutional Review Board on 27.02.2023. Approval number is 2023.068.IRB1.020

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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CASE REPORT
General Urology

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Robot-assisted Management of Anterior Calyceal Diverticular Calculi

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Abstract

Calyceal diverticula are rare outpouchings of the upper collecting system that likely have a congenital origin. The incidence of the stone formation in the calyceal diverticula is up to 50%. The most effective diagnostic method is the computed tomography urogram. Treatment options for symptomatic patients include shock -wave lithotripsy, ureteroscopic or percutaneous methods, and laparoscopic surgery. The treatment option should be selected based on the basis of the diverticulum location and stone burden. This paper reports an interesting case of a 19-year-old boy with a stone burden of 1.663 mm^3 in the calyceal diverticula of the right kidney. The patient underwent a robot-assisted procedure using the daVinci© Xi system.

Keywords: Robot assisted surgery, calyceal diverticular calculi, robotic therapy

Introduction

Calyceal diverticula are rare eventrations of the upper collecting system lying within the renal parenchyma, and stones have reportedly been found in 9.5% to 50% of cases (1,2). They were first described as cysts more than 180 years ago (3), with more similar definitions to follow (4-6) until finally, the term calyceal diverticula was first mentioned (7). The majority of authors favor congenital over acquired origin regarding the cause of calyceal diverticula, although there is no consensus about the timing of the anomaly relative to birth (8,9). Some authors have reported approximately 35 days as the time when the ureteric bud develops (10), whereas others have supported a timeline that places the formation of the calyceal diverticula just before birth (11). The condition affects approximately 63% of women and approximately 37% of men, and has no predilection toward a particular side of the body, with the average diverticulum size being 1.72 cm ranging from 0.5 to 7.5 cm, and the average stone size is 12.1 mm and ranges from 1 to 30 mm (12). Asymptomatic calyceal diverticular calculi with no signs of infection can be managed just with surveillance. For symptomatic patients, the treatment choice mainly depends on the location of the calyceal diverticular calculi, stone burden, and patient preference. Several therapeutic options for managing symptomatic caliceal diverticular calculi are available, varying from extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), ureterorenoscopy (URS), and retroperitoneal laparoscopic approach for stone extraction. With the introduction of the robotic system, this minimal invasive treatment can be added in selected cases.

Case Presentation

A 19-year-old boy, with an unremarkable medical history, was initially examined for persistent discomfort in the right lumbar region, lasting more than a year. The physical examination was age-appropriate, without any signs of infection. Vital signs and the laboratory test results were within the normal range. The urine tests were sterile and without signs of micro- and gross hematuria. The body mass index was 23 kg/m^2. The initial ultrasound examination discovered a stone formation of 2 cm in diameter in the middle calyces of the right kidney. For further clarification, a computed tomography (CT) urogram was performed, which confirmed the diagnosis of 2 cm stone formation in the anterior diverticula with a narrow neck, thin overlying parenchyma, and stone density of 1.035 Hounsfield

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units. No further abnormalities were found except for proximal ureter kinking (Figure 1). The patient had no previous cases of urolithiasis. Conservative versus operative options were discussed with the patient. The chosen form of treatment, which was assumed to be definitive, involved surgery due to persistent discomfort and occasional pain in the right lumbar region. The following therapy options were discussed: ESWL, PCNL with possibly a simultaneous ureteroscopic approach, retroperitoneal-laparoscopic, and finally transperitoneal robot-assisted surgery. Ultimately, the patient decided to undergo a robot-assisted definitive treatment. A four-port setting was used. The procedure lasted 63 min and was performed in several steps. After identifying the diverticulum, the parenchyma overlying the lesion was incised. Although one solitary stone of 2 cm in diameter was described in CT, there were actually at least 5 separate stones of different sizes, ranging from 3-5 mm. The laser usage was not necessary, and all stones could be removed using a grasped (Figure 2). The remaining sand-like material was aspirated. Blood loss was 15 mL. The calyx neck was closed using a 2/0 monofilament, non-nonabsorbable polypropylene suture for hemostasis. The renal defect, renal fascia, and peritoneum were then also sutured. No drain was placed. Postoperative laboratory tests were within the normal range. The ultrasound examination performed after the surgery was unobtrusive. Metamizole was administered for 2 days, and the patient was discharged on the 3rd postoperative day. The one-month follow-up was without any deviation from the normal postoperative course. The discomfort in the right lumbar region has disappeared.

