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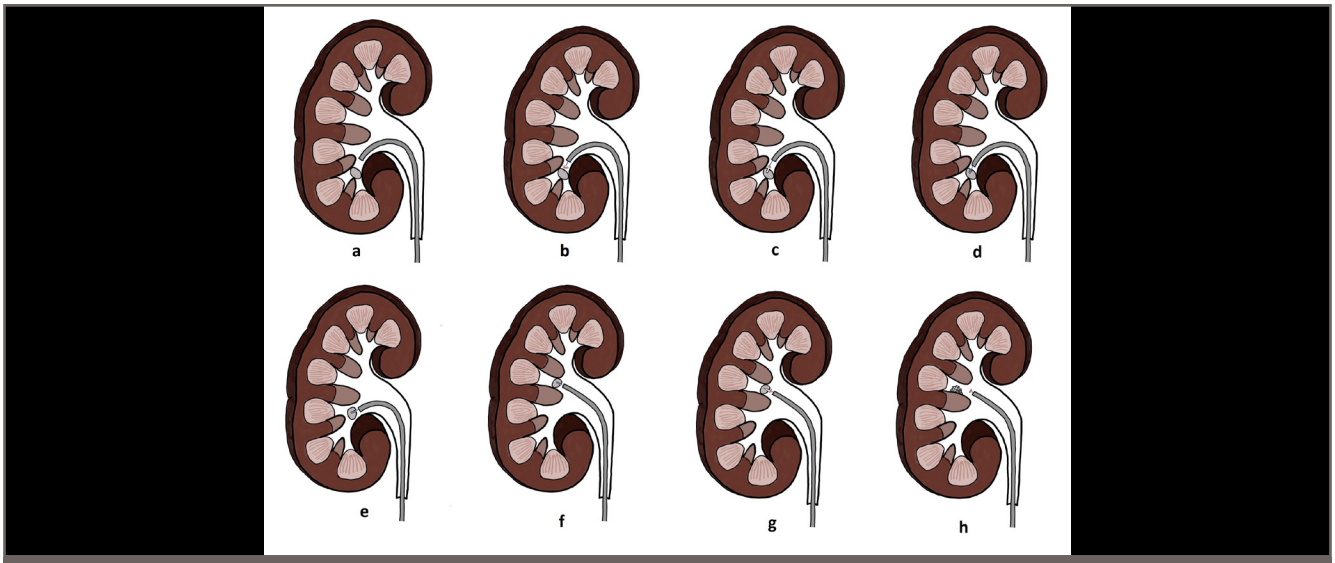

Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K. **A Novel Technique for Relocating Renal Lower Calyceal Stones During Retrograde Intrarenal Surgery: "Jab and Pull".**
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Dear Colleagues,

We are pleased to have published the first issue of The New Journal of Urology for 2024. This issue includes four (4) original articles, two (2) reviews and one (2) case report. Published articles consist of uro-oncology, general urology, urolithiasis, neuro-urology and andrology. Published articles consist of general urology, urooncology, paediatric urology and reconstructive urology. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies.

The New Urology Journal has been indexed in the TUBİTAK-ULAKBİM TR Index since the first issue of 2011. Our journal is indexed in Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, OAJI, Ideal Online Database, EuroPub, J-GATE, and DOAJ databases, EBSCO and InfoBase Index. In addition, the New Journal of Urology is in collaboration with the Orcid and CrossRef DOI systems. The indexing process of our journal in ESCI, Pubmed, and EMBASE continues. The editorial team is very grateful to all the authors and reviewers who have contributed to this issue.

We are aware that this is a painstaking effort, and we cannot thank you enough for it. We request that you submit your articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Respectfully yours,

Ali İhsan Taşçı
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RESEARCH ARTICLE

A Novel Technique for Relocating Renal Lower Calyceal Stones During Retrograde Intrarenal Surgery: ''Jab and Pull"

Mehmet Uslu[1], Mehmet Ezer[1], Umit Yildirim[1], Murat Bagcioglu[2], Kemal Sarica[3]

[1] Department of Urology, Medical School, Kafkas University, Kars, Türkiye
[2] Department of Urology, Medical School, Bahcesehir University, İstanbul, Türkiye
[3] Department of Urology, Sancaktepe Şehit Prof Dr Ilhan Varank Training and Research Hospital, İstanbul, Türkiye

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Correspondence
Mehmet Uslu, MD
Şehitler Mah., Kafkas University, 36100, Merkez, Kars, Türkiye
E-mail: dr.mhmtuslu@gmail.com

ORCID
M.U. 0000-0002-8370-3793
M.E. 0000-0003-4422-6768
U.Y. 0000-0003-3065-9001
M.B. 0000-0003-4927-9164
K.S. 0000-0002-2473-1313

Abstract

Objective : It is advised to move the stones from the lower calyx to the middle or upper calyx using a nitinol basket. In order to protect the flexible ureterorenoscopy and increase the stone-free rate during retrograde intrarenal surgery

In this descriptive study, we presented a method for moving stones to other calyces where the need for deflection is less, using holmium fiber in cases where the nitinol basket is not available.

Materials and Methods: With the "Jab and Pull" method we have described, 32 patients who underwent RIRS for symptomatic (pain or infection) renal lower calyceal stones with a diameter of 4-10 mm in our clinic, between 2012 and 2021 were retrospectively analyzed.

Demographic data, stone size, Hounsfield unit, number of stones, opaque non-opaque status, stone localization, infundibulopelvic angle, perioperative-postoperative complications, and control imaging were evaluated.

Results: The mean age of the patients was 51.12, and the female-male ratio was equal. The median stone size was 8mm (min:5, max:10), and the Hounsfield unit was 805 (±396.72). 75% (24) of the stones were single and 53.1% (17) were opaque. The median infundibulopelvic angle was 38 (min:19 max:52) degrees. 27 (84.4%) patients achieved stone-free status using this method. The renal lower calyx neck of two patients was too narrow, the stones of two patients were too soft, and the stone of one patient was inaccessible, preventing total success in these patients.

Conclusions: In cases where a nitinol basket is needed but cannot be reached during treatment of kidney lower calyx stones, the "jab and pull" method can be considered as an alternative in suitable patients.

Keywords: kidney stone, lower calyx, displacement, basket catheter

INTRODUCTION

The use of minimally invasive surgical procedures began to be applied more commonly than ever during the past two decades due to advancements in endoscopic equipment technology. Parallel to this, as a less invasive management option than the percutaneous approach, retrograde

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intrarenal surgery (RIRS) tended to play a significant role in managing kidney stones with the effective use of holmium laser technology (1). The European Association of Urology (EAU) urolithiasis guidelines recommend both RIRS and extracorporeal shock wave lithotripsy (ESWL) techniques as the first-line therapy options for renal lower-calyceal stones sizing less than 10 mm (2,3). As the ultimate goal of modern endourological applications is to achieve the highest stone-free status possibly in a single session, RIRS seems to be more advantageous than ESWL (4).

Flexible ureterorenoscopic (fURS) holmium laser treatment of lower calyceal stones is possible if the stone is reached with an effective deflection of the scope. Insertion of the holmium laser fiber through the working channel of the flexible scope may even restrict the deflection range, making it more difficult to access such stones(5). This difficulty may affect the stone-free rates and also reduce the durability of the flexible ureterorenoscope due to difficult, forced deflection maneuvers. In such situations, nitinol baskets were used to move the stones from lower calyx to the middle or upper calyceal position to increase the stone-free rates and protect the flexible URS. This maneuver was called a relocation or repositioning (6,7). However, it is clear that the use of a nitinol basket will bring an additional cost for the RIRS procedure(6,8,9).

In this descriptive survey study, we presented a new technique of displacing the symptomatic (pain or infection) lower-pole stones to the middle- or upper-pole calyces with the help of holmium laser fiber in cases where the nitinol basket cannot be manipulated well or additional cost of the baskets becomes a concern for the centers.

MATERIAL AND METHODS

Departmental data of patients undergoing endoscopic flexible ureteroscopy for renal stones between 2012 and 2021 was evaluated in a retrospective manner. All surgeries were performed by a single surgeon. Each patient underwent a preoperative, radiological evaluation consisting of non-contrast computed tomography (NCCT) and kidney-ureter-bladder (KUB) radiography. The opacity status of the stones was determined preoperatively using KUB. Patients in whom the lower calyceal stones were managed with the "jab and pull" technique used were evaluated in detail with respect to patient (age, gender, infundibulopelvic angle), stone (size, Hounsfield unit, number, opacity, location), and procedure (success, complication rates, hospitalization) parameters. Modified Clavien–Dindo classification was used for grading complications. A flowchart is given in Figure 1.

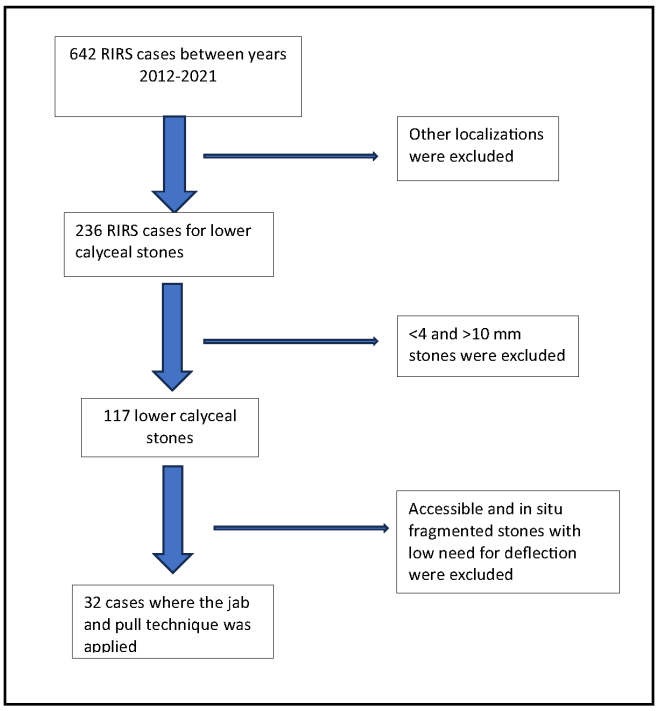

Figure 1. Flowchart of the study

Statistical Analysis

Statistical analyses were conducted using the SPSS-22.0 package program. Categorical variables were given count and percentage. The normality of data distribution was checked with the Shapiro-Wilk test. Normally distributed variables were expressed as mean (±Standart deviation), and the non-normally distributed ones were expressed as median (minimum, maximum).

Operative Technique

Our newly described technique consists of four steps. Following the placement of the ureteral access sheath, displacement of the stone is performed by our technique, and the stone is disintegrated with the help of a Ho-YAG laser. In the last step, a double-J stent is placed.

Placement of Ureteral Access Sheath

After performing semi-rigid ureterorenoscopy to examine the ureteric lumen and to dilate the orifice region, a 0.038-inch, soft-tipped safety guide wire is placed up into the involved renal collecting system under fluoroscopy (Figure 3a). Retrograde pyelography is done to identify the stone(s) and

the characteristics of the renal collecting system. Following this procedure, a ureteral access sheath (10.7/12.7 Fr, Cook Medical, Bloomington, IN) is placed over the guide wire under fluoroscopy. A 7.5 F flexible ureterorenoscope (Storz FLEX-X2) is then passed into the renal pelvis through the access sheath. Starting from the upper pole, all calyces are systematically examined to identify radiolucent stones and their locations. In general, both active and passive deflection is required to guide the flexible scope to the stone in the lower-pole calyx (Figure 3b). However, in vitro studies have shown that the angle of deflection is limited when the 200-mm holmium laser fiber is places through the channel of the flexible ureterorenoscopy, which may reduce the performance of in situ stone fragmentation(5). Based on these facts, depending on the extent of reduction in deflection and the position of the stone, access and fragmentation of the stone in the lower pole may not be possible. In these cases, the stone has to be repositioned into a more dependable position for an easy and effective disintegration.

Stone Relocation with the Use of Laser Fiber

The flexible ureterenoscope is extended to its maximum deflection in order to reach the stone. In the upper third of the stone that can be reached, a hole is drilled large enough for the laser fiber to go through it (Figures 2a, 2b, 2c). This hole is used to insert the tip of the laser fiber (Figure 2d) into the stone body for displacement into the renal pelvis or upper pole by using the flexible ureterorenoscope by bringing its tip from deflection into flexion (Figures 2e, 2f, 3c). The crucial point is to be able to access at least a third of the stone's upper portion to perform this transport. Additionally, the lower calyx neck should also be larger than the stone size for an effective relocation.

Fragmentation of the Stone

The holmium laser fiber is withdrawn and removed from the stone. Then, with a laser setting of 0.6 J at 10 Hz, the stone is fragmented into <4 mm size for a successful spontaneous fragment passage after surgery (Figures 2g, 2h, 3d).

Double J Ureteral Stent Placement

Based on the amount of stone load residing at the end of the surgery, the performance of ureteral dilatation during the surgery, and the degree of trauma to the collecting system during manipulation, a double J stent will be placed after the completion of the procedure under fluoroscopy.

Stone-free Assessment

NCCT was used to establish a conclusive assessment of stone-free status 3 months after surgery.

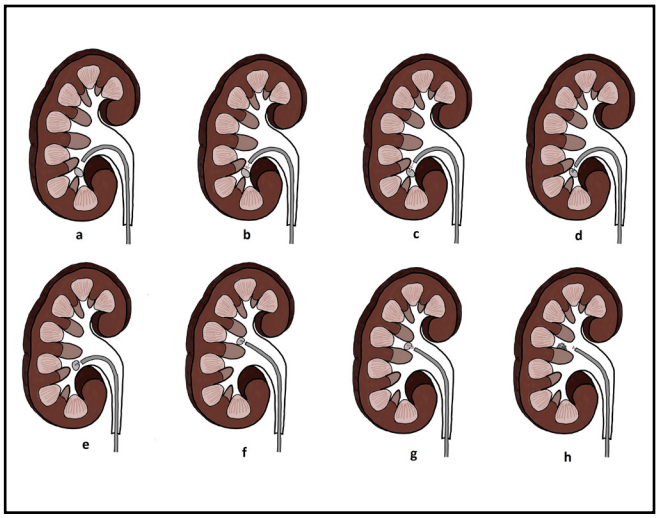

Figure 2.a-h: Explaining the technique with figures. The stone is seen in the lower calyx (a). The laser probe is advanced through the flexible ureterorenoscope (b). A hole is drilled in the upper part of the stone (c). The laser probe is inserted into the hole (d).The stone moves to the upper calyx (e, f). The laser probe is pulled through the stone (g). The stone is fragmented into pieces smaller than one millimeter (h).

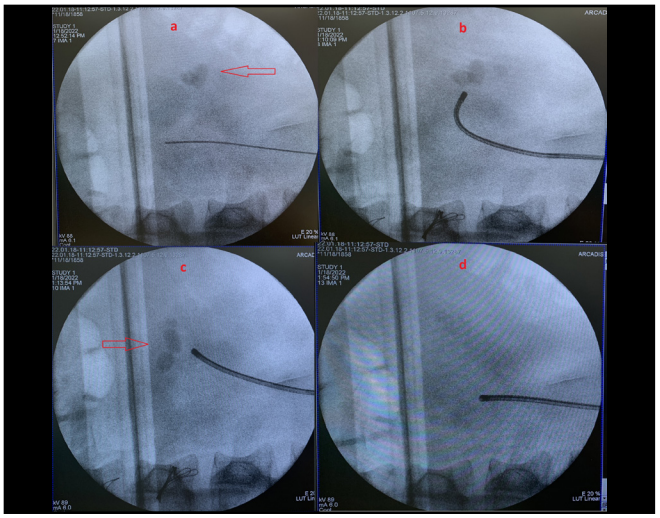

Figure 3.a-d: Fluoroscopy image of the technique. The stone is seen in the lower calyx(a). Angle of flexible ureterorenoscope and stones(b). Relocating stones to the upper calyx(c). Fragmentation of all stones(d).

RESULTS

Thirty-two patients (male/female 1:1) undergoing the "jab and pull" technique for lower pole stones sizing 4–10 mm were included in the study program. Mean age of the patients was 51.12 (±15.18). Stones were on the right side in 17 (53.1%) patients and on the left side in 15 (46.9%) patients. Regarding the stone-related factors, while the mean Hounsfield unit was 805 (±396.72), the median size was 8 mm (min:5, max:10). 75% (24) of the stones were single, and 53.1% (17) of them were opaque. The median infundibulopelvic angle was 38 degrees (min:19, max:52). Patients' characteristics and clinical findings are given in Table 1.

Evaluation of our findings demonstrated that, in 27 of 32 patients, the lower pole stones were disintegrated successfully following relocation into the pelvis or upper calyx using our technique. Regarding the underlying causes of failure in five unsuccessful cases, while the stones could not be displaced from the lower pole due to the narrow calyceal neck in two cases, stones were soft and the upper part was broken while drilling the hole in two other cases. The remaining part of the stone could not be reached for this maneuver. Lastly, the stone escaped to another lower calyx during manipulation, and tip of the scope with the laser fiber could not reach to the stone in this new position in the fifth case.

Table 1. Patients' Characteristics and Clinical Findings

		Count	**% or ±SD**
Gender	Male	16	50%
	Female	16	50%
Age		51.12	±15.18
Lateralization	Right	17	53.1%
	Left	15	46.9%
Presence of Hydronephrosis		8	25%
The success of the technique	Yes	27	84.4%
	No	5	15.6%
Number of Stones	Single	24	75%
	Mutiple	8	25%
Hounsfield Unit		805.78	±396.72
Opacity	Opaque	15	46.9%
	Non-Opaque	17	53.1%
Length of stay in hospital (day)		2	±0
Operative Time (min)		54.31	±9.24
		Median	**Min-Max**
Charlson Comorbidity Index		1.75	0-5
Infundibulopelvic Angle (°)		38	19-52
Size (mm)		8	5-10

DISCUSSION

Optimum treatment of renal lower calyceal stones is still to be defined due to certain factors such as stone size, calyceal anatomy and associated comorbidities(10). While ESWL and RIRS are defined as first options in the treatment of renal lower calyceal stones sizing smaller than 1 cm, percutaneous nephrolithotomy (PCNL) is being offered as second-line therapy(2,3).

However, accumulated data has clearly shown that flexible ureteroscopic laser disintegration could also be applied effectively in patients with bleeding diathesis, unfavorable intrarenal anatomy, morbid obesity, or ESWL-resistant stones(8). While Margaret P et al. found no significant difference in stone free rates in cases undergoing RIRS or ESWL for lower calyceal stones smaller than 1 cm, Sener E et al. found RIRS to be more effective for this aspect (4,11).

Although flexible scopes could be used effectively in the management of such stones, prolonged use and forced deflection may damage these devices any time during such manipulations(12). Moreover, passing a basket or laser fiber through the working channel of these fine instruments will certainly reduce the degree of deflection. Studies have clearly shown that the loss in the deflection angle is higher when one uses a 200-mm holmium laser fiber compared to the use of 3,2 Fr nitinol basket (5). Based on these facts, endourologists began to reposition (displace) the stones located in lower-calyceal position during and place them into middle or upper calyx in an attempt to increase the disintegration rate and reduce the extent of possible scope damage caused by forced manipulations (7). A nitinol basket has been generally recommended for this particular maneuver. With this aim, the lower calyx stone(s) is grasped with a nitinol basket and repositioned into the pelvis, middle calyx, or upper calyx of the involved kidney – a maneuver that protects the instrument by decreasing tension applied(8).

Additionally, moving the stone from the lower calyx to middle/upper calyx provides higher stone-free rates (6). In their original study, Schuster et al. demonstrated higher stone-free rates in the medium-sized (1–2 cm) lower-pole stones replaced and fragmented by using a basket than the stones fragmented in situ (13). In addition, in a study performed by Golomb et al. on 480 patients with lower-pole stones, the authors reached a stone-free rate of 94% using the basket and displacement technique in all cases (14). Finally, in a study published by Preminger G et al., the team examined 112 patients with lower-pole stones, in whom the stones were moved to another calyx with a basket during RIRS, and they found 85% of the cases to be stone-free(15).

On rare occasions, the stone grasped with the nitinol basket may be stuck in the calyx neck during the maneuver, and excessive, uncontrolled traction may break the basket. The flexible ureterorenoscope is removed from the body in this instance after the distal end of the basket catheter is cut. The stone that has become lodged in the basket is then broken up by entering from the side of the basket using a flexible ureterorenoscope, releasing the basket from the jammed location. In situations where this method is unsuccessful, percutaneous nephrolithotomy could be the option to remove the stone and basket fragments from the body (9,16).

With the new technique described in this study, 27 patients with lower calyceal stones sizing 4–10 mm were managed by moving the stones from the lower calyces to the middle and upper calyces without using a basket for displacement. All cases were completely stone-free, as demonstrated with NCCT performed at the postoperative 3-month follow-up evaluation. No complications were found in the complication evaluation based on the Modified Clavien Dindo classification. In the absence of a nitinol basket use, we think that this technique may be performed in cases in which the upper portion of the stone is accessible and the calyx neck is not narrow. We believe that this technique will decrease the operational time and cost of the procedure, due to the lack of need for a basket, and increase the success rates by enabling the surgeons to disintegrate the stones in a more effective manner.

Limitations

It is impossible to claim that our study is without flaws. It should be noted here that, because it is a retrospective study with a limited sample size, the results may not be very generalizable. Second, the study did not compare its findings to the basket displacement, which is the most popular technique for moving stones. Future studies should incorporate this kind of comparison. It should also be noted that there are baskets with a thickness of less than 3.2 Fr that improve the deflection angle. This method also needs to be compared using baskets of different thicknesses. Lastly, the inability to perform stone analysis in any of the patients due to laboratory inadequacies is one of the shortcomings of the current study.

CONCLUSIONS

Regarding the treatment of lower-calyx stones, our newly defined "jab and pull" method could be applied successfully in cases where the nitinol basket cannot be passed into the stone site for various reasons during RIRS procedure. Our current results have demonstrated that this technique can be considered as an alternative in selected cases to increase the stone-free rates and reduce the possibility of scope deterioration due to excessive (forced) deflection. However, we believe that further studies with larger series of patients are needed to support the clinical effectiveness of our technique.

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Ethical Approval: The study was approved by Ethics Committee of Kafkas University (Approval number: 80576354-050-99/90). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions: Conception and design: Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K, Data acquisition: Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K, Data analysis and interpretation: Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K, Drafting the manuscript: Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K, Critical revision of the manuscript for scientific and factual content: Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K, Statistical analysis: Uslu M, Ezer M, Yildirim U, Bagcioglu M, Sarica K.

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RESEARCH ARTICLE

Effect on Endoplasmic Reticulum Stress of the Combined Oral Contraceptives in the Kidney

Esma Kirimlioglu[1*], Seval Turk[2], Alexandra Cernomorcenco[1]

[1] Department of Histology and Embryology, Faculty of Medicine, Akdeniz University, Antalya, Türkiye

[2] Department of Dentistry, Department of Basic Sciences, Antalya Bilim University, Antalya, Türkiye

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Correspondence
Esma Kirimlioglu (PhD),
Akdeniz University, Faculty of Medicine, Department of Histology and Embryology, Antalya, Türkiye
E-mail: esmakirimlioglu@gmail.com

ORCID
E.K. 0000-0002-5689-5670
S.T. 0000-0002-0850-4671
A.C. 0000-0003-3882-426X

This study was presented at the International Congress on Natural & Medical Sciences as an oral presentation. 02-04 September 2022 / Ege University, Izmir, Türkiye

Abstract

Objective: This study aimed to analyze the effects of combined oral contraceptive active ingredients, Drospirenone, Ethinyl Estradiol, and Ethinyl Estradiol+Drospirenone, on liver histopathological changes and endoplasmic reticulum stress levels.

Material and Methods: In the study, 37 Balb/c female mice were used. Mice were randomly divided into the Control, Sham, Drospirenone, Ethinyl Estradiol, and Ethinyl Estradiol+Drospirenone groups. The experimental groups were administered with gavage to 8-week-old female mice for 35 days. Kidney tissue sections were applied with Hematoxylin&Eosin, Orcein, Mallory's Azan, and Periodic Acid-Schiff to detect histopathological changes, and Chop and Grp78 were used to detect Endoplasm Reticulum Stress.

Results: Significant loss of microvilli and a decrease in glycogen accumulation were observed in the apical part of some of the proximal tubules of animals in the Drospirenone and Ethinyl Estradiol+Drospirenone groups. The amount of collagen fiber stained with Mallory's Azan increased in the parietal layer of Bowman's capsule of the kidney tissues of the Drospirenone and Ethinyl Estradiol+Drospirenone applied groups, but no difference was observed in elastic fibers in all groups. The expression level of Grp78 and Chop proteins in the kidney tubules of female mice given Drospirenone, Ethinyl Estradiol, and Ethinyl Estradiol+Drospirenone was significantly higher compared to the control group.

Conclusion: In this study, it was shown that the expression of Grp78 and Chop markers detected in the mouse kidney increased as a result of Drospirenone, Ethinyl Estradiol and Ethinyl Estradiol + Drospirenone administration, thus causing kidney cell apoptosis by inducing ER-dependent death pathway activity.

Keywords: Combined oral contraceptive, drospirenone, ethinylestradiol, kidney, Grp78, Chop

INTRODUCTION

Combined oral contraceptives (COCs), which contain 17-ethinyl estradiol (EE) as an estrogen component and drospirenone (DRSP) as the progestogen, are preferred not only for preventing pregnancy but also for managing menstrual cycle irregularities, relieving postmenopausal symptoms, and addressing various acne problems in women (1). The EE in combined oral contraceptives alters certain estrogen-sensitive

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hemostatic variables and liver-produced proteins, thereby exerting estrogenic effects. DRSP, present in a combined oral contraceptive (30 mg EE/3 mg DRSP), is a 17α-spirolactone derivative with a unique pharmacological profile that combines potent progestogenic, anti-mineralocorticoid, and antiandrogenic activities (2). These novel progestins designed with high specificity, aim to avoid interactions with other receptors and prevent estrogenic, androgenic, or glucocorticoid-related side effects (3). Furthermore, studies have reported that COC use contributes positively to health by reducing the risk of certain cancers, such as ovarian and endometrial cancer, lowering the risk of rheumatoid arthritis, preventing ectopic pregnancy, and increasing insulin sensitivity (4). However, COCs may also lead to side effects such as depression (5), breast and cervical cancer (6), cardiovascular diseases, venous thromboembolism (7), high systolic blood pressure (8), changing homeostasis parameter (9), benign or malignant liver tumors (10).

The kidneys are among the organs that play a crucial role in maintaining internal balance. They regulate blood pressure, pH, renal excretion, water, and electrolyte intake to control the osmolality and volume of body fluids. Additionally, the kidneys remove waste products formed from cellular metabolism from the blood (11). The kidney contains amino acids and peptides involved in protein metabolism, and it plays essential roles in pathways such as degradation, filtration, reabsorption, and excretion (12).

The endoplasmic reticulum (ER) is an organelle that plays a vital role in protein homeostasis, including protein synthesis, folding, modification, and degradation. Under pathological conditions, Endoplasmic reticulum stress (ERS) is induced by the accumulation of unfolded or misfolded proteins in the ER lumen. Consequently, when ERS is induced, unfolded protein response (UPR) sensors serve as an adaptive response or can cause apoptosis in cells when stress is severe. The Glucose-regulated protein of 78 kD (Grp78) is a chiefly ER chaperone protein critical for protein quality control of the ER, and a master regulator of the UPR. Grp78 is included in the activation of IRE1 (the type-I ER transmembrane protein Kinase), Perk (protein kinase RNA-like ER kinase), and ATF-6 (ATF-6 N terminal domain) pathways contributing to the ERS response. Under ERS, Grp78 releases and activates unfolded protein response sensors to restore ER homeostasis. In response to prolonged and severe ERS, the UPR triggers apoptotic pathways that lead to cell death (13). C/EBP-homologous protein (Chop), a proapoptotic transcription factor, is activated in ERS -mediated apoptosis (14).

In the kidneys, various biological disturbances can induce ERS, including increased levels of protein synthesis, oxidative stress, insufficient autophagy, hypoxia, inflammatory stress, nutrient starvation, energy deprivation, cellular stress factors, and including proteostasis disorders. Adaptive responses to these stresses often utilize evolutionarily conserved biological pathways to eliminate or reduce the stress intensity that causes by protein misfolding and aggregation maintain vital functions and cellular homeostasis (15).

We aimed to determine how DRSP and EE, a commonly used combined contraceptive method in women, affect the ERS response in kidney cells, a metabolically active organ.

MATERIAL AND METHODS

In present study, 37 Balb/c female mice (weighing 20±25 g, 6-8 weeks old) were provided from the Akdeniz University Experimental Animals Research and Application Center. Each mouse was kept in standard laboratory conditions (without water and food restrictions; 12 hours light/12 hours dark cycle). The Institutional Animal Ethical Committee of Akdeniz University (Antalya, Türkiye) approved the study. (Authorization reference number: 2022.01.009).

The mice were divided into five groups; EE Group (n:9), DRSP Group (n:9), EE+DRSP Group (n:9), Sham Group (n:5), and Control Group (n:5). EE, DRSP and EE+DRSP were administered via gavage when all mice were in the meta-estrus phase. Because it was thought that during this estrous cycle phase, plasma concentrations of gonadotropins, estrogen, and progesterone would be close to those induced by oral contraception (16). Female mice were given 60 μg of DRSP for DRSP group and 0,6 μg of EE for the EE group by gavage every day for 35 days. EE and DRSP were dissolved in 100% Ethanol. Ethanol-EE containing DRSP was mixed with sesame oil. The sesame oil-ethanol mixture was kept in an incubator at 37° for 24 hours to evaporate the alcohol. Yasmin®, Germany tablets were dissolved in water and administered to the EE+DRSP group by gavage for 35 days. To the Sham group, sesame oil with evaporated ethanol was given by gavage for 35 days. Nothing was administered to the Control group.

At the end of 35 days, the mice were anesthetized with ketamine (100 mg/kg; Alfasan) + xylazine hydrochloride (10 mg/kg; Bayer). Mice were sacrificed by cervical dislocation, and kidney tissues were taken. Tissues were fixed in 4% paraformaldehyde and then dehydrated and embedded in paraplast.

Histopathological Staining

Sections of 5µm thickness were taken, deparaffinized, and rehydrated by general protocol. The kidney sections were stained via Haematoxylin&Eosin (H&E), Mallory's Azan (MA), Orcein, and Periodic Acid Schiff (PAS). Then, the sections were taken into distilled water and dehydrated, cleared in xylene, and the slides closed with entellan. The preparations were detected using a light microscope and photographed.

Immunohistochemical Staining

Kidney tissues were dewaxed with xylene, rehydrated in graded alcohol, and washed with deionized water. Antigen retrieval was performed by incubation with 0.1 M sodium citrate (pH 6.0) at 95-100°C for 25 min. The sections were washed Tris-buffered saline (TBS) and in Tris-buffered saline-tween20 (TBS-T). The samples were blocked with 3% hydrogen peroxide (H_2O_2) for 20 min. After blocking with 5% normal goat serum for 30 minutes at room temperature before application of the primary antibody. Afterward, tissues were incubated with primary antibodies Grp78 (ab109659, 1:200) and Chop (ab63392, 1:200) at +4°C overnight. Then at room temperature, the sections were washed and incubated with secondary antibodies (Cell Signaling, 8114S) for 30 minutes. Diamino benzidine tetrachloride (DAB) was used as the chromogen. The slides were counterstained in Mayer hematoxylin. Then, the sections are taken into distilled water and dehydrated, cleared in xylene, and the slides closed with entellan. The preparations were evaluated using a bright-field microscope and photographed.

Statistical Analysis

In order to determine whether there was a statistically significant difference between the groups, the data were measured with Image J and, then post hoc Bonferroni test and One Way ANOVA tests were applied using the GraphPad (Prisms10) program. Analyses were presented as mean±standard error of the mean (SEM);p<0.05 was considered statistically different.

RESULTS

Histochemical Results

The histopathological differences between the experimental groups as a result of H&E, MA, Orcein, and PAS staining in the kidney are shown in Figure 1.

As a result of microscopic examinations, mouse kidneys in H&E-stained sections showed, that was observed typical histological structures in the control and sham groups (Figure 1A). Significant loss of microvilli in proximal tubule epithelial cells (Figure1A, arrows) and decreased glycogen accumulation in the cells of proximal convoluted tubules showed PAS-positive luminal brush border in all groups. In addition, it was revealed that tubular basement membranes showed more intense positivity with PAS staining in the EE+DRSP group compared to other groups (Figure 1D). While the amount of collagen fibers stained with MA increased in the parietal layer of Bowman's capsule of the kidney tissues of the DRSP and EE+DRSP applied groups (Figure 1B arrows), no difference was observed in elastic fibers in all groups (Figure 1C).

Immunohistochemical Results

We evaluated the ERS levels in the kidney tissue by examining the expression of two UPR molecules, Grp78 and Chop, by immunohistochemical staining.

As shown in Figures 2 and 3, EE, DRSP, and EE+DRSP treatment increased the expression levels of ERS markers. As shown in Figure 2A and B, the immunohistochemistry study reported that Grp78 was plentifully expressed in the tubules from the EE, DRSP, and EE+DRSP groups. This increase in the experimental groups was considered statistically different compared to the Control group (Figure 2B, EE p:0.0212(*); DRSP p<0.0001(****); EE+DRSP p<0.0001(****), respectively).