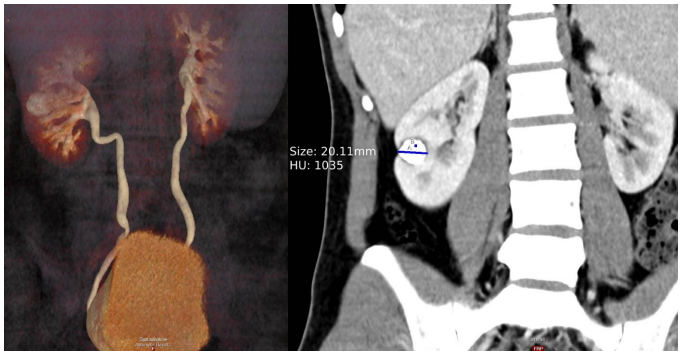

Figure 1. Computerized tomography urogram (left), size and density of the stone (right)

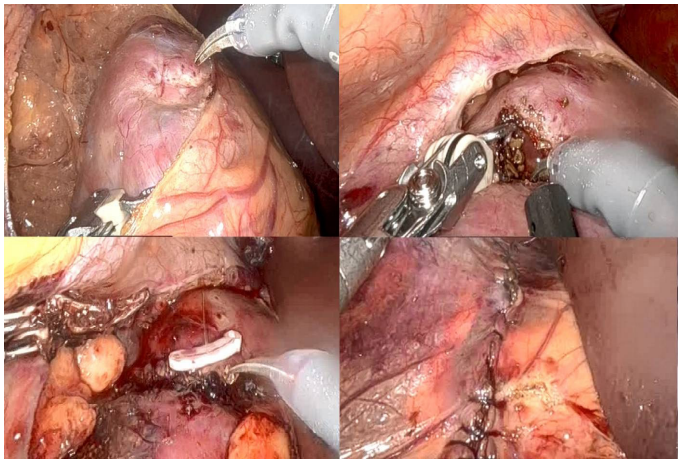

Figure 2. Main steps during the surgical procedure

Discussion

The majority of patients with calyceal diverticula are asymptomatic before stone formation, the condition occurs equally in both sexes, and the diagnosis is usually made on imaging performed for other reasons (13). For asymptomatic calyceal diverticular calculi with no signs of infection, regular follow-up is indicated. Once the patient becomes symptomatic in any way (14), several treatment options, mainly dependant on the location of the calyceal diverticular calculi and stone burden, are available (15).

The principal minimally invasive modalities, including ESWL, PCNL, URS and laparoscopy are well-documented (16). Although ESWL can be offered as the first-line, non-invasive treatment option for all diverticular calculi, the relatively low stone-free rates (4-20%) could be a setback (17). ESWL can also cause symptomatic ease in 36-70% of patients (18). PCNL produces better results compared with ESWL monotherapy (12). Nevertheless, the percutaneous approach can be challenging because of the small cavity and difficult diverticular neck identification (19). The stone-free rates after PCNL are approximately 80%, and some authors have reported complication rates of 54% (20). Some other authors have reported complications such as severe hemorrhage, damage to the surrounding organs, or the kidney parenchyma, partly due to the anatomical position of the diverticulum, sepsis, or even death (15). Our blood loss was 15 mL. With the advancement of URS, the introduction of flexible instruments with excellent picture quality and laser devices, this technique can be used for stones in the upper and middle calyces and produces durable results with low morbidity. However, the calyceal neck cannot be identified during a retrograde approach in up to 30% of patients (21). During our procedure, the calyceal neck was good visualized. Some authors have reported a symptom-free rate of just 35% after 6 weeks and stone-free rates of just 19% (22). Even so, URS has enough advantages with a short duration of hospitalization and low risk of complications (23). All the above-mentioned procedures carry the burden of radiation exposure, which is also an important aspect of therapy selection. Compared to other methods, retroperitoneal laparoscopy is considered the most invasive approach and is usually reserved for cases with large stones in the anterior diverticula, with a narrow neck and complex branched calculi, with thin overlying parenchyma (21).

Perioperative outcomes of laparoscopic surgery for calyceal diverticula are encouraging, and its long-term results appear to be durable (12).

The introduction and further development of robotic systems, three-dimensional vision, magnification, dexterity, and ergonomic comfort have been added to the laparoscopic approach. However, the literature about robot-assisted treatment is scarce, with just a handful of reports published (24,25). Nonetheless, this paper demonstrates that the robot-assisted treatment is effective and safe with good short -term stone-free results.

Conclusion

The robot-assisted laparoscopic technique is a legitimate therapy option and should be added to other treatment options for caliceal diverticular calculi in the robotic era. The procedure is technically well feasible with minimal morbidity, an excellent stone-free rate, and a short hospital stay. More extensive series on robot-assisted techniques, which may require a multi-institutional effort due to the relative rarity of the disease, are needed.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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IMAGES IN CLINICAL UROLOGY
General Urology

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Prostatic Urethral and Vesical Synechiae Secondary to Recurrent Urinary Tract Infection and Bladder Outlet Obstruction: An Intraoperative Surprise for the Urologist

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Abstract

Synechiae are intracavitary adhesions rarely reported in the urological literature. To date, very few cases of ureteral and vesical synerchiag (after urological surgery) have been reported. We report a rare case of prostatic urethral and vesical synechiae secondary to recurrent urinary tract infection (UTI). This was incidentally diagnosed on cystoscopy. A patient with known case of diabetes mellitus and ischemic heart disease presented with storage and voiding lower urinary tract symptoms. He had left epididymoorchitis and recurrent UTI. Investigations showed a left solitary functioning kidney with hydronephrosis and small capacity bladder. He had leucocytosis, raised serum creatinine, and positive urine culture. Under antibiotic cover, he was planned for cytoscopy left Double J (DJ) stenting. During cytoscopy, the patient had a short segment bulbar urethral stricture, which was managed with optical internal urethrotomy. Multiple bladder and prostatic urethral synechiae were found along with bladder diverticula and small bladder capacity. The left ureteric orifice was identified at 1-o'clock. Retrograde pyelography showed an upper ureteric kink and DJ stenting was difficult. The patient improved clinically and is under follow-up. Till date, retained suture material due to urological surgery has been identified as the cause of synechiae. However, our patient didn't have a history of surgery. No foreign material was identified during cystoscopy. Hence, we postulate that recurrent UTI and bladder outlet obstruction (stricture urethra) contributed to the development of synechiae. Laser incision of synechiae is recommended as the treatment.

Keywords: Urology, synechiae, urinary tract infection

Introduction

A 76-year-old gentleman presented with fever with voiding and storage lower urinary tract symptoms. He was a known case of diabetes mellitus and ischemic heart disease. He had a history of recurrent urinary tract infection (UTI). On local examination, he had left epididymoorchitis. Blood investigations showed leukocytosis (20.000/cu.mm) and raised serum creatinine levels (3.0 mg/dL). Urine routine microscopy showed loaded pus cells. Urine culture was positive and the patient was started on 3rd generation cephalosporins. Non-contrast computed tomography scan findings were: Left solitary functioning kidney with hydronephrosis, right poor functioning kidney, and trabeculated small capacity bladder. Under antibiotic cover, the patient was planned for cytoscopy and left Double J (DJ) stenting.

During cytourethroscopy, the patient had a short segment bulbar urethral stricture. This was managed with optical internal urethrotomy (1). Cystoscopy showed multiple prostatic urethra and bladder synechiae, bladder diverticula, and small bladder capacity (Images 1, 2). A stalagnate like pillar, classical of vesical synechiae, was identified (Image 3) (2). With difficulty, the left ureteric orifice was identified at 1-o'clock. Retrograde pyelography showed an upper ureteric kink and DJ stenting was performed. Bladder biopsy was avoided as the patient was on antiplatelets. The patient improved clinically and serum creatinine declined. He was discharged 2 days later and is under follow-up. He is being planned for laser incision for synechiae after clinical optimization.