The increase in Chop expression in kidney tubule cells in the EE, DRSP, and EE+DRSP groups was statistically different compared to the control group (Figure 3B, p:0.0023(**); p:0.0002(***); p<0.0001(****), respectively). Chop nuclear stained and were significantly increased in the experimental kidneys (p<0.05), paralleled with their enhanced protein expression.

In conclusion, these findings suggest that ERS is induced and maintained in renal tubule cells of mice receiving EE, DRSP, and both.

DISCUSSION

The kidney is a vital organ for the organism to perform several fundamental functions, such as detoxification and discharge of drugs and toxic metabolites. The waste products formed from metabolism in the cells and given to the blood are removed from the blood by the kidneys (11). Also, metabolites of DRSP and EE are excreted in the urine and feces. This study was designed to find out and compare the changes induced in the kidneys of female mice after treatment with EE, DRSP, and combined (progesterone and estrogen) oral contraceptive pills.

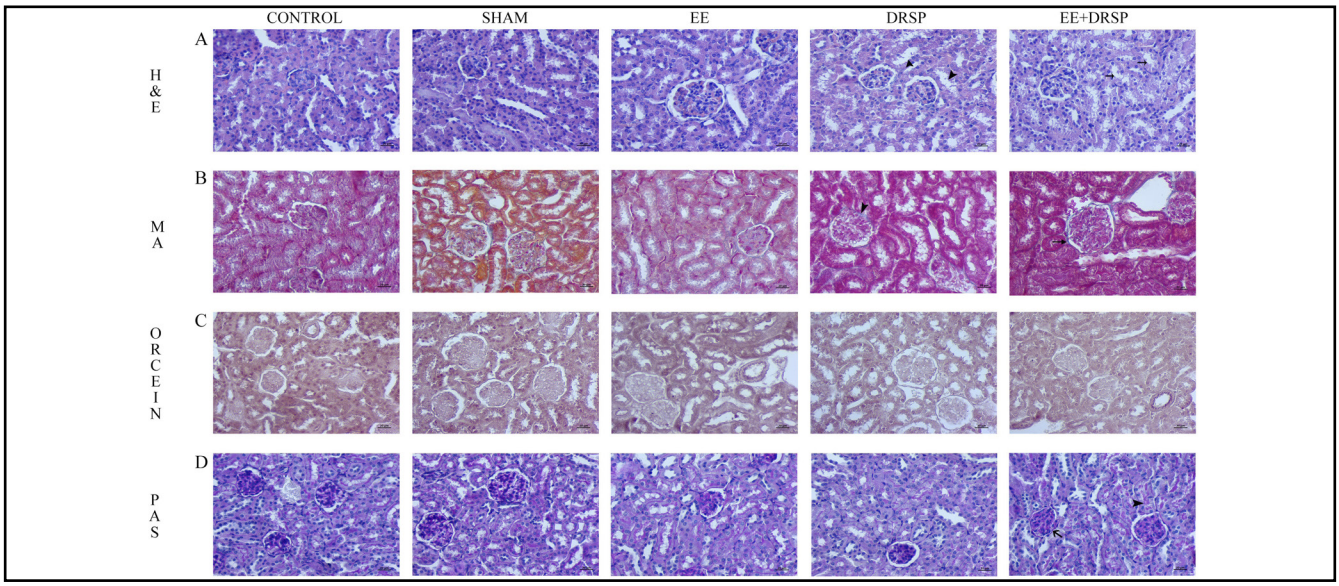

Figure 1. Histological structure and collagen, elastic fiber, and glycogen changes of kidney tissue in Control, Sham, EE, DRSP, and EE+DRSP groups. Scale bars show 40 μm and are apply to all panels. **(A)** Representative histology images of H&E staining. Section of kidney from the Control, SHAM, and EE groups showing normal tubules and normal glomeruli. Section of kidney from the DRSP (arrowheads) and EE+DRSP (arrows) groups significant loss of microvilli in proximal tubule epithelial cells **(B)** MA staining shows increased collagen fiber density around the central vein in the kidney of DRSP (arrowhead) and EE+DRSP (arrow) groups compared to the control. **(C)** Orcein staining of the kidney. Elastic fiber density no was observed to be different in all groups. **(D)** PAS staining in the kidney. Glycogen accumulation in the proximal tubules of the cortex (arrowhead) and thickening in the parietal layer of Bowman's capsule (arrow) of the EE+DRSP group.

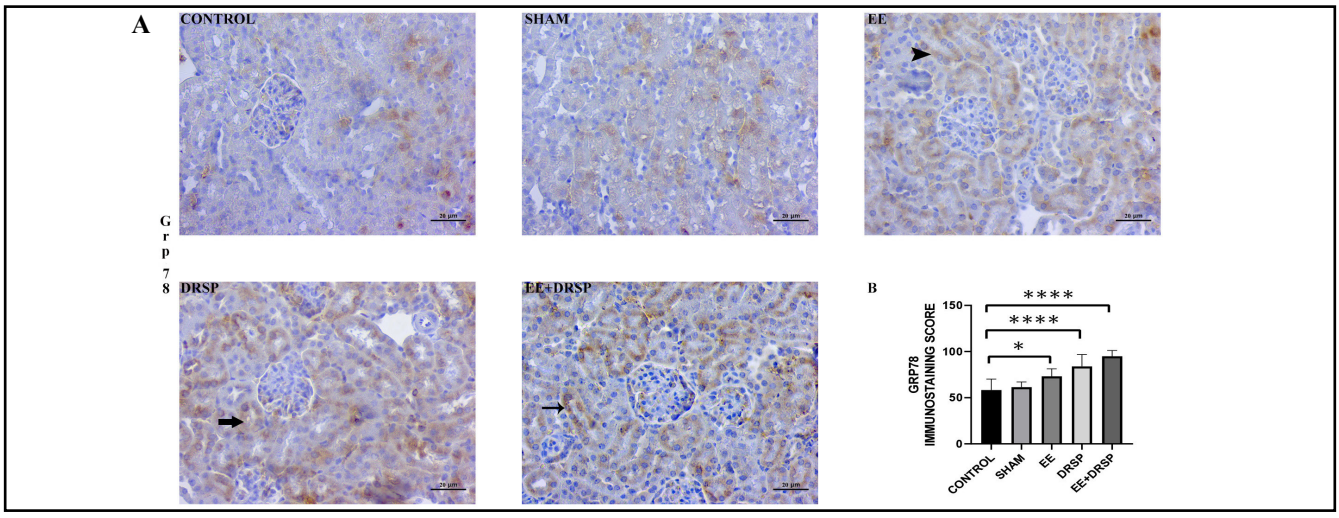

Figure 2. A. Immunohistochemical staining of ERS markers in the kidney. Representative photomicrographs showing Grp78 staining in Control, Sham, EE, DRSP, and EE+DRSP groups. Compared to the Control mice, EE (arrowhead), DRSP (thick arrow), and EE+DRSP (thin arrow) groups displayed increasingly positive immunoreactivity cells. **B.** Quantitative analysis of Grp78 staining. Statistical analysis was done by one-way ANOVA with all pairwise multiple comparison procedures with the Bonferroni test. Values are given as mean±SEM. $p<0.0001$(****). Statistically significant increase in Grp78 protein expression level in EE (p:0.0212(*)), DRSP ($p<0.0001$(****)) and EE+DRSP ($p<0.0001$(****)) groups compared to the control group.

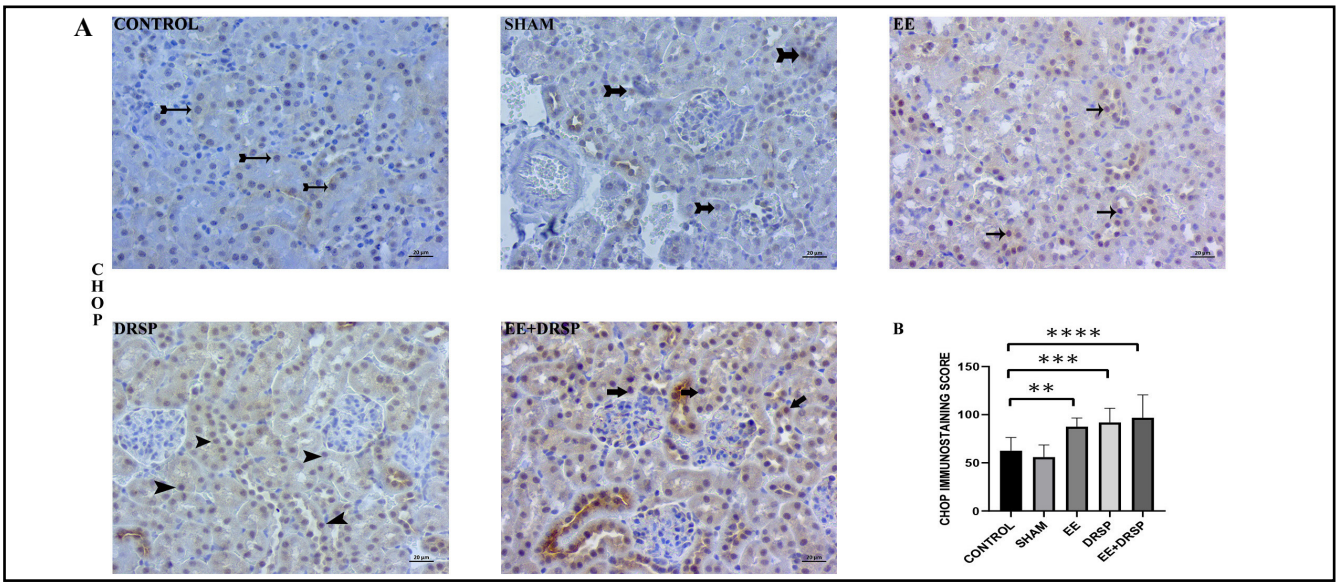

Figure 3. A. Immunohistochemical staining of ERS markers in the kidney. Representative photomicrographs show Chop staining in Control, Sham, EE, DRSP, and EE+DRSP groups. EE, DRSP, and EE+DRSP groups displayed increasingly positive immunoreactivity cells compared to the Control mice (arrows). **B.** Quantitative analysis of Chop staining. Statistical analysis was done by one-way ANOVA with all pairwise multiple comparison procedures with the Bonferroni test. Values are given as mean±SEM. It was found that Chop expression in kidney tissue of EE (p:0.0023(**)), DRSP (p:0.0002(***)), and EE+DRSP (p<0.0001(****)) groups increased statistically significantly compared to the control group.

DRSP counteracts estrogen-induced stimulation of the renin-angiotensin-aldosterone system and binds to aldosterone receptors in the kidney, blocking the effects of aldosterone and has demonstrated strong antimineralocorticoid activity (17). In one study, Schürmann and colleagues reported no change in serum potassium level when comparing women with mild to moderate renal impairment to healthy controls who received 3 mg of DRSP daily for 14 days (18). While another study showed significant increase of creatinine level in women who used oral contraceptive in compared with women do not used oral contraceptive, each woman should analyze parameters that affect the kidney function before using these contraceptives (19). A study conducted on Wistar rats suggests that the use of oral contraceptives may alter the functionality of the kidney, thus leading to kidney deterioration (20).

As DRSP is a spironolactone analog with anti-mineralocorticoid activity, it can potentially induce hyperkalemia in high-risk patients with renal insufficiency. After 14 days of oral DRSP 3 mg daily in women with moderate renal impairment, mean serum DRSP levels were 37% higher than in women with normal renal function. Therefore, DRSP exposure is slightly increased in women with renal impairment; DRSP/EE 3 mg/20µg (24/4) is contraindicated in both groups (21). The study has shown that mini-pills (progesterone only) have less pronounced histological effects on the rabbits' kidneys compared to combined pills (estrogen and progesterone) (22). These results can be supported by Sitruk-Ware et al., who stated that progestin-only contraceptives are much safer than combined pills (23). In contrast, a study by Taneepanichskul et al. (24) reported that oral contraception (OC) containing DRSP was well tolerated and did not affect kidney function in women. In a further study, Al-Jomard and Al-Youzbaki (25) noticed no significant differences in the use of COC in renal function tests in women aged 19-35 years. Our study showed that increased Grp78 and Chop apoptotic markers in mouse kidneys induced ER-dependent death pathway activity give rising to apoptosis in kidneys in the use of EE, DRSP, and EE+DRSP.

Abdel Kader et al. (22) demonstrated that using combined birth control pills caused marked changes in the form of damaged rabbit's renal tubules with cell swelling, loss of the brush border, and enlarged glomeruli with hypercellularity. In addition, a statistically different increase in peritubular, peri, and intraglomerular collagen content was noticed. In parallel with these findings, Al-Ani et al. (26) observed an increase in the cellularity of the renal corpuscles of OC and

attributed this to mesangial cell proliferation. Our study reported that significant loss of microvilli in proximal tubule epithelial cells and collagen fibers increased in the parietal layer of Bowman's capsule of the kidney tissues of the ethinyl estradiol+drospirenone applied group. In parallel with our findings, PAS staining revealed thickening of tubular basement membranes in rabbits treated with the combined pill (22). Karem et al. in their biochemical analysis as a result of Yasmin administered to mice, they recorded a significant increase in the ranges of hepatic variables (AST, ALT, ALP) and kidney (creatinine) in the blood serum of all mice treated with Yasmin compared to the control group. As a result, they reported that the combined oral contraceptive tablet (Yasmin) has the potential to impair liver and kidney function and may lead to liver damage and kidney failure (27).

ERS stimulates adaptive UPR to maintain ER homeostasis and proapoptotic UPR to eliminate cells under prolonged stress, which modulates the ERS state to protect the kidney against pathogenic environments. Studies have showed a relationship between the UPR pathway and glomerular and tubular cell damage in several kidney diseases (13). Moreover, many recent studies have reported that ERS is associated with many metabolic diseases, including diabetes, chronic heart failure (28), diabetic kidney disease (29), and renal fibrosis (30). However, there has not been enough research on the kidney histological structure and immunohistochemical studies of combined oral contraceptives. More comprehensive studies are needed for the results of this effect of the long-term use of COCs on ERS.

Our study showed that increased Grp78 and Chop apoptotic markers in mouse kidneys induced ER-dependent death pathway activity leading to apoptosis in kidneys using EE, DRSP, and EE+DRSP. UPR modulators may protect kidney cells against functional dysregulation caused by COC use.

Conflict of Interest

The authors related to this article declare no conflict of interest.

Ethics Committee Approval

Permission was obtained from The Institutional Animal Ethical Committee of Akdeniz University (Antalya, Türkiye) approved the study. (Authorization reference number: 2022.01.009).

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This study was presented at the International Congress on Natural & Medical Sciences as an oral presentation.

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Author's Contributions

A.C. and E.K. performed the Combined Oral Contraceptives Method on mice.

S.T. collected samples, took sections from paraffin blocks, did histological and immunohistochemical staining and statistical analysis, and wrote the manuscript.

E.K. created the project, optimizing experiments and data interpretation, and assisted to wrote the manuscript.

N.D. was the thesis advisor of E.K. and A.C. Moreover, his vast knowledge was consulted when performing the Combined Oral Contraceptives Method on mice. N.D. died on 21.12.2022.

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RESEARCH ARTICLE

Examination of Complementary Treatment Use of Individuals with Interstitial Cystitis: Descriptive Study

Yeliz Culha[1], Ezgi Seyhan Ak[2*], Mehmet Gokhan Culha[3]

[1] Fundamentals of Nursing Department, Istanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, İstanbul, Türkiye
[2] Department of Surgical Nursing, Istanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, İstanbul, Türkiye
[3] Department of Urology, University of Health Sciences, Prof.Dr. Cemal Tascıoglu City Hospital, İstanbul, Türkiye

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Correspondence
Ezgi Seyhan Ak, PhD, BSN
Istanbul University-Cerrahpaşa
Florence Nightingale Faculty of Nursing
Department of Surgical Nursing
Address: Abide-i Hurrriyet Street. Sisli-Istanbul / Türkiye
E- mail: ezgi.seyhanak@iuc.edu.tr

ORCID
Y.C. 0000-0002-5460-5844
E.S.A. 0000-0002-3679-539X
M.G.C. 0000-0003-4059-2293

Abstract

Objective: The aim of this study was to examine the use of complementary therapy in individuals with interstitial cystitis.

Material and Methods: This study, which was carried out in a descriptive research design, was carried out with 80 female patients over 18 years of age with interstitial cystitis, who applied to the Urology Outpatient Clinic of a city hospital in Istanbul between January and July 2023. The data were collected by face-to-face (onsite) interview method using a form prepared by the researchers in line with the literature to determine the socio-demographic characteristics of the patients and their use of complementary therapy. Data were analyzed using SPSS 22 statistical software for Windows. Results are reported as mean ± SD. Ethics committee and institutional permission were obtained before starting the study.