Synechiae are intracavitary adhesions rarely reported in the urological literature. To date, very few cases of ureteral synechiae

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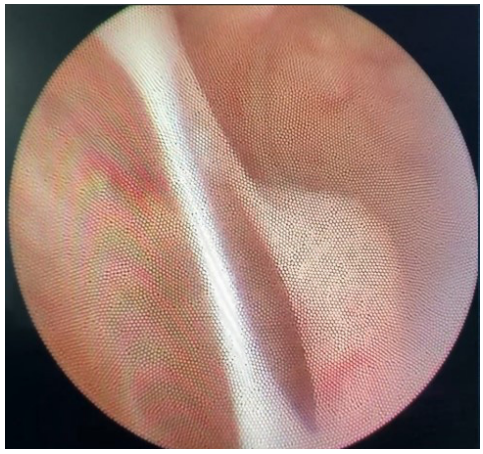

Image 1. Cystoscopy view of prostatic urethral synechiae

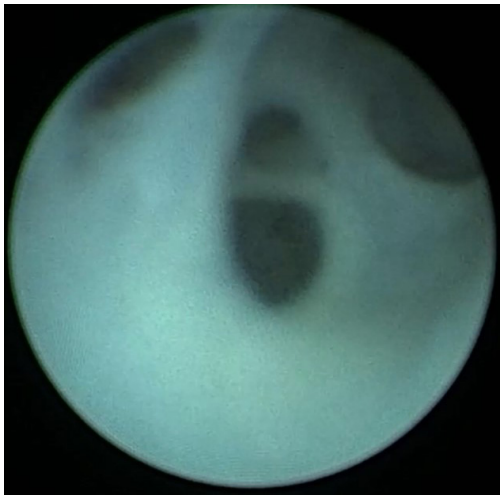

Image 2. Cystoscopy view of vesical synechiae

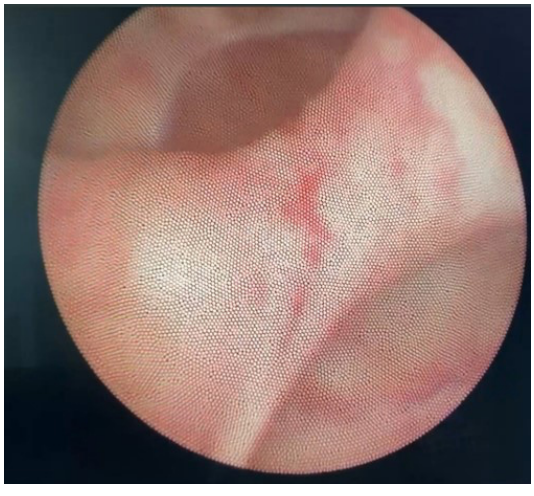

Image 3. Cystoscopy view of stalagnate like pillar, classical of vesical synechiae

(after ureteric reimplantation) and bladder synechiae (after ureteroneocystostomy during cadaveric renal transplantation) have been reported (1). Two cases of bladder synechiae (after anti-incontinence surgery in females) have been reported (2). We report a rare case of prostatic urethral and vesical synechiae secondary to recurrent UTI and bladder outlet obstruction (BOO). This was incidentally diagnosed on cystoscopy. To date, urological synechiae have been identified after the history of any urological surgery. Retained foreign body-like suture material can cause inflammation and synechia formation. The index patient did not have a history of any surgery to cause synechiae. Also, we could not identify any foreign body that caused urological synechiae. Hence, we postulate that recurrent UTI and BOO (Stricture Urethra) caused synechiae. When bacteria invade the bladder mucosal wall, an inflammatory reaction called cystitis are produced (3). Recurrent episodes of UTI can contribute to the development of urethral and vesical synechiae. The stalagnate like pillar formation would have drifted the ureteric orifice to 1-o'clock position. Synechiae are diagnosed on cystoscopy and cannot be diagnosed preoperatively on radiological imaging. Hence, knowledge of such a rare finding can avoid intraoperative surprises. These synechiae can be managed with a Holmium laser incision. Management of BOO and UTI is integral to the management of urological synechiae.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Laparoscopic Bladder Diverticulum Excision in Boys: Three Case Reports

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Abstract

Bladder diverticula can be congenital or acquired in children. In this study, we present three male patients with congenital bladder diverticulum who underwent laparoscopic diverticulum excision. The main presenting symptoms of the patients were abdominal pain and urinary tract infection. Two patients also had vesicoureteral reflux. Postoperatively, symptoms associated with the urinary system disappeared in all patients. Laparoscopic diverticulum excision is preferred as an effective surgical method in children.

Keywords: Bladder diverticulum, congenital, laparoscopic

Introduction

A bladder diverticulum (BD) is a prolapse of the bladder mucosa outward from a weak area of the detrusor muscle (1). BD is a rare pathology in children, and its incidence is reported as 1.7% in the literature (2). In the pediatric age group, the diverticulum is observed in an anatomical region close to the ureteric orifices. Therefore, vesicourethral reflux may be associated with disruption of the submucosal tunnel (3).

These patients usually visit the outpatient clinic with signs of infection. In addition, these urinary tract infections must be surgically corrected because they will cause kidney damage. Correction of the diverticulum and related reflux can be performed by the open method or successfully laparoscopically by experienced clinicians. In this article, we present a rare case of congenital BD in three boys.

Case Presentations

Case 1 is a 4-year-old male patient with a history of urinary tract infection Urinary system ultrasonography (US) revealed 23x13 mm diverticulum in the right lateral aspect of the bladder. No vesicoureteral reflux (VUR) was detected during voiding cystourethrography (VCUG). Excess diverticulum filling is observed on the right. Renal functions were normal on static renal scintigraphy (DMSA), and no scar was observed. No feature was detected except for the bladder with increased capacity. Two wide-mouthed diverticula on the right cystoscope were observed. Diverticulum excision was performed laparoscopically. Case 2 is an 8-year-old male patient with a history of abdominal pain and urinary tract infection. During US, 28x20 mm diverticulum was detected in the right posterolateral aspect of the bladder. In VCUG, 3x2 cm diverticulum in the bladder and grade 1 VUR on the right were observed. In the DMSA performed, the right kidney function was 34.5%. In the urodynamic study, there were phasic detrusor contractions, bladder capacity was decreased, and postvoid residual urine was detected. Cystoscopy revealed diverticula in the right orifice The orifice was at the 5 o'clock position of the diverticulum. Diverticulum excision and right ureteroneocystostomy were performed laparoscopically. Case 3 is a 9-year-old male patient with a history of fever and abdominal pain. In US, the right kidney is smaller than the left. A focal ectatic area is observed in the upper pole of the right kidney. No diverticula appearance in the bladder was observed in the VCUG, but grade 4 VUR was observed on the right. In the DMSA performed, the right kidney function was 30.6%. A diverticulum was found on the right side on cystoscopy. The right ureteral

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orifice opened into the diverticulum. Diverticulum excision and right ureteroneocystostomy were performed laparoscopically. Pathological diagnosis of all patients compatible with bladder diverticula.

Technical details of the surgical procedure are presented in the video. A ureteral stent was placed by cystoscopy, as shown in the video. A Fogarty catheter was placed in the diverticulum. While the ureteral stent provided safe dissection of the ureter, the Fogarty catheter provided ease of dissection. Diverticulum excision was performed using a tissue-sealing instrument. Detrusor repair was performed using absorbable, synthetic, braided, and monofilament continuous sutures. The ureteral stent was removed postoperatively.

Discussion

Bladder diverticula in the pediatric age group are usually congenital. Bladder diverticula are rare clinical findings in pediatric populations. The frequency of bladder diverticula diagnosis has increased from 0.7% to 1.7% since urinary infections have been systematically studied (4). Bladder diverticula are predominantly seen in males rather than females.

Although the etiology is not clearly explained, it is associated with higher bladder pressure in the in utero and early postnatal period in boys, depending on micturition physiology (5).

Congenital bladder diverticula are typically diagnosed when patients are aged between 3 and 7 years (6). Likewise, the patients in the present cases were diagnosed at 3, 8, and 9 years during the investigation for urinary tract infections and abdominal pain.