Results: When the characteristics of the individuals included in the study were examined; The mean age was 42.80±10.68 years, 60% did not have a chronic disease, 65% used any complementary treatment method, 43.2% used herbal treatment method, 50% did not receive complementary treatment. 55% received this information from the physician, 50% used complementary therapy to reduce their pain, 61.5% did not experience any side effects after using complementary therapy, 80.8% believed that complementary therapy was effective. It was determined that 53.8% of them did not share the complementary treatment methods they used with the physician or nurse.

Conclusion: It was seen that the majority of individuals with interstitial cystitis used any complementary treatment, half of them did not get information before using the treatment, and more than half did not share the complementary treatment methods they used with the physician or nurse.

Keywords: Complementary medicine, complementary therapies, interstitial cystitis, painful bladder syndrome

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INTRODUCTION

Interstitial cystitis (IC) is a chronic condition characterized by symptoms such as pelvic pain, sudden urge to urinate, increased urinary frequency, urinary incontinence, nocturia and low voiding volume (1,2). In European guidelines, it is stated that the prevalence rate in women is 1.2-21/100,000/ year, with a prevalence between 0.005% and 0.05%, and that it is 5 times more common in women than in men (3,4). Considering the prevalence rates of the disease, it is known that in a considerable proportion of patients, working life and many daily life activities, especially sleep and sexuality, are adversely affected, and due to the difficulty in determining the diagnosis of the disease, the lives of patients are negatively affected until they reach the right treatment and care (3,4). The diagnosis of interstitial cystitis can be made when alternative diagnoses such as urinary tract infection, neoplasia and bladder stones are excluded. Due to the lack of definitive diagnostic criteria or tests for IC as well as symptomatic overlap with other conditions (e.g., overactive bladder), the true prevalence of IC is difficult to determine. Prevalence estimates of IC fluctuate widely based on the study methodology and diagnostic criteria used (5). It is reported to be 3-7% in the literature (1).

Pain/discomfort, urgency/frequent urge to urinate and nocturia are common symptoms of interstitial cystitis (6). Current guidelines recommend that the treatment of interstitial cystitis should be multidisciplinary, including myofascial physical therapy, pain management, intravesical hyaluronic or intravesical botulinum injection, and conservative treatments to reduce and eliminate the symptoms of interstitial cystitis (7). Conservative treatment includes stress management, dietary modification, and behavioral modifications such as physical therapy, timed voiding to prolong voiding intervals, and bladder training. When combined with other treatments, conservative treatment and behavioral recommendations are reported to be effective in long-term symptom management and cost-effective (1). The American Urological Association (AUA) recommends that first-line treatment for patients with interstitial cystitis should include patient education, behavioral modification and stress management (7). Urology nurses, who are part of the multidisciplinary team, have an important role in providing patient education and individualized care necessary for the successful management of interstitial cystitis together with the urologist (8).

Today, many patients use complementary therapies to improve their quality of life, reduce symptoms and side effects related to medications, strengthen the immune system, and provide physical and psychological support (9,10). According to the definition made by the National Center for Complementary and Alternative Medicine (NCCAM), it includes "different practices and products applied by trained people, different from the scientific treatments used in conventional medicine" (11). Complementary therapies include phytotherapy, larva therapy, mesotherapy, prolotherapy, music therapy, hypnosis, cupping, homeopathy, ozone therapy, leech therapy, osteopathy, acupuncture, reflexology, chiropractic (12).

Complementary treatment methods used unconsciously by individuals often cause interactions between drugs, leading to dysfunction of organs and exacerbation of the disease (13). The fact that the complementary treatment practices used are not deemed necessary to be shared by patients, not questioned sufficiently by healthcare professionals and the fear of not being approved by healthcare professionals are among the reasons why patients do not access information about complementary treatment practices from the right sources (14,15). Therefore, health professionals, especially nurses, have important roles and responsibilities in diagnosing the appropriateness of complementary therapy use and providing guidance and education to individuals about its safe use. The objective of this study was to examine the use of complementary therapies in individuals with interstitial cystitis.

MATERIAL AND METHODS

The study was conducted as a descriptive cross-sectional study. The study was conducted with 80 patients with interstitial cystitis, over the age of 18, no vision or hearing problems, admitted to the Urology Outpatient Clinic of a City Hospital between January-June 2023. Illiterate patients and patients with cognitive-perceptual problems were excluded.

The study is a descriptive study. The number of patients applying to the tertiary urology clinic specified during the study dates was determined as 20 per month. It was decided to include at least 76 patients with %80 reliability and 5% margin of error in the population where 25% of the patients seen in a total month were known to have interstitial cystitis. The study was completed with 80 patients. A case report form consisting of two sections prepared by the researchers in line with the literature was used for data collection. The questions in the first part will consist of 6 questions about the socio-demographic characteristics of the patients including age, gender, marital status, educational status and employment status. The second part consists of a total of 8 questions to determine the complementary treatment utilization status of the patients (13,16). The data were collected with the

case report form using the face-to-face interview method in the Urology Outpatient Clinic after being informed about the purpose and scope of the study. A pilot study was conducted with 8 patients to evaluate the comprehensibility of the questions. At the end of the pilot study, the questions were finalized. Patients included in the pilot study were not included in the sample.

Data were analyzed using SPSS 22 statistical software for Windows (SPSS, Chicago, IL, USA). Results were reported as mean ± SD. Ethics committee approval (16/2023) and institutional permission from the institution where the research will be conducted were obtained before starting the study.

Before the data were collected, the individuals to be included in the study were informed about the purpose and content of the study and that their data would be kept confidential, and their informed consent was obtained in line with the principle of voluntariness. This study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

The mean age of the patients included in the study was 42.80±10.68 years, 55% (n=44) were married, 60% (n=48) were primary school graduates, 60% (n=48) had no chronic disease and did not use medication continuously (Table 1).

In the study, 65% (n=52) of the patients used complementary and alternative medicine (CAM) methods, 43.2% (n=32) preferred herbal treatment as a CAM method, 55% (n=22) had physicians as their source of information on CAM use, and 50% (n=20) used CAM methods to reduce pain, It was observed that 61.5% did not experience any side effects after using CAM, 80.8 % (n=42) believed in the effect of CAM, and 53.8% (n=28) did not share the CAM method they used with the physician or nurse (Table 2).

DISCUSSION

Although the products used vary from region to region, many complementary alternative medicine (CAM) methods are widely used all over the world (17). Compliance with treatment and achieving the desired outcome in chronic diseases depends on various factors and this affects quality of life. Individuals may turn to CAM methods or different searches in order to improve their quality of life and better manage the symptoms associated with their disease (18). While Karakoc (17) determined that the rate of participants applying CAM methods was low in his study, Nural and Cakmak (18) and Hasan et al. (19) determined that the rate of CAM use was high in individuals with chronic diseases. Jia et al. (20) found that the majority of patients diagnosed with interstitial cystitis used CAM methods. In this study, it was observed that the majority of patients used complementary therapy.

Table 1. Individual Characteristics of Patients (N=80)

Characteristics		**n**	**%**
Age Mean ± SD () (Min:- Max:)	42.80±10.68(21-65)		
Marital Status	Married	44	55
	Single	36	45
Education status	Primary school graduate	48	60
	High school graduate	32	40
Employment status	Yes	32	40
	No	48	60
Chronic disease status	Yes	32	40
	No	48	60
Continuous medication use	Yes	32	40
	No	48	60

SD: Standard Deviation, Min: Minimum, Max: Maximum

Table 2. Characteristics of Patients Regarding the Use of Complementary Medicine (N=80)

Characteristics		n	%
Use of CAM method	Yes	52	65
	No	28	35
CAM method used*	Body and mind therapies	9	9
	Herbal Treatments	32	4.2
	Dietary Support	8	10.8
	Massage	12	15
Status of receiving information about CAM	Yes	40	50
	No	40	50
CAM information source	Physician	22	55
	Nurse	6	15
	Other health professional	8	20
	Another patient with interstitial Cystitis	4	10
Reasons for applying CAM method	To reduce pain	20	50
	Reducing stress	6	15
	Just out of curiosity.	4	10
	To relieve side effects of medicines	2	5
	Because recommended by a doctor or nurse	8	20
Presence of any side effects after using CAM	Yes	20	38.5
	No	32	61.5
Belief in the effectiveness of the CAM method used	Yes	42	80.8
	No	10	19.2
Sharing the CAM methods used with the physician or nurse	Yes	24	46.2
	No	28	53.8

*More than one answer was given.

CAM: Complementary and Alternative Medicine

Patients with interstitial cystitis often experience a reduced health- related quality of life associated with physical limitations, reduced vitality, increased sleep dysfunction, more pain and more problems with sexual/social functioning (21). Complementary and alternative medicine treatment options for interstitial cystitis are many and should be individualized for each patient (22). Leong et al. (23) reported that nutritional changes and physical treatment modalities were included in the alternative treatment category in patients with chronic pelvic pain. In the study by Oh-Oka (24) evaluating intensive systematic dietary manipulation in female patients with IC, he stated that the diet was clinically effective in reducing IC symptoms. Kanter et al. (25) indicated that there was a significant improvement in symptoms and pain self-efficacy in women with interstitial cystitis who applied mindfulness. Bouchard and Campeau (26) reported that the use of nutraceuticals may be useful in reducing IC symptoms. In the study of Jia et al. (20), it was reported that the majority of patients with interstitial cystitis used diet or physical therapy from complementary medicine methods. In this study, it was observed that the majority of patients used herbal treatment. This finding suggested that this may be due to the fact that herbal products are obtained naturally and they are easily accessible. Due to the paucity of data evaluating the efficacy of treatment approaches and inadequate understanding of the etiology of interstitial cystitis, no single approach is useful

for all patients (21). Therefore, it is important to inform patients about the lack of robust evidence for complementary therapies (27).

Today, access to information has become easier with advances in technology. Television and internet are considered as significant sources of information in determining health behaviors (12). The education and awareness status of individuals using these methods, their cooperation with health professionals, and the approach of health professionals to these practices affect the course of treatment (18). CAM practices should be applied by physicians who have been certified. Reasons such as difficult and costly access to medical treatments, the emergence of side effects of drugs, the idea that natural products do not have many side effects, and the lack of benefit from medical treatments have led patients to resort to these methods (10). In the study of Nural and Cakmak (18), it was determined that the main source of information about CAM methods of patients was television, followed by relatives, family and friends. In Jia et al. (20) study, more than half of the patients reported that their physicians recommended CAM. In this study, similar to the study of Jia et al. (20), it was observed that the source of information about complementary medicine was physicians. This finding may be associated with the awareness of the patients in the study about the use of CAM.

The meaning of the disease for the individual and the nature of the symptoms affect the health-seeking behavior of individuals. In Nural and Cakmak (18) study, it was determined that the most common reasons for patients to use CAM methods were to lower blood pressure and reduce pain. Manya et al. (28) reported that almost half of the patients with diabetes used one or more CAM methods to improve diabetes or general health, and Erdogan et al. (25) reported that almost half of the patients with heart failure thought that these methods were useful and used them because they felt good. In this study, it was determined that half of the patients used complementary medicine to reduce pain. Since pain is one of the most common symptoms in patients with interstitial cystitis, it is an expected result that they use CAM methods for pain.

In the literature, it has been reported that patients obtain information about CAM methods from the internet, media and relatives and that the rate of informing and consulting their physicians about their use of CAM is low (12). Similar to this finding, it was observed that more than half of them did not share their CAM usage status with physicians and nurses. This finding appears to be an important result of the study. Because incorrect and incomplete information about CAM methods may lead to poor patient outcomes. For this reason, health professionals, especially physicians, should be aware of such tendencies of their patients and raise awareness of their patients about these methods, question their attitudes towards CAM methods and provide information that will protect them from misuse.

Limitations

There are some limitations in this study. The first of these is the small number of samples. Despite of the fact that, the sample size of the study was calculated, it is still cannot represent a large population. Another limitation is that there were only female patients in the study. One of the limitations is that the treatments received by the patients were not evaluated using validated and comprehensive inquiry forms.

CONCLUSION

It was observed that the majority of individuals with interstitial cystitis used any complementary treatment, half of them did not receive information before using treatment, and more than half of them did not share the complementary treatment methods they used with the physician or nurse. To conclude, it is recommended that individuals with interstitial cystitis should be guided and counseled by health professionals to prevent complications that may develop due to unconscious use of complementary therapies.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.

Ethical Approval

The study was approved by Istanbul Prof. Dr. Cemil Tascıoglu Clinical Research Ethics Committee Board (approval date and number: 2023/16). Patients were informed as to the study. And their verbal and written consent was taken.

Author Contributions

Conception and design; YC, ESA, MGC, Data acquisition;YC, MGC, Data analysis and interpretation; YC, ESA, MGC, Drafting the manuscript; YC, ESA, Critical

revision of the manuscript for scientific and factual content; YC, ESA, MGC, Statistical analysis; YC, MGC , Supervision; YC, ESA.

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RESEARCH ARTICLE

Evaluation of Perioperative Clinical Parameters and Quality of Life in Patients Undergoing Radical Perineal or Retropubic Prostatectomy: A Prospective Randomized Study

Utku Can[1*], **Alper Coskun**[1]

[1] Department of Urology, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Türkiye

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Correspondence
Utku Can MD, Asst. Prof.,
Address: Şemsi Denizer Cad. E-5 Karayolu Cevizli Mevkii 34890 Kartal / İstanbul, Türkiye
E-mail: utkucan99@yahoo.com

ORCID
U.C. 0000-0002-9805-3930
A.C. 0000-0003-4745-5160

Abstract

Objective: The objective of study is to investigate the effects of radical retropubic and perineal prostatectomy methods in addition to the effect of pelvic lymph node dissection on perioperative morbidities, oncological outcomes and 1-year quality of life in patients with clinically local stage prostate cancer.

Material and methods: Patients admitted to our clinic between January 2013 and March 2015 and diagnosed with clinically localized stage prostate cancer were included. A total of 103 patients were randomized into 3 groups in which 38 patients received radical perineal prostatectomy(RPP), 31 had radical retropubic prostatectomy(RRP), and 34 RRP with pelvic lymph node dissection(PLND). Age, comorbidities, preoperative Gleason scores and serum prostate-specific antigen(PSA) data as well as the surgical parameters, clinical and pathological stages, and 1-year follow-up data were recorded for each patient."Extended prostate cancer index composite (EPIC)" and "SF-12v2™ Health Survey(Version 2.0)" questionnaires were used for overall and disease-specific quality of life at month 0, 1, 6 and 12 visits.

Results: No difference was found between the groups with regard to preoperative data such as age, serum PSA levels, clinical stage, biopsy Gleason score and Charlson comorbidity index while intraoperative data for the amount of bleeding and the average amount of transfusion were significantly lower in RPP group(RPP:645cc, RRP:960cc, RRP+PLND:890cc).1-year recurrence-free survivals for RPP, RRP, and RRP+PLND groups were 9.9 months, 11.2 months and 10.2 months, respectively, with no significant difference.Overall and prostate cancer-specific quality of life was similar for all 3 groups.No additional benefit with nerve-sparing surgery was shown in any of the groups in terms of incontinence and erectile functions.

Conclusion: Perineal dissection is beneficial in terms of the amount of bleeding and blood transfusion while prolonged postoperative drainage and wound infection rates are higher compared to retropubic approach.All 3 groups were similar in urinary, sexual, gastrointestinal and hormonal functions as well as the quality of life.

Keywords: prostatectomy, prostate cancer, perineal, retropubic, quality of life

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INTRODUCTION

Prostate cancer (PCa) is the 2nd most frequent cancer in men and the 2nd most frequent cause of cancer-related deaths following lung cancer. The risk of developing a prostate cancer during a lifetime in men is 16% and the risk of death from prostate cancer is 2.9%(1). Prostate cancer is denoted as an important health problem particularly among the elderly male population in developed countries(2).

The number of patients with early diagnosed prostate cancer (PCa) has increased due to the widespread use of digital rectal examination(DRE), prostate specific antigen (PSA) and transrectal ultrasound (TRUS)(3,4). Today, the common use of predictive models (Partin tables, Kattan nomograms) allows prediction of pelvic lymph node metastases so that lymph node dissection can safely be excluded(5). Pelvic lymph node dissection (PLND) is recommended when the risk of nodal metastasis is higher than 5% in these nomograms(6). In low-risk PCa, PLND is shown to be unrelated to biochemical recurrence-free survival(7). This led to radical perineal prostatectomy (RPP) draw attention again. This technique has a low rate of mortality and morbidity and also incorporated nerve-sparing surgery in late 1980's(8). Perineal approach may become more popular by description of robot assisted RPP in 2015(9) and performing robotic PLND via perineal approach(10).