The main factors that cause these patients to develop clinical findings and therefore to be diagnosed with BD are urinary tract infection and associated fever, abdominal pain, and hematuria. The cause of urinary tract infection is urinary stasis in the diverticulum and associated VUR.

The first pathology to be considered in patients who are examined for urinary tract infection is VUR. When performing US and VCUG, which are imaging methods used in reflux research, BD may occur. (7). In patients with suspected BD on US and VCUG imaging, urodynamic examination should be performed for neurogenic bladder exclusion. However, these patients should undergo cystoscopy to confirm the diagnosis and plan the treatment properly (8). All cases in the series underwent cystoscopy to confirm the diagnosis of diverticula.

Accepted indications for surgical intervention include voiding dysfunction, urinary stasis, stone formation, and large diverticulum size, which are predisposing to urinary tract infection (7).

However, because there is a risk of urinary stasis, stone formation, and malignancy in the later stages of life, surgical correction is recommended in asymptomatic cases (9).

Because of bladder detrusor defects in these patients, surgical correction is required. Surgery can be performed intravesically or extravesically. If diverticulum is associated with reflux, reimplantation can be performed using both methods.

However, with the development of technology, we believe that extravesical and laparoscopic correction of surgery in these patients is more appropriate in terms of patient comfort and surgical time.

Two of our patients had VUR. Diverticulectomy with laparoscopic ureteroneocystostomy was performed. In one patient, only laparoscopic diverticulum excision was performed because he did not have reflux. No complications were observed during the 6-month postoperative period.

Conclusion

It is characterized by BD, urinary tract infection, lower urinary tract symptoms, and bladder storage or emptying disorders. The aim of surgical repair of these diverticulums is to improve voiding dysfunction and prevent urinary tract infections. We suggest that the laparoscopic method can be successfully performed in selected cases.

Video 1. https://youtu.be/afiBPmXBOdo

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Y., Z.İ., Concept: S.Y., Z.İ., Design: S.Y., Z.İ., Data Collection or Processing: S.Y., Z.İ., Analysis or Interpretation: S.Y., Z.İ., Literature Search: S.Y., Z.İ., Writing: S.Y., Z.İ.

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

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

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VIDEO ARTICLE
General Urology

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A Rare Case of Bladder Endometriosis Mimicking a Bladder Tumor

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Abstract

The presence of endometrial stroma and/or glandular epithelium in organs other than the uterus is called endometriosis. Urinary system endometriosis is observed in approximately 1% of women with endometriosis and is most commonly seen in the bladder. A 27-year-old female patient was admitted to the urology clinic with cyclic complaints of painful and frequent urination. Ultrasonography revealed a lesion extending to the lumen of approximately 15x10 mm in the left side wall of the bladder. On cystoscopy, a suspicious area with irregular borders was observed, approximately 15 mm, at the left-posterior lateral wall of the bladder, and transurethral resection was performed. The pathological result of the patient was reported as bladder endometriosis. Although rare, bladder endometriosis should be considered in the differential diagnosis, especially in women of reproductive age with cyclic urological complaints.

Keywords: Bladder, endometriosis, tumor

Introduction

The presence of endometrial stroma and/or glandular epithelium in organs other than the uterus is called endometriosis. Endometriosis rarely occurs in extragonadal organs, such as the bladder and intestinal tract, causing organ-specific symptoms (1).

From studies conducted in Europe, urinary system endometriosis was observed in 0.3-12% of women with endometriosis (2,3). The incidence of urinary system endometriosis is as follows: 85% bladder, 9% ureter, 4% kidney, 2% urethra (4).

Bladder endometriosis (BE) is defined by the presence of endometriotic tissue in the detrusor muscle of the bladder (5) and is most commonly seen in the bladder base and bladder dome (6). Typically, women with BE present with dysuria, frequency, hematuria, and urinary incontinence (7,8). Anamnesis and imaging methods are important in the diagnosis of BE. The differential diagnosis includes intraluminal bladder lesions, urinary tract infection, urinary tract stone, and interstitial cystitis (9).

The aim of BE treatment is to relieve symptoms and prevent possible kidney damage. Treatment can be conservative, medical, or surgical by evaluating the patient and the extent of endometriosis.

Case Presentation

A 27-year-old female patient was admitted to the urology clinic with complaints of painful urination and frequent urination, which started every month with her menstrual periodfor approximately 1 year. There was no disease or operation history in the medical history. In terms of gynecological history, she had 3 pregnancies, 2 deliveries, and 1 abortion. No erythrocyturia or leukocyturia was observed during complete urinalysis. Ultrasonography revealeda lesion extending to the lumen of approximately 15x10 mm in the left side wall of the bladder. On cystoscopy, a suspicious area with irregular borders was observed, approximately 15 mm, at the left-posterior lateral wall of the bladder, and transurethral resection (TUR) was performed (Video 1). During the resection, brown gelatinous material was observed (Figure 1). The pathology result of the patient was reported as BE (Figure 2-4). No pathology was found in the gynecological

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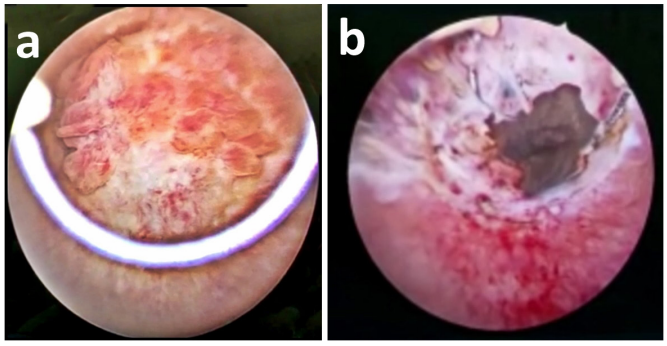

Figure 1. a. On cystoscopy, a suspicious area with irregular borders was seen, approximately 15 mm, at the left- posterior lateral wall of the bladder; **b.** During the resection procedure, brown gelatinous material which is typical endometriosis appearance was seen

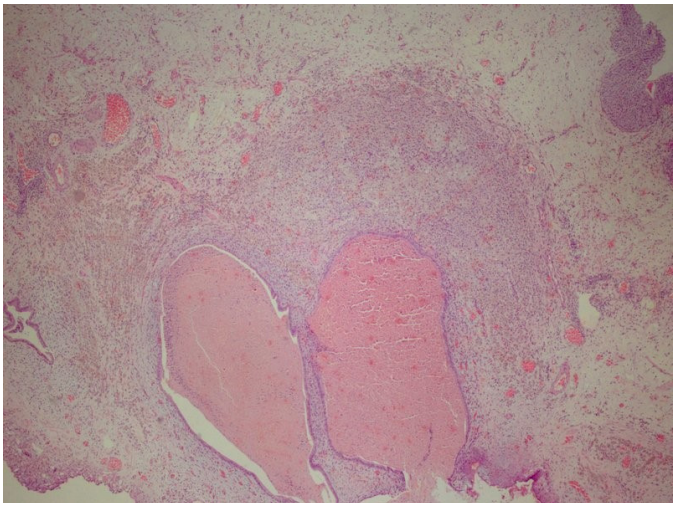

Figure 2. In the upper right corner, cystic dilated gland structures lined with bladder urothelial epithelium and endometrial epithelium in the lamina propria (x40)

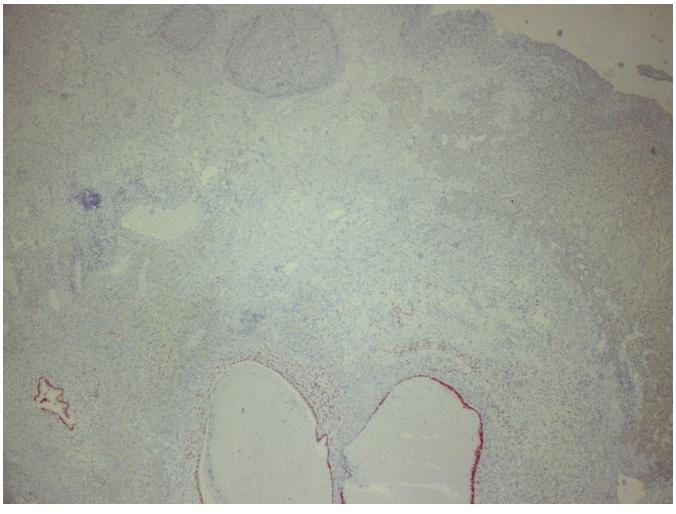

Figure 3. Immunohistochemical positivity of estrogen hormone receptor (Clone SP5) in the endometrial epithelium lining the cystic gland structures in the lamina propria (x40)