Large series have been published that compare the definitive treatments, radical retropubic prostatectomy(RRP) and RPP. Overall oncological outcomes and complication rates are similar, while less blood loss and need for transfusion are observed in RPP group in addition to a shorter hospital stay and less analgesic use(11–15)as a historical open procedure, is modified to incorporate contemporary surgical ideas. There is relatively little in the literature regarding modern adaptations of perineal prostatectomy. This method of anatomic radical perineal prostatectomy has been developed to accomplish a minimally invasive method of achieving goals of disease control and preservation of genito-urinary functions.\n\ nMETHODS: Prospective outcome data is accumulated on 508 consecutive radical perineal prostatectomies by a single surgeon. Pathologic stage and PSA detectability are measures of cancer control. Pad use and ability to complete intercourse measure urinary and sexual function. General complications and other outcome measures are evaluated.\n\nRESULTS: Freedom from PSA detectability by pathologic stage is 96.3%, 79.4%, and 69.4% for organ confined, specimen confined and margin positive in the absence of seminal vesical invasion with an average 4 years follow up (3-114 months. In addition, side effects secondary to surgical treatment have a substantial impact on quality of life (QoL) in clinically local stage PCa group patients with longer life expectancy. Therefore, a choice of primary definitive treatment that can minimize these side effects would be a rational approach(16). Moreover, there is a limited number of studies that investigate the influence of PLND on perioperative morbidities and no study is found in the literature on overall and PCa-specific QoL. We, therefore, aimed to prospectively compare the perioperative morbidities of RPP, RRP, and RRP+PLND techniques that we randomly applied to patients with clinically local stage PCa, and to compare the effects of surgical modalities on overall and PCa-specific QoL during the postoperative period of 1 year.

MATERIAL AND METHODS

Patients admitted to our clinic between January 2013 and March 2015 and diagnosed with clinically localized PCa (pT1-pT2) with a risc of lymph node invasion less than 5% according to Partin table were included in this study. Following the approval of ethics committee, 120 subjects that were planned to be included in the study were randomized into 3 groups. After giving informed consent to participate in the study, 120 subjects of the three groups received RPP, RRP, and RRP+PLND, respectively. 17 subjects who were lost to follow-up due to postoperative social issues or chose to discontinue were excluded from the study. The interventions were performed in our clinic by two experienced surgeons who had completed training on both surgical techniques. Subjects who had unilateral or bilateral nerve-sparing surgery were recorded.

Age, comorbidities, preoperative Gleason scores and serum PSA data as well as the duration of surgery, perioperative amount of bleeding and need for transfusion, postoperative drainage periods, and clinical and pathological stages were recorded. Clinical staging before the surgery was made using total PSA levels, DRE and TRUS-biopsy. Additionally, bone scan and pelvic MRI were performed in subjects with a total PSA level higher than 10 ng/dL. Clavien scoring system was used for perioperative complications and morbidity.

Tumor grade was determined according to Gleason grading system. All biopsy and histologic samples were graded according to 2009 TNM classification and urologic pathology samples were interpreted by an experienced pathologist. Postoperative follow-ups were carried out by clinical evaluation in each visit and by PSA levels at 1, 3, 6 and 12 months. A postoperative PSA value higher than 0.2 ng/dL was considered biochemical progression. None of the subjects with incontinence received additional medical therapy for this condition. Phosphodiesterase-5 inhibitor

was initiated in some of the patients with erectile dysfunction taking into consideration the contraindication issues and patient preferences.

Quality of life was evaluated in two steps. The first one was "The Expanded Prostate Cancer Index Composite (EPIC)" (17), a questionnaire that specific for PCa and the second was "Medical Outcomes Study 12-item Short Form Health Survey (SF-12)"(18) questionnaire that evaluated the overall QoL. Scores from these two questionnaires were recorded individually for each group before surgery (t0) and at postoperative 1 (t1), 6 (t2) and 12 (t3) months. Final scores were between 0-100 and higher scores were considered as better health related QoL. During statistical analysis, t0 score was taken as a basal value and compared to the data at postoperative 1, 6 and 12 months. Then, 3 treatment groups were compared with regard to the changes in scores during postoperative follow-ups.

Patients were asked to evaluate sexual functions using the EPIC form compared to their performance when they were not taking phosphodiesterase-5 inhibitors. The questionnaires were applied by a single doctor verbally by face to face interview with each patient. Patients given preoperative hormone replacement therapy, those with an additional disorder such as arthrosis, ankylosis or coxarthrosis that hamper exaggerated lithotomy position, and those who underwent pelvic or abdominal major surgery were excluded from the study. Post-treatment inquiries were discontinued in patients that were included in the study but were administered postoperative radiotherapy and/or hormone therapy for biochemical recurrence since the QoL scores might influence the outcomes of the study. In patients who underwent additional surgical interventions for postoperative anastomotic strictures, evaluation of the inquiry forms was continued after the second procedure.

The primary endpoint of the study was the comparison of subjects in 3 groups by urinary, sexual, gastrointestinal, hormonal, mental and physical functions and their impact on QoL at preoperative and 1 year of the postoperative period. The secondary endpoint was the comparison of subjects in 3 groups by the average duration of surgery, duration of hospitalization, duration of catheter drainage, amount of bleeding and the need for transfusion, surgical margin positiveness, complications, and 1-year biochemical recurrence.

All participants were informed that their data would be used for clinical research purposes and gave written informed consent to have their clinical data recorded in a private database. This study was approved by Kartal Dr Lütfi Kırdar Training and Research Hospital Ethic Committee (Registration number and date:514/62/17, 26.03.2015). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice

Statistical Analysis

Statistical analyses and randomization of the groups were carried out using SPSS (Statistical Package for Social Sciences) 22.0 statistical software package. Suitability of the variables for normal distribution was tested using One sample Kolmogorov-Smirnov. Variables with normal distribution were indicated as the mean and standard deviation. Chi-square, Kruskal-Wallis, Kaplan-Meier, one-way variance analysis (one-way ANOVA) was used for statistical analysis and ANOVA tests were used for repeated measures. Variance homogeneity was tested by Levene test. Paired post-hoc comparisons for groups with meaningful ANOVA results were made using Tukey's HSD test. $P<0.05$ was considered as statistically significant.

RESULTS

Among 103 patients that were included in the study, 38 received RPP, 31 received RRP and 34 received RRP with PLND. No intraoperative or postoperative mortality was observed. Demographic data and clinical findings before surgery are shown in Table 1. There was no significant difference between groups in terms of mean age ($p>0.05$). Mean serum PSA levels were similar in all 3 groups ($p>0.05$). The comorbidity score was higher in RPP group; however, there was no significant difference between 3 groups ($p>0.05$). There were no significant differences between the groups in terms of clinical stage and Gleason scores from 12-core prostate biopsies ($p>0.05$).

The mean amount of bleeding during surgery, transfusion given, duration of surgery and the duration of postoperative hospital stay are shown in Table 2. The mean amount of bleeding was significantly lower in RPP group compared to other two groups ($p<0.05$). Similarly, mean amount of blood transfusions was significantly lower in RPP group compared to RRP+PLND group. The mean duration of the surgical procedure was equal in RRP and RPP groups while it was 28 minutes longer in RRP+PLND group. No statistically significant difference was observed between the groups in terms of hospital stays ($p>0.05$).

Data regarding prostatectomy pathologies and biochemical recurrence are demonstrated in Table 3. No significant difference was observed when 3 groups were compared for pathological stage and surgical margin positiveness. Among

34 subjects in RRP+PLND group 2 subject had lymph node invasion. Although number of subjects without recurrence was higher in RPP group at the end of the year, no statistically significant difference was found between 3 groups (p>0.05). Similarly, Kaplan-Meier method was used for 1-year average recurrence-free survival and no statistically significant difference was found between 3 groups (Figure 1).

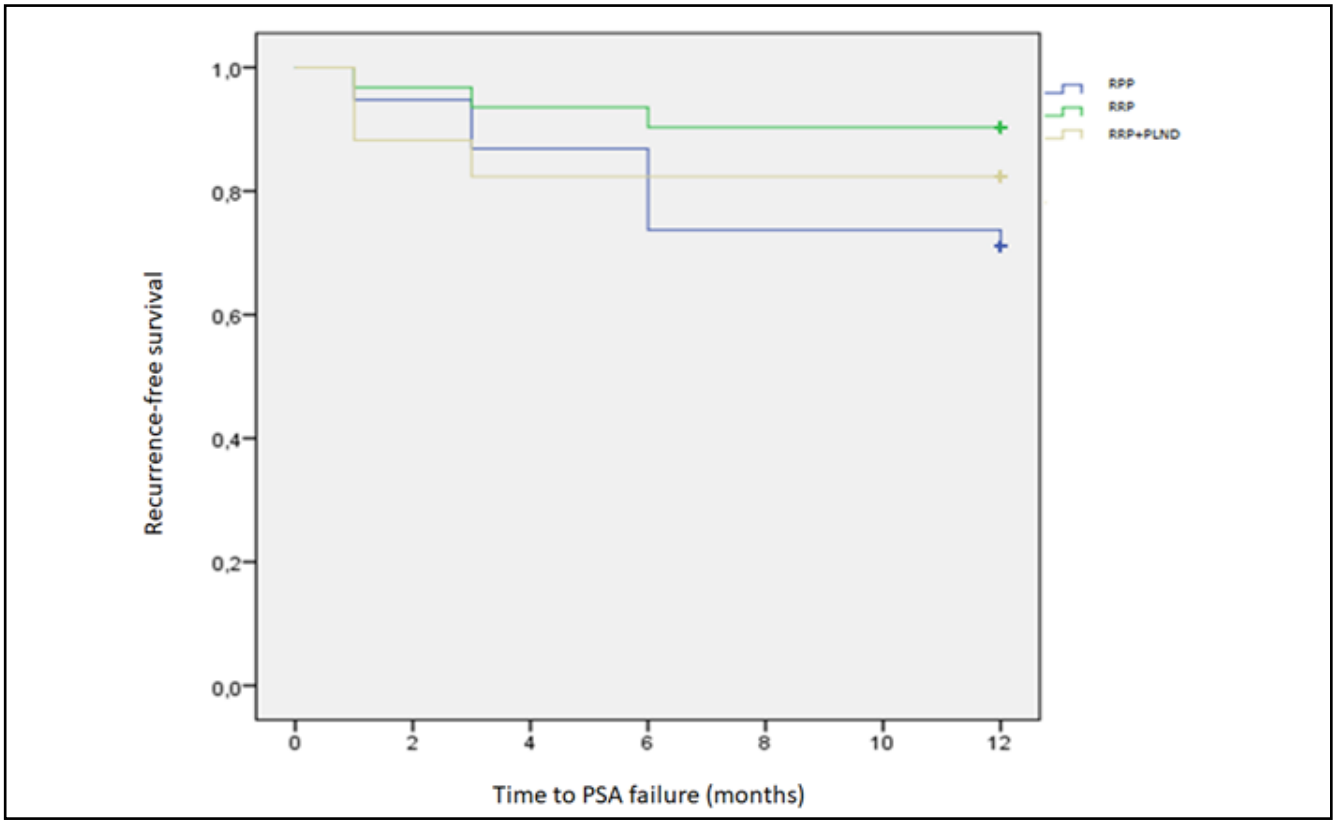

Figure 1. Kaplan-Meier curves for biochemical recurrence-free survival after RPP (blue), RRP (green) and RRP+PLND (gray)

Table 1. Preoperative demographic data and clinical findings by groups

	RPP n=38	RRP n=31	RRP+PLND n=34	p
Age (year)				
Mean(SD)	63.3(6.8)	62.7 (5.1)	63.5 (5.9)	[1]**0.875**
PSA (ng/dl)				
Mean(SD)	6.1 (2.3)	6.6 (2.8)	7.5 (3,2)	[1]**0.105**
Clinical stage				
T1	24 (63%)	18 (58%)	18 (52%)	[2]**0.680**
T2	14 (37%)	13 (42%)	16 (47%)	
Biopsy gleason score				
6 ≤	31 (82%)	28 (90%)	26 (77%)	[2]**0.334**
7	7 (18%)	3 (10%)	8 (23%)	
Charlson comorbidity score				
Mean(SD)	1.2 (1)	0.6 (0.8)	1(0.9)	[3]**0.055**

[1]*One Way Anova p<0.05* [2]*Pearson Chi-square p<0.05* [3]*Kruskal-Wallis p<0.05*

Table 2. Intraoperative and postoperative data by groups

	RPP n=38	RRP n=31	RRP+PLND n=34	p
Amount of bleeding (cc)				
Mean(SD)	645 (340)	960 (468)	890 (420)	[1]**0.004** [3]*(RPP< RRP and RRP+PLND)*
Transfusion(units)				
Mean(SD)	0.4 (0.8)	0.8 (1.2)	1.1 (1.1)	[2]**0.032** [4]*(RPP< RRP+PLND)*
Operative duration (min)				
Mean(SD)	117 (25)	117 (40)	145 (40)	[1]**0.001** [3]*(RPP and RRP< RRP+PLND)*
Hospital stay (days)				
Mean(SD)	5.2 (3.2)	4.6 (2.1)	4.6(1.9)	[2]**0.845**

[1]*One Way Anova p<0.05* [2]*Kruskal-Wallis p<0.05* [3]*Tukey HSD* [4]*Mann-whitney-U*

The complications were classified into 3 groups as intraoperative, postoperative short-term and postoperative long-term and are shown in Table 4 according to Clavien-Dindo system. Approximately one-half of the subjects in RRP+PLND group received blood transfusion which was lower in RPP and RRP groups. The proportion of patients with prolonged drainage was higher in RPP group. Anostomotic stricture, a long-term (first year) postoperative complication, was higher in RRP group. Considering overall complications, no significant difference was observed when 3 groups were compared in terms of presence of at least one complication (p>0.05).

Quality of life scores are summarized in Table 5. Comparison of SF-12 scores demonstrated a significant decrease in terms of physical health in all 3 groups at 1 month compared to preoperative assessment. In the comparison made according to EPIC scores, a significant decrease was observed in total urinary score including urinary function, satisfaction, continence and obstructive irritative symptoms in RPP group at 1 month compared to the preoperative assessment, and a significant increase was seen in RPP and RRP+PLND groups at 12 months compared to the preoperative assessment. Total bowel scoring that evaluates bowel functions and satisfaction showed no significant change in the groups at 1 month while a significant increase was observed at 6 and 12 months. Total hormone scores showed no statistically significant change within the first 6 months in all 3 groups while there was a significant increase only in the RRP+PLND group at 12 months compared to the preoperative assessment. Total sexual score was significantly lower in all 3 groups throughout the visits compared to the preoperative assessment.

There was no significant difference in the visits in terms of SF-12 scores when the groups were compared for the changes in scores. In terms of EPIC scoring, the 3 groups showed no significant difference in the visits by total urinary and incontinence scores in addition to total hormone scores and total sexual scores. When only irritative and obstructive symptoms were compared to preoperative data, the improvement at 12 months was significantly lower in RRP group compared to the other groups.

Eighteen subjects in RPP group, 14 in RRP group and 17 in RRP+PLND group received no nerve-sparing surgery while 15 in RPP group, 12 in RRP and 17 in RRP+PLND had unilateral, and 5 in RPP, 5 in RRP and 10 in RRP+PLND groups had bilateral nerve-sparing surgery. There were no significant differences between the groups with regard to having received nerve-sparing surgery (p=0.273).

In Table 6, EPIC incontinence and sexual function scores were given as means at 1 month and 12 months in 3 groups with regard to whether nerve-sparing surgery is performed or not. Thus, no significant difference is found in terms of incontinence scores in 3 groups regarding nerve-sparing surgery (p>0.05). Based on the assessment for sexual function scores, 12th-month sexual function scores were higher without statistical significance in patients in all 3 groups undergoing nerve-sparing surgery compared to those who are not (p>0.05).