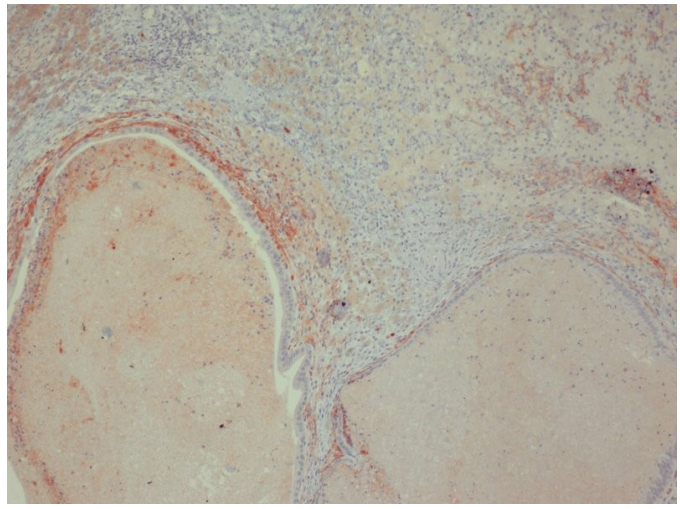

Figure 4. CD10 immunohistochemical positivity in the endometrial stroma surrounding gland structures (x100)

evaluation of the patient. The case was evaluated as primary BE. A gonadotropin-releasing hormone (GnRH) analog was started as additional treatment. The patient did not have any symptoms during the 3-month follow-up after surgery. The follow-up of the patient continues.

Discussion

BE is observed in women of reproductive age and usually around 35 years of age. While the cases that are accepted as primary are found at a rate of 11%, secondary cases are mostly detected because of a reason such as cesarean section or previous pelvic surgery. The frequency of involvement of endometriosis in the urinary system is 85% in the bladder, 9% in the ureter, 4% in the kidney, and 2% in the urethra (4).

Patients with BE present to the clinic with dysuria, frequent urination, bladder pain, and less frequent hematuria, urgency, and urinary incontinence (7,8). Dysuria has been reported in 21-69% of patients. Hematuria is a less frequent symptom reported in 0-35% of cases and occurs when the bladder lesion infiltrates the mucosa. Although ultrasonography is the first choice at diagnosis, magnetic resonance imaging may be helpful, especially in cases with suspected ureteral involvement (1). In patients who are scheduled for cystoscopy, it would be more appropriate to evaluate the lesions by considering the menstrual cycle (10).

Treatment should be planned by considering the patient's age, pregnancy desire, and the spread of the disease. Medical treatment of BE reduces symptoms and is used palliatively. Postmenopausal women with a single bladder lesion 5 mm are ideal candidates for medical treatment. The most commonly

used drugs are GnRH agonists and antagonists, progestins, and combined oral contraceptives (10).

The aim of surgical treatment is the complete removal of the endometrial tissue, and it is the only cure method for BE (10). Surgical treatment options include TUR of the bladder, partial cystectomy, and total cystectomy. If possible, the recommended treatment is complete resection with transurethral surgery (11). A combination of TUR-M and hormone therapy may be preferred in young patients who want to preserve fertility (10). In cases where endometriosis invades the urothelial mucosa from the outside of the bladder, TUR-M treatment is not sufficient and partial cystectomy should be considered (12).

Follow-up is recommended for women with deep (e.g. bladder) and ovarian endometriosis, but there is no set follow-up program in the guidelines. The frequency and type of follow-up should be evaluated according to the severity of the disease and symptoms (13).

Conclusion

Although rare, BE should be considered in the differential diagnosis, especially in women of reproductive age who have pelvic pain in the cyclical cycle and a mass in the bladder.

Video 1. https://youtu.be/ih1oBnoksvQ

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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

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Ali Furkan Batur
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