Table 3. Pathological results and biochemical recurrence data

	RPP n=38	**RRP n=31**	**RRP+PLND n=34**	**p**
Pathological stage				**[1]0.353**
T2	25 (66%)	25 (81%)	23 (68%)	
T3	13 (34%)	6 (19%)	11 (32%)	
Surgical margin				**[1]0.710**
Positive	9 (24%)	8 (26%)	6 (18%)	
Negative	29 (76%)	23 (74%)	28 (82%)	
Localisation of surgical margin				
Apex	4 (11%)	3 (10%)	3 (9%)	
Bladder neck	1 (3%)	2 (7%)	0 (0%)	
Lateral	2 (5%)	1 (3%)	0 (0%)	
More than 1	2 (5%)	2 (7%)	3 (9%)	
Number of patients with biochemical recurrence-free n (%)	27 (71%)	28 (90%)	28 (82.4%)	**[1]0.125**
Recurrence free survival mean (months)	9.9	11.2	10.2	**[2]0.157**

[1]*Pearson Chi-square p<0.05* [2]*Kaplan-Meier p<0.05*

Table 4. Intraoperative and postoperative complications (Clavien-Dindo classification)

	RPP n=38	**RRP n=31**	**RRP+PLND n=34**	**Müdahale**
Clavien grade/Complication				
Intraoperative				
II Bleeding	9 (26%)	10 (29%)	16 (46%)	Blood Transfusion
Postoperative short period				
I Wound infection	4 (11%)	1 (3%)	3 (9%)	Antibioterapy, bedside intervention
Prolonged drainage	7 (18%)	1(3%)	0 (0%)	Long time urethral cateterisation
Id Anastomotic leakage	1 (3%)	0 (0%)	0 (0%)	Long time urethral cateterisation
II Urinary infection	0 (0%)	2 (7%)	1 (3%)	Antibioterapy
Hematuria	1 (3%)	0 (0%)	0 (0%)	Conservative approach+ blood transfusion
Postoperative long period				
IIIa Anastomotic stricture	1 (3%)	5 (16%)	2 (6%)	Endoskopik bladder neck incision
Total (At least 1 complication)	20 (53%)	15 (48%)	18 (53%)	**[2]P=0.919**

[2]*Pearson Chi-square p<0.05*

Table 5. HRQoL scores by treatment groups (EPIC and SF-12)

	RPP Mean(SD)	RRP Mean(SD)	RRP+PLND Mean(SD)	P value (repeat measures of ANOVA)	
SF-12					
Physical health				**0.557**	
Preoperative (t0)	53.8 (7)	55 (5.9)	54.5 (5.4)		Not significant
1st month (t1)	49.1 (6.6)*	45 (6.3)*	43.5 (7.3)*		Not significant
6th month (t2)	53.5 (4.9)	54.7 (3.4)	53.1 (5)		Not significant
12th month (t3)	54 (6.4)	54.2 (3.9)	53.7 (5.1)		Not significant
Mental health				**0.242**	
Preoperative (t0)	52.8 (6.5)	50.3 (6.7)	51.8 (4.2)		Not significant
1st month (t1)	53.4 (5.8)	50.9 (8.2)	51.9 (6.5)		Not significant
6th month (t2)	54.4 (5.9)	53.7(3.8)+	55.3(1.9)*		Not significant
12th month (t3)	54.9 (6)	54.5 (3.2)*	55.3 (2.2)*		Not significant
Total urinary				**0.218**	
Preoperative (t0)	84.7 (11.8)	81.3 (13.3)	83.9 (14.4)		Not significant
1st month (t1)	74.6 (13)*	78.4 (13)	79.4 (11.9)		Not significant
6th month (t2)	90 (10.1)	84.6 (14.7)	89.2 (11.2)		Not significant
12th month (t3)	94.7 (8.6)*	86.8 (14.2)	92.5 (8.4)+		Not significant
Incontinence				**0.811**	
Preoperative (t0)	99 (2.9)	99 (3)	99.3 (2)		Not significant
1st month (t1)	54.2 (25.5)*	69.6 (23.2)*	66.2 (24)*		Not significant
6th month (t2)	86.9 (17.7)*	83.2 (22.3)*	86.4 (23.6)*		Not significant
12th month (t3)	95.6 (11.7)	90.2 (14.3)*	92.6 (17.2)		Not significant
Irritative/obstructive symptoms				**0.019**	
Preoperative (t0)	79 (16.8)	73 (18.5)	75.9 (20.5)		Not significant
1st month (t1)	89 (8.6)*	85.5 (8.3)*	89.4 (8.7)*		Not significant
6th month (t2)	92.5 (7.8)*	86.6 (10.8)*	91.7 (5.8)*		Not significant
12th month (t3)	95 (8)*	86.6 (13.5)*	93.1 (5.6)*		**Significant**
Total Bowel				**0.612**	
Preoperative (t0)	93.8 (6.7)	95.4 (3.8)	95.9 (2)		Not significant
1st month (t1)	93.3 (7.4)	94.2 (5.6)	93.5 (5.8)+		Not significant
6th month (t2)	97.4 (6)*	97.2 (3.6)*	98.3 (2.8)*		Not significant
12th month (t3)	97.2 (5.9)*	98 (2.3)*	97.9 (2.7)*		Not significant
Total Hormone				**0.644**	
Preoperative (t0)	97.6 (3)	96.7 (3.2)	96.7 (3.8)		Not significant
1st month (t1)	96.8 (2.8)	96.3 (4.3)	95.5 (4)		Not significant
6th month (t2)	97.6 (2.5)	97.8 (2.9)	96.8 (3.3)		Not significant
12th month (t3)	97.9 (3.9)	97 (3.7)	99.1 (1.9)*		Not significant
Total sexuel				**0.529**	
Preoperative (t0)	71.6 (11)	72.4 (7.5)	70.4 (11.3)		Not significant
1st month (t1)	22 (5.8)*	22.5 (6.7)*	21.4 (3.8)*		Not significant
6th month (t2)	26.4 (15)*	28.6 (16.8)*	25.9 (12.6)*		Not significant
12th month (t3)	33.3 (20)*	36.5 (19.9)*	30.4 (15.1)*		Not significant

** p <0.01, The difference between before and after treatment is significant*

+p <0.05, The difference between before and after treatment is significant

Table 6. Incontinence and sexual function scores at 1 month and 12 months according to whether nerve-sparing surgery is performed or not

Nerve sparing surgery				
		No **n (SD)**	**Yes** **n (SD)**	**P** *(One Way ANOVA)*
Incontinence score				
RPP	t0 (n=38) t12 (n=29)	54 (23.5) 95 (12.1)	59.1 (28.4) 96 (11.8)	**0.558** **0.807**
RRP	t0 (n=31) t12 (n=27)	72.4 (23.8) 89.8 (15.3)	66 (21.2) 90.7 (13.9)	**0.437** **0.878**
RRP+PLND	t0(n=34) t12 (n=28)	60.5 (19.3) 94.2 (11.1)	69.6 (27.8) 90.7 (22.6)	**0.273** **0.605**
Sexuel function score				
RPP	t0 (n=38) t12 (n=29)	6.1 (5.3) 21 (17.1)	6.4 (6) 25.7 (27.1)	**0.867** **0.606**
RRP	t0 (n=31) t12 (n=27)	7.7 (6.6) 23.7 (25.3)	6.3 (4.9) 26.4 (23)	**0.501** **0.777**
RRP+PLND	t0 (n=34) t12 (n=28)	4.9 (2.1) 16.6 (13.8)	6.4 (5.1) 24.3 (24.2)	**0.261** **0.303**

DISCUSSION

Factors including the lack of equivalence among patient groups in terms of demographic data, biochemical and oncological parameters demonstrate the need for prospective randomized trials. Differences were found regarding preoperative data (serum PSA, clinical stage, etc.) in some previous non-randomized trials(14,15,19–20) that compare various routes of dissection which led to nonobjective assessments of intraoperative and postoperative data and pathologic results. In a prospective randomized study published by Martis et al. in 2007, 200 subjects were administered RPP and RRP where two groups were similar in terms of both pathological and clinical data which enhanced the reliability and the quality of the study(13). Similarly, in our study, no significant difference was found between 3 groups in terms of preoperative data including age, serum PSA, clinical stage, biopsy Gleason score and Charlson comorbidity index. Despite the benefit seen with perineal dissection in terms of the amount of bleeding and transfusion, no additional benefit was shown with regard to the duration of the procedure (compared to RRP without lymph node dissection), duration of hospital stay, pathological data and biochemical recurrence-free survival. Large trials that compare series of RPP and RRP highlight a shorter hospital stay and a lower amount of bleeding in the perineal group while no difference is observed in terms of oncological and functional outcomes(15,20). In Clavien complication assessment, perineal dissection has similar benefits in terms of blood transfusion while the duration of postoperative drainage and wound infection is higher compared to other groups. The duration of hospital stay is longer in RPP group in this study compared to other trials. We associate this with increased wound discharge seen in RPP group leading to a prolonged hospital stay. Our study shows similarities with regard to sample pathology, Gleason grading, surgical margin positiveness and biochemical recurrence data when compared to other studies(21,22). In addition to predictive factors that influence the data, we think that surgical experience and good anatomical knowledge are also parameters that affect the outcomes.

Quality of life have been employed in many large series following PCa treatment and were shown to demonstrate no difference with regard to treatment method used(23–25). We observed in our study that physical health has reached preoperative values in the long-term while mental health was better than preoperative values. We think that this demonstrates the positive effect of surgery on overall quality of life. EPIC that we used in this study is an extensive and up-to-date questionnaire that evaluates the functional status of the patients and their satisfaction regarding this condition after PCa treatment (17). Accordingly, there was no statistically significant difference when 3 groups were compared in terms of the change in urinary functions. What draws attention is that the total urinary score including irritative and obstructive symptoms and patient satisfaction was increased at 12 months

in all 3 groups compared to preoperative data. This has shown that the QoL regarding urinary system may be improved in patients with preoperative lower urinary system symptoms provided that appropriate postoperative incontinence rates are achieved. A multicenter study performed by Namiki et al. (14) that compared RRP, RPP, and LRP methods, evaluated the overall QoL (SF-36) and UCLA prostate cancer index (UCLA-PCI) during the 1-year follow-up. Evaluations of physical and mental health show similarities to our study while the urinary function was found to be worse in all 3 groups in all postoperative visits. This may be associated with the absence of questions in UCLA-PCI regarding irritative and obstructive symptoms. In a retrospective study by Mirza et al. in 2011 that included a total of 463 subjects who received RPP, RRP and RALP (robot-assisted laparoscopic prostatectomy),(26) no significant difference was found between the 3 groups in terms of total urinary score and the use of pads in addition to sexual, intestinal and hormonal parameters when EPIC scores in the time window of 12-18 months were evaluated in some of the subjects. The absence of preoperative basal data and retrospective design have been emphasized as the weaknesses of the study. Similarly, no difference was observed between the groups for total sexual scores while postoperative low scores were still being seen at 12 months. In the literature, the rates of postoperative erectile dysfunction have been reported to be 25-90%(27,28). However, potency is shown to be between 31-86% among those who received bilateral nerve-sparing surgery. In this study, erectile function at 12 months was better in subjects who underwent nerve-sparing surgery compared to those who did not in all 3 groups where no additional benefit was shown statistically on continence and erectile functions.

Published complication rates for PLND vary between 4% and 53% led by lymphocele and lower limb edema, DVT, pelvic abscess, ureteral injury, neurovascular injury, and ileus are rare complications. In the study by Daimon et al. (7), no relation was found in low-risk PCa between PLND and biochemical recurrence-free survival, while the shorter duration of surgery and lower mortality rates were underlined in subjects without lymph node dissection. However, the general opinion is that morbidity due to PLND is minimal(29). In this study, lymph node dissection resulted in no additional morbidity in 34 patients that received RRP+PLND and no disadvantages in terms of 1-year overall and PCa-specific QoL. No study in the literature has demonstrated the influence of PLND on QoL. We demonstrated the positive or negative effects of PLND on both PCa-specific and overall QoL by applying PLND in one of the groups. We found no disadvantage on EPIC score or both physical and mental QoL, or postoperative complications. Furthermore, intraoperative parameters indicated that the duration of surgery was approximately 28 minutes longer and the rate of blood transfusions was higher in PLND group compared to the other two groups. The impact of prolonged surgery on the anesthesiologist might have led to the higher transfusion rates seen in RRP+PLND group despite the lack of significant difference in the average amount of bleeding compared to RRP.

The strengths of the study may be that it has a prospective randomized design, involves homogenized subject groups, and uses follow-up questionnaires specific to PCa. The low number of subjects, the short duration of follow-up for oncological results as well as the scoring being done by face-to-face interviews between the doctor and the patient due to the absence of Turkish validation of the EPIC inquiry form are the weaknesses of this study.

CONCLUSION

Outcomes with higher levels of evidence may be achieved by a prospective randomized study that involves the effects of PLND on QoL, that includes a higher number of homogenized subjects and longer duration of follow-up and that can also compare methods that are specified as minimally invasive.

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Protection of human and animal subjects: The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent: The authors declare that no patient data appear in this article.

Author Contribution:

U Can; Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

A Coskun; Data collection or management, Manuscript writing/editing.

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CASE REPORT

Testicular Angiomyolipoma: A Case Report and Review of the Literature

Sukru Ali Altan[1], Zuhre Selma Karaman[2 *], Oztug Adsan[1]

[1] Department of Urology, Faculty of Medicine, TOBB University of Economics and Technology, Ankara, Türkiye

[2] Faculty of Medicine, TOBB University of Economics and Technology, Ankara, Türkiye

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Correspondence
Zuhre Selma Karaman
Faculty of Medicine, TOBB University of Economics and Technology, Ankara, Türkiye
E-mail: zuhreselma@gmail.com

ORCID
S.A.A. 0000-0001-7786-5975
Z.S.K. 0009-0008-2972-5407
O.A. 0000-0003-2416-8556

Abstract

Angiomyolipoma (AML) is a benign mesenchymal tumor, that is composed of thick-walled blood vessels, smooth muscle cells and adipose tissue. They are commonly seen in kidneys, testicles are not a typical location for AML's; many solid testicular tumors are germ cell malignancies. Here we report the sixth testicular AML case in the literature, to our knowledge. An 80-year-old male undergone bilateral orchiectomy with the diagnosis of local invasive prostate cancer, without any testicular symptoms. Pathological analysis demonstrated a tumor, involving nearly the whole left testicle, composed of muscle cells, vessels and fat tissue, diagnosed as testicular AML. In this article our case is reported and we also make a literature review about testicular AML's.

Keywords: angiomyolipoma, angiolipoma, testis, orchiectomy

INTRODUCTION

Angiomyolipoma (AML) is a rare tumor of mesenchymal origin, composed of adipose tissue, thick-walled blood vessels, and smooth muscle cells. They are sporadic in most of the cases, however less than a quarter of the cases might be a component of tuberous sclerosis complex (TSC), as a result of mutations in TSC1 or TSC2 tumor suppressor genes. Kidney is the most frequent solid organ that AML's locate, followed by the liver [1]. Testicles are very atypical organs for AML location; to our knowledge only five testicular AML's and an intratesticular angiolipoma without the muscle cell component have been reported [2,3,4,5,8,9]. Here, we report the sixth case which is the second incidental testicular AML.

CASE PRESENTATION

An 80-year-old male patient was admitted to our outpatient clinic with a diagnosis of locally invasive prostate cancer. Preoperative physical examination of the testes was completely normal. Due to his age and stage, bilateral orchiectomy was planned instead of radical surgery for treatment. Testicular imaging was not performed before bilateral orchiectomy because of the absence of pathological findings on physical examination. In the routine pathological examination of the patient after orchiectomy, an incidental angiomyolipoma was detected in the left testicle.

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Macroscopic Findings

The dimensions of the right testicle were 8x6x5 cm's, the left one was smaller, 6x4x3 cm's. The right testicle was normal in cross section, however the cross-section of the left testicular specimen was rich in fat tissue and the tumoral lesion was macroscopically involving the whole testicle and the residual testicular tissue was not noticeable.

Microscopic Findings

Microscopic examination showed well circumscribed, yellow colored, tumor which was composed of numerous large vessels, mature fat tissue and bundles of smooth muscle fibers (Figure 1). Smooth muscle fibers were concentrated around the dilated thick-walled hyalinized vessels, and surrounded by adipocyte islands. All three components (angio-myo-lipoma) were mature histologically, and any cytological atypia, mitosis, pleomorphism or necrosis was not detected in the lesional cells. No sarcomatoid changes or hemorrhage were present. There were atrophic remnants of the seminiferous tubules around the tumor. In epididymal sections, lumens of the ducts were empty, any spermatocytes had not been observed.

Immunohistochemistry showed that the tumor cells were actin positive (Figure 2), and HMB-45 negative, only in a very small area showed a pale HMB-45 positivity (Figure 3).

Discussion and Review of the Literature

AML is a benign tumor, more commonly seen in women, and after the fifth decade. The cellular origin of testicular AML remains unknown, perivascular epitheloid cells are thought to be the source [5].

Testis is not a well-known site for AML's, testicular AML is not listed in World Health Organization (WHO) histological types of testicular tumors; they are commonly seen in kidneys (77%), and secondly in liver (14%) [3,6]. Only five cases of testicular AML have been reported to date.

Although AML's are benign tumors, epitheloid AML (EAML) was reported as a metastasizing sub-type, also may present nuclear atypia [6].

Five cases have been reported in the literature, summarized in (Table 1).

The tumor in the present case was nearly involving the whole testicle.

There is not an identical treatment recommendation for testicular AML's, since the majority of testicular tumors are germ cell tumors (GCT), which should be diagnosed and treated promptly; radical orchiectomy is the standard treatment option. Testicular AML might be a challenging pathological diagnosis, as a result of its rarity.

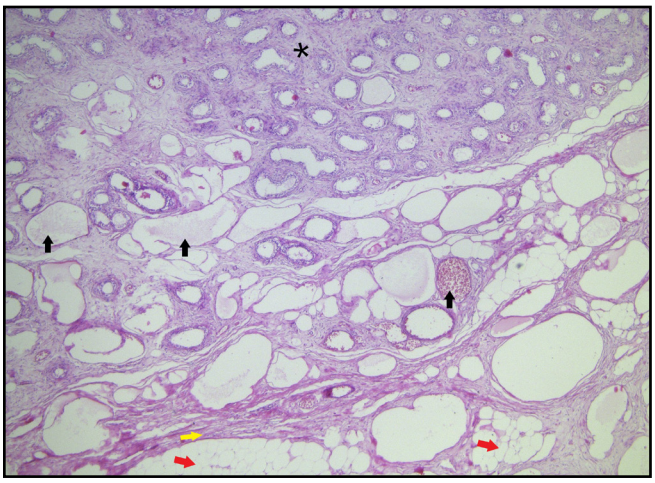

Figure 1. Large vessels, mature fat tissue and smooth muscle fibers. Black arrows refer to vessels, yellow arrow refer to smooth muscle cells, asterisk refers to normal testicular tissue, red arrows refer to fat tissue.

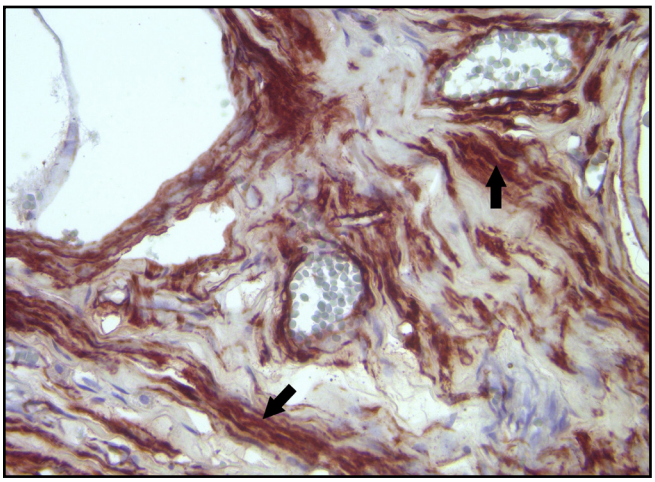

Figure 2. Actin, chromogen DAB. Black arrows refer to smooth muscle cells.

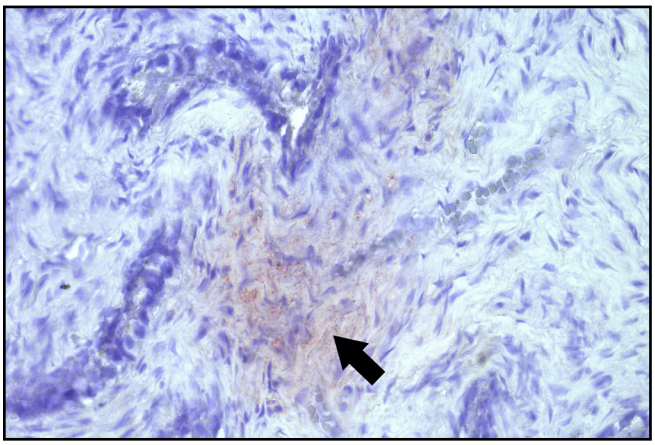

Figure 3. HMB-45, chromogen DAB. Black arrow refers to the pale HMB-45 positive area.

Ultrasound is generally the choice of imaging of the testicles, besides the physical examination. Other imaging modalities are seldom used. In our case orchiectomy is performed because of the diagnosis of local invasive prostate cancer, so neither detailed examination of testicles nor the ultrasound had not been performed. Although perioperatively any tumoral lesions were not visible or palpable in the testicles.

The role of frozen section analysis is limited in testicular lesions. All large testicular tumors are being treated by radical orchiectomy as a standard treatment modality. However, if the lesion is non-palpable, incidentally diagnosed in a routine imaging, the patient does not belong to any risk groups for testicular cancer, and the tumor is small enough (<1.5 cm's in diameter), orchiectomy may be an overtreatment, thus intraoperative frozen section may be an option in these cases [5].

Endothelial marker (CD34) and smooth muscle actin are the immunohistochemical (IHC) markers that are typically expressed in all AML's, we used the actin, and the result was positive. Another IHC marker that we use, HMB-45 is a monoclonal antibody that reacts against an antigen present in melanocytic tumors such as melanomas, and HMB stands for Human Melanoma Black. It is interestingly positive in renal and liver AML's, and negative in cutaneous and testicular AML's [5]. Renal positive HMB-45 used in differential diagnosis of resected benign renal specimens [7]. Our case showed general HMB-45 negativity, except a focal pale positive area, that shored up our diagnosis of testicular AML. It is thought that intense HMB-45 expression in kidney or liver AML cases is related to poor outcomes such as malignancies [3]. In our case HMB-45 was negative, which may indicate testicular AML's do not carry the risk of malignancy. That can lead us to think there might be significant biological differences between testicular AML and typical AML in the kidney [3]. In the cases mentioned above HMB-45 negativity was observed. Further research is required in order to make concrete deductions.

Because of the lacking cumulative data about testicular AML's, long term follow-up might be a safe option, however our patient died in several months after bilateral orchiectomy because of prostate cancer.

Despite of the fact that ages of the patients differ significantly according to the literature, because of the limited number of observed cases, making a decision about age group for testicular AMLs can not be done.

Based on observation, some cases presented with symptoms such as pain and swelling while others presented with no symptoms. Also some symptoms such as pain and swelling are common for testicular diseases. Thus testicular AML should be considered during diagnosis.

Table 1. Features of the reported testicular AML cases

Publication	Age	Symptoms	Size	Additional pathology
Lane TM et al. (2004)	56	no (incidental)	1.6 cm at the upper pole of right testicle	left hydrocele
Saito M et al. (2008)	22	pain + swelling	3.0 cm irregular margin tumour at left testicle	para-aortic LAP (1 cm)
Giulianelli R et al. (2012)	53	pain + swelling	not identified, left testicle	not present
Ceifo W et al. (2015)	25	pain + swelling	not identified, right testicle	right atrophic testicle
Waked H et al. (2020)	75	Painless swelling + hardness	3,5x3x2,6 cm, right testicle	Moderate hydrocele
Presented case	80	no (incidental)	not identified, left testicle	prostate cancer

CONCLUSION

Testicular AML is a very rare tumor; however, it may be in the differential diagnosis list of an urologist or pathologist in case of an atypical testicular mass. Each case should be diagnosed, treated and followed up individually according to clinical and pathological findings.

ACKNOWLEDGMENTS

Conflict of Interest: Authors declare no conflict of interest

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CASE REPORT

Spontaneous Urethrocutaneous Fistula in Child with Spastic Cerebral Palsy: A Case Report

Sinan Kilic [1], Samed Verep [2]

[1] Department of Pediatric Surgery, Gebze Yuzyil Hospital, Gebze, Kocaeli, Türkiye

[2] Department of Urology, Gebze Yuzyil Hospital, Gebze, Kocaeli, Türkiye

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Correspondence
Sinan Kilic, MD
Department of Pediatric Surgery, Gebze Yuzyil Hospital, Gebze, Kocaeli, Türkiye
E-mail: dr.sinankilic@yahoo.com

ORCID
S.K. 0000-0003-3454-5538
S.V. 0000-0002-1086-6380

Abstract

Urethrocutaneous fistulas are complications that usually seen after hypospadias repair. Spontaneous urethrocutaneous fistulas are extremely rare disorders unless related to the surgery of hypospadias. These fistulas are not associated with hypospadias repair, infection and trauma. While there are few cases reported in adults, there are no cases reported in children. Urethrocutaneous fistulas may rarely be encountered post-trauma, infection or due to weakness of spongious tissue of penis as well as.

Children with spastic cerebral palsy often face various problems due to prolonged hospitalizations. Pressure ulcers are among the most common of these issues. Urinary catheterization is frequently performed in these patients for urine monitoring. A 6-year-old male patient with cerebral palsy developed a urethrocutaneous fistula while being monitored in the pediatric intensive care unit. Pre-existing unnoticed partial prepuce and weakness in the corpus spongiosum were present in the patient. We suspect that the development of the urethrocutaneous fistula is attributed to frequent urethral catheterization and the development of decubitus ulcer in the penile region. Since a similar case is not found in the pediatric literature, our aim is to present this case for reference.

Keywords: Cerebral Palsy; Hypospadias; Urethral fistula; Decubitus ulcer.

INTRODUCTION

Urethrocutaneous fistulas are an undesirable opening in the penile skin through which urine can leak. The condition may be congenital or develop as a complication of an infection, injury, or surgery. Urethrocutaneous fistulas are rare but recognised disorders. There is currently no universally accepted classification for these disorders. Urethral fistulas can be classified into two forms: congenital and acquired (1). Congenital urethral fistulas are rarely reported anomalies and are generally associated with anorectal malformations. They occur due to two main causes: either a rupture in the embryonic urethra located after a congenital blockage or a partial insult in the embryonic development, resulting in the failure of the mesoderm to surround the forming groove where the fistula devolops (1, 2).

Acquired urethral fistulas are generally reported to result from various clinical conditions such as neoplasms, trauma, or infection-related complications (3). Straddle

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injury and blunt penile trauma are the most commonly recognized forms of urethral trauma leading to urethral fistulas (3). Complications after some types of penile surgery such as circumcision and corporal-spongial and corporal-saphenous shunts for priapism, may also include urethral fistulas (4). Additionally, urethrocutaneous fistulas are one of the most frequently observed complications of hypospadias surgery, often necessitating repeated surgical interventions. Urethrocutaneous fistulas have been reported to be observed in 7,5% of cases after complex hypospadias repair (5,6). Cerebral palsy (CP) is a neurological condition affecting brain development and leading to abnormalities in muscle tone, movement, and motor skills. Its treatment requires a comprehensive approach, including neurological rehabilitation to address issues with muscle tone and the implementation of physical and occupational therapies. Managing associated conditions such as epilepsy, cognitive impairment, visual and hearing impairments, and disruptions in growth and gastrointestinal function is also integral to treatment process (7).

It is known that children who require frequent hospitalizations often experience problems associated with prolonged immobility in the same posture and frequent infections.

We present this case due to its rarity as a complication and the absence of reported cases of spontaneous urethrocutaneous fistula in children.

CASE REPORT

A 6-year-old male patient was diagnosed with microcephaly and CP shortly after birth. He underwent surgery for a cleft palate. Due to the prolonged hospitalization, a tracheostomy was initially performed, and percutaneous endoscopic gastrostomy (PEG) tube was inserted for nutritional purposes.

Like many children with cerebral palsy, this patient continues his life with a home ventilator and requires periodic monitoring in the intensive care unit due to episodes of pneumonia. During his hospitalization in intensive care unit due to respiratory distress and pneumonia, urine output monitoring was conducted using a urethral catheter. As a result of the urine output monitoring, a spontaneous fistula developed in the penoscrotal region (Figure 1). No bacterial infection was demonstrated in the urinary analysis. The patient underwent surgery for fistula repair and also because of the possibility of infection. A cystofix catheter was inserted to ensure urinary drainage until the fistula healed (Figure 2). The operation involved cutting the ventral penile skin. It was observed that the penile urethra was completely destroyed up to the penoscrotal region (Figure 3). A new urethral orifice was created in the penoscrotal area (Figure 4). Debridement was performed on infected tissues. Subsequently, the plan was to perform a vesicostomy or Mitrofanoff procedure, but due to the family's refusal, the patient's condition continued to be monitored in its current state.

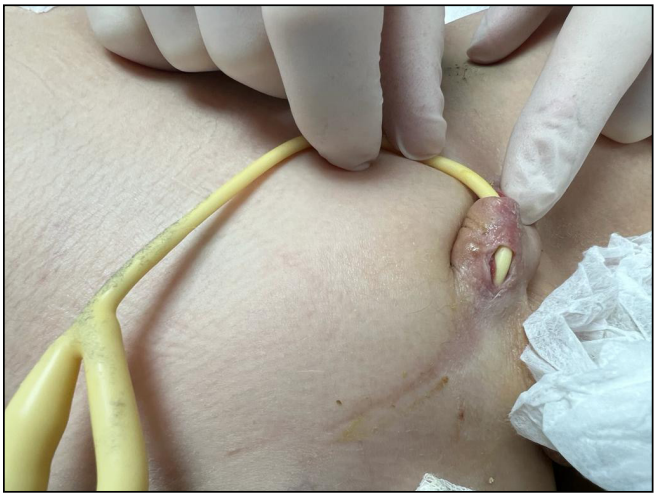

Figure 1. Urethral fistula in the penoscrotal region.

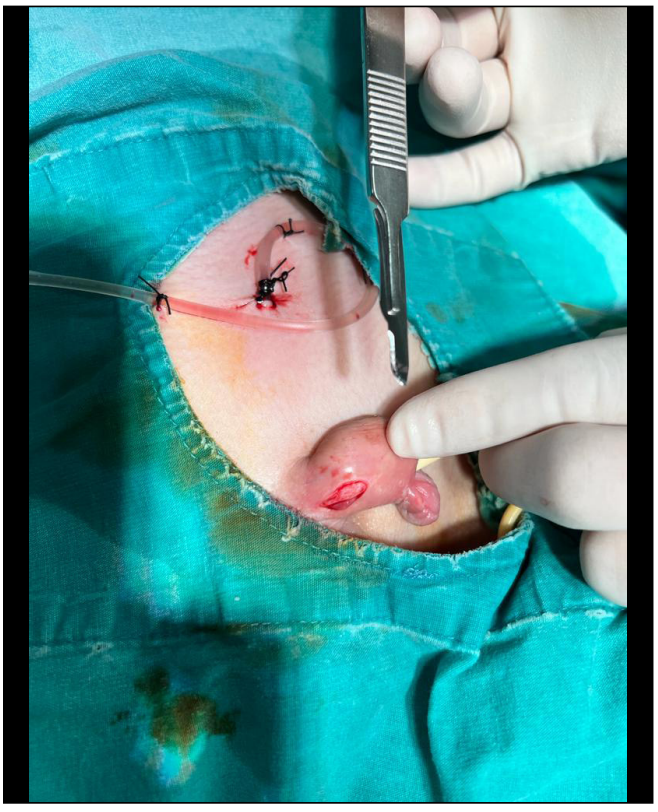

Figure 2. At the beginning of the operation, a cystofix catheter was inserted under ultrasound guidance.

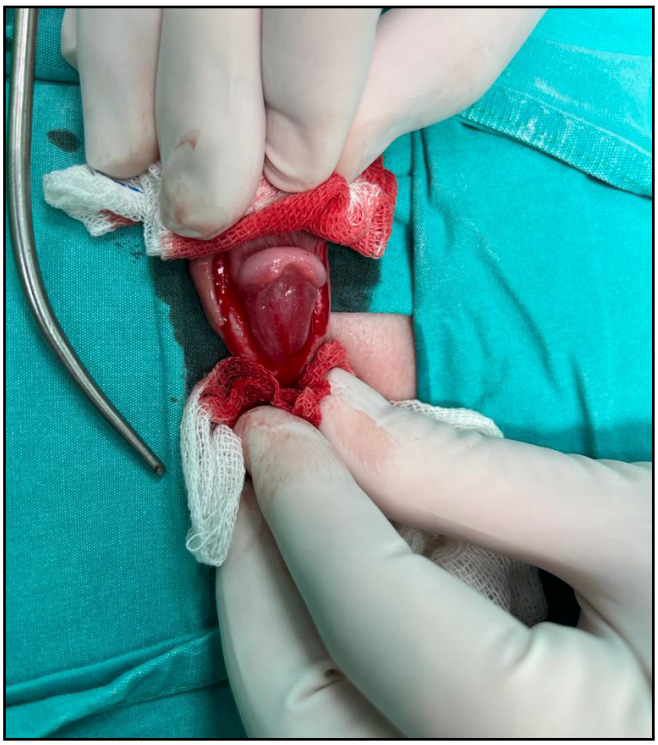

Figure 3. Corpus spongiosum was hipoplazic and the distal urethra was completely destroyed.

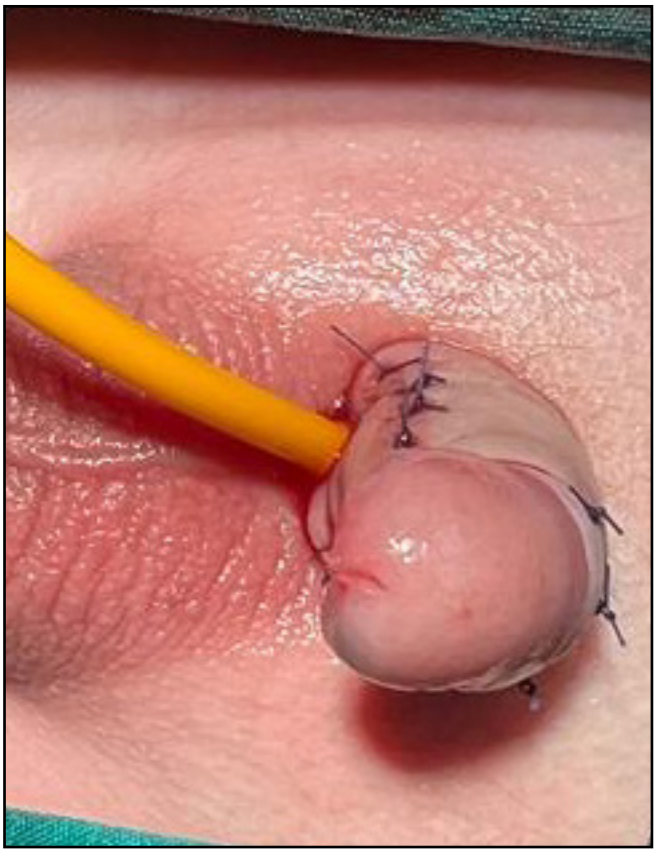

Figure 4. After the repair of fistula and new urethra.

DISCUSSION

Undoubtedly, the occurrence of the spontaneous ventral urethral fistula can be attributed to the underdevelopment of the corpus spongiosum during fetal development. Hence, to investigate the origin of this spontaneous ventral urethral fistula, we needed to delve into the mechanisms underlying the congenital hypoplasia of the corpus spongiosum. The causes of fetal anomalies can generally be categorized into genetic and environmental factors. In this particular case, it appears that environmental factors played a significant role in the pathogenesis of the patient's congenital deformity. Considering the potential risk factors during pregnancy and the presence of congenital hypoplasia of the corpus spongiosum at birth (8,9).

Children with cerebral palsy frequently experience pneumonia. Due to pneumonia or other respiratory failure, these patients require intensive care and have prolonged hospital stays. Without adequate and regular changes in posture, pressure ulcers can develop. While pressure ulcers commonly occur on the back and extremities, they can also appear in atypical areas such as the penis (10). Although we cannot definitively determine the exact cause in this patient, we suspect that it is a complication related to a pressure sore or an infection. It is likely that underlying hypoplasia of the corpus spongiosum, which is congenital in nature, contributed to its occurrence. Urethral fistulas often occur as a result of straddle injuries and blunt penile trauma. Additionally, certain penile surgeries like circumcision, as well as corporal-spongial and corporal-saphenous shunts for priapism, can lead to complications including urethral fistulas. It is worth noting that retracting a urethral catheter with a balloon can potentially result in the inadvertent cutting of the urethra resulting in multiple parts.

Spontan or non-congenital urethrocutaneous fistula is extremely rare and no cases have been reported in children This anomaly was previously reported in only two cases in adults (11). One report was about a severely infected young man due to poorly controlled diabetes and the second report concerned a healthy man with unknown etiology (12). It seems plausible to conclude that the patient was born with congenital defect of hypoplasia of corpus spongiosum. The authors should more clearly state that although the cause of this anomaly is not definitively known, there are several theories which have been proposed.

This patient likely had a partial preputium, and there was also weakness in the associated corpus spongiosum. We believe that the development of a decubitus ulcer, following frequent catheterization and immobility due to

spastic cerebral palsy, led to the subsequent development of a urethrocutaneous fistula.

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Consent for publication: Consent for publication was obtained from the family of the patient.

Availability of data and material: Not applicable.

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Authors' contributions: Not applicable.

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REVIEW

Current Approaches for the Diagnosis and Conservative Treatment of Stress Urinary Incontinence - A Guideline of Guidelines

Bedriye Muge Kaynar[1 *], **Senad Kalkan**[1]

[1] Department of Urology, Bezmialem Vakıf University, İstanbul, Türkiye

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Correspondence
Bedriye Muge Kaynar
Bezmialem Vakıf Üniversitesi, Urology Anabilim Dalı, Adnan Menderes Bulvarı, 34093 Fatih, İstanbul, Türkiye
E-mail: b.mugeeker@gmail.com

ORCID
B.M.K. 0000-0001-9905-2860
S.K. 0000-0001-6000-8504

Abstract

Urologists utilize evidence-based guidelines organized by urological organizations in the management of stress urinary incontinence (SUI). The objective of this study is to provide guidance in the clinical management of stress urinary incontinence (SUI) by reviewing key guidelines.

We conducted a medical literature analysis in the following databases: PubMed, Medline, Embase, National Guideline Clearinghouse, the National Institute for Health and Care Excellence, and Cochrane Library. We also manually searched the websites of the following international and national societies to identify relevant guidelines for inclusion in this review: the International Consultation on Incontinence, American College of Obstetrics and Gynecology, American Urogynecologic Society, American Urological Association/Society of Urodynamic, Female Pelvic Medicine and Urogenital Reconstruction, National Institute for Health and Care Excellence, European Association of Urology, and Canadian Urological Association. The recommendations in the guidelines are summarized in different areas, including the diagnostic standards of SUI, examination and evaluation methods, and conservative treatment methods. This 'guideline of guidelines' presents the similarities and differences between prominent authorities in the management of SUI.

Keywords: Guidelines; lower urinary tract symptoms; pressure-flow study; stress urinary incontinence

INTRODUCTION

Stress urinary incontinence (SUI) refers to unintentional leakage of urine that occurs during activities involving physical exertion (such as sports), as well as during episodes of coughing or sneezing (1). Urinary incontinence (UI) has a negative effect on the social activities of patients, including social interactions, physical exercise and sexuality (2). Of women with SUI, 77.5% state that they have bothersome symptoms, and 28.8% report moderate and moderate-severe symptoms (3). The prevalence of SUI in adult women is 14.9%, and it has the highest prevalence among all incontinence types (2, 4). The widespread occurrence of SUI and its potential consequences for patients are widely acknowledged. In the evaluation and treatment of patients with incontinence, an accurate diagnosis is as important as evaluating its impact on the patient's quality of life (5).

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Due to the aging population and the increasing number of elderly people, SUI increasingly leads to the use of significant healthcare resources, including conservative treatment, surgical treatment, and management of complications (6, 7). To date, many independent professional organizations and countries have established various guidelines to guide clinicians and standardize the diagnosis, treatment and follow-up processes of patients with incontinence (8). Clinical practice guidelines are an important component of medicine since they provide physicians and other healthcare professionals with evidence-based advice on the management of care for patients with diseases or other clinical conditions (9). However, guidelines issued by organizations or countries may represent patient populations affected by very different health systems and, in some cases, external factors. Thus a standardized recommendation may not be universally applicable or valid. Therefore, in this study, we aimed to establish a common view concerning the approach to patients with SUI by considering current guidelines from different venues.

Methodology

We performed a medical literature analysis of the following databases: PubMed, Medline, Embase (using the Ovid interface), National Guideline Clearinghouse, the National Institute for Health and Care Excellence (NICE), Cochrane Library search for the period from January 2010 to November 2020 to identify relevant guidelines addressing SUI in women.

Inclusion criteria and exclusion criteria

The study included consensus statements and clinical guidelines in the English language providing recommendations on the management of patients for the diagnosis and treatment of SUI. Guidelines written specifically for local regions, those without full text or with only abstracts, and old version of the updated guidelines of the same organization were excluded from the study.

Guidelines Reviewed

Two researchers reviewed the identified guidelines. Table 1 presents the guidelines by the publishing organization and year of publication and/or update. Additionally, we conducted a manual search on the websites of the following international and national societies to identify relevant guidelines for inclusion in this review: the International Consultation on Incontinence (ICI), American College of Obstetrics and Gynecology (ACOG), American Urogynecologic Society (AUGS), American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), National Institute for Health and Care Excellence (NICE), European Association of Urology (EAU), and Canadian Urological Association (CUA).

ICI produced the sixth edition of recommendation in 2017 (first published in 1998) on a number of topics initially analyzed by subcommittees, in collaboration with the International Scientific Committee. The ICI guideline recommendations are established through a review of the available published literature, along with subjective opinion of a group of recognized experts in the field (10).

ACOG regularly releases practical bulletins and evidence-based documents to summarize current information on the clinical management and techniques of gynecological problems. Similar to previous EAU guidelines, the recommendations of the ACOG guideline are based on the quality and quantity of A-C grade evidence. In collaboration with AUGS, ACOG first released practice bulletins for women with UI in 2005. This bulletin was revised in 2015 and reaffirmed in 2018 (11).

AUA primarily emphasized on surgical interventions for female SUI and conducted a meta-analysis from the literature review in 1997 which was most recently updated in collaboration with SUFU in 2017. The aim of the AUA guideline was to offer clinicians standards, recommendations, and choices to assist them in the management of SUI (12). In addition, AUA cooperated with SUFU to create a separate guideline for the diagnosis and treatment of overactive bladder (OAB), referred to as the AUA/SUFU OAB guideline (13).

The NICE guideline concerns the management of women with UI and was last updated in 2019 after several updates since it was first published in 2006. The ICI guideline similarly provides recommendations for the management of patients with pelvic organ prolapse. The NICE group uses its own synthesis of evidence and a systematic review of the available literature to generate recommendations using the OVID platform (14).

The EAU guideline was first published in 2001 and initially based on both ICI and NICE literature reviews as the core framework. In later updates, Excerpta Medica dataBASE, MedLine and Cochrane Center publications were used. The EAU guidelines are updated annually, and we took into account the most recent updates in the current study. In 2018, the EAU guideline switched to the modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system, in which the previous grade

recommendations of 'A', 'B' and 'C' were replaced by 'Strong' and 'Weak' categories (15). The CUA guideline first presented its UI recommendations in 2005 and was updated in 2012 based on the latest PUBMED, Cochrane Center publications and MedLine reviews. The grading of recommendation is similar to the updated EAU grading system, but an additional Grade D recommendation has been made available for inconclusive recommendations (16).

Table 1. Guidelines reviewed

Guideline	Year of publication/update
EAU	2019
AUA/SUFU	2017
CUA	2012
ICI	2017
ACOG	2018
NICE	2019

EAU: European Association of Urology; **AUA:** American Urological Association; **SUFU:** Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction; **CUA:** Canadian Urological Association; **ICI:** International Consultation on Incontinence; **ACOG:** American College of Obstetrics and Gynecology; **NICE**: National Institute for Health and Care Excellence.

RESULTS

Initial Evaluation

The guidelines are not necessarily comprehensive, but they offer a valuable overview of the evidence-based management of index patients.

All guidelines recommend conducting an office evaluation as the initial and crucial step in the evaluation of women with UI. The initial workup should include a detailed history, physical examination, assessment of the severity of symptoms, degree of bother, presence (or absence) of urgency, other lower urinary tract symptoms and treatment expectations(17). In addition, urinary tract infection (UTI) and postvoid residual urinary volume (PVR) should be assessed. A simple cough stress test should be done and, if positive, provides objective confirmation of the diagnosis of SUI. Furthermore, all guidelines emphasize the significance of obtaining a thorough and detailed medical and surgical history and considering the possibility of other disorders that can cause and/or complicate SUI.

The AUGS, EAU, and NICE guidelines clearly indicate the importance of determining the effects of hematuria, history of recurrent UTI, pelvic surgery or radiotherapy, continuous discharge of urine indicating the presence of fistulas, fecal incontinence (NICE only), difficulty voiding or suspected neurological disease, pad use, and SUI-related symptoms on the activities of the daily lives of women (5, 14, 17).

In addition to the urological history, a detailed medical and neurological (e.g., diabetes, multiple sclerosis, lumbar disc disease, and stroke) history is recommended. While the ICI, AUGS, ACOG and AUA/SUFU guidelines recommend a neurological assessment for all patients presenting with UI, the EAU and NICE guidelines do not recommend it as standard practice (5, 10, 11, 14, 17, 18). A complete list of drugs, including prescription and nonprescription medications used by the patients should be compiled. Clinicians should be aware that there are drugs that can affect the bladder and urethra or cause voiding difficulties (5, 11, 19).

Although there is a lack of high-quality evidence-based information showing that physical examination improves the management of patients, all guidelines concur that conducting this examination is a crucial component of the evaluation and diagnosis of SUI. All guidelines suggest that a diagnosis of SUI can be made by physical examination provided that there is an observable manifestation of urine leakage accompanied by increased abdominal pressure (positive cough stress test). The AUA guideline recommends that stress testing should be conducted as a component of the evaluation of patients presenting with UI (12). The AUA/SUFU SUI guideline provides a 'clinical principle' suggesting that SUI should be evaluated in the supine and standing positions and with a full bladder (minimum bladder volume 300 mL) prior to any surgical intervention (12). The ACOG (Level C) and AUA (Expert Opinion) guidelines state that the use of traditional methods, such as the Q-tip or cotton swab test in the evaluation of urethral mobility during the physical examination of SUI can be effective in the treatment decision (11, 12). However, the NICE guideline does not recommend using the Q-tip test (or the Bonney, Marshall and Fluid-Bridge tests) in the evaluation of SUI (Evidence Level 4) (14). According to the AUGS guideline, if the standing cough stress test is negative and the patient reports symptoms of SUI, multichannel urodynamic testing (UDS) should be performed (5).

All guidelines agree that in addition to assessing the presence of incontinence on physical examination, an evaluation of the general status (mental status, obesity, mobility) of the patient, abdominal examination, and assessment of pelvic floor muscles and pelvic organ prolapse (POP) are also necessary. In addition, the NICE guideline

endorses pelvic floor assessment for patients with SUI to determine whether pelvic floor muscle training (PFMT) can be recommended (Expert Opinion) (14). The CUA (Grade C), EAU and ICI guidelines recommend pelvic floor muscle evaluation (10, 16, 17). ACOG, AUGS and EAU guidelines suggest evaluating the presence of POP on physical examination to differentiate complicated SUI. The presence of POP may reduce or cover up the severity of SUI symptoms; therefore, they recommend that all pelvic compartments (anterior, posterior and apical) should be examined in detail. Examination of the pelvic compartments may also reveal the presence of a fistula or an ectopic ureter opening into the vagina (5, 11, 17). In addition, rectal examination is valuable in assessing anorectal pathologies and fecal impaction, which can be related to UI in older women (5). Table 2 presents the detailed recommendations of all guidelines during the initial evaluation of patients.

Table 2. Initial evaluation

Recommendation	EAU	AUA/SUFU	CUA	ICI	ACOG	NICE
Detailed history to characterize UI	+	+	+	+	+	+
Detailed partum history	+				+	
Pad test	+	+		+		+
Exclusion of other diseases (e.g., ectopic ureter and malignancy)	+				+	
Detailed physical examination	+	+	+	+	+	+
Neurological examination		+		+	+	
Stress test for the objective evaluation of SUI		+			+	
Bladder/voiding diary	+			+		+
Questionnaires	+		+	+		

EAU: European Association of Urology; **AUA:** American Urological Association; **SUFU:** Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction; **CUA:** Canadian Urological Association; **ICI:** International Consultation on Incontinence; **ACOG:** American College of Obstetrics and Gynecology; **NICE:** National Institute for Health and Care Excellence; **UI:** urinary incontinence; **SUI:** stress urinary incontinence; **ICIQ:** ICI Questionnaire

Questions and Questionnaires

The varying scope and purpose of each guideline leads to differences concerning the use and recommendations regarding questionnaires. The EAU guideline includes the use of appropriate validated questionnaires in the 'Strong' category of recommendations in the standard evaluation of patients with UI. However, EAU acknowledges that there is lack of evidence supporting the use of questionnaires in the follow-up of patient response to treatment, since these questionnaires are validated in patients without UI (17). The CUA and ICI guidelines recommend the use of the ICI Questionnaire (ICIQ) in conjunction with additional questionnaires as a first choice 'Grade A' recommendation in the assessment of the specific clinical condition in patients with UI. In the CUA guideline, questionnaires received a 'Grade B' recommendation (10, 16). Similarly, according to AUA, an evaluation of patient expectations is recommended as a 'Panel Consensus (12). The NICE guideline endorses the use of questionnaires to assess the impact of UI-specific symptoms on quality of life and post treatment status. In addition, similar to other guidelines, the NICE guideline also recommends the use of ICIQ-like questionnaires (14). Although the ACOG guideline does not contain specific statements concerning the use of questionnaires, it advocates the use of validated questionnaires to assess the discomfort and severity of SUI symptoms (11). Despite the recommendations of these guidelines, two systematic reviews evaluating eight different questionnaires in the diagnosis of UI reported a low level of questionnaire use in the diagnosis of SUI (20, 21).

In addition to the use of questionnaires, some guidelines

suggest the use of a voiding to document micturition frequency, amount voided, number of pads per day, and UI episodes in the initial evaluation of UI. The ICI and NICE guidelines recommend a 3-day diary while the AUGS and ACOG guidelines recommend a four- to five-day diary (5, 10, 11, 14). To reveal the patient's day time and night time status and evaluate the response to treatment for similar purposes, the EAU guideline recommends the use of a three- to seven-day voiding diary (Strong) (17). Although the guidelines recommend various timeframes for the voiding diary, the NICE guideline states that the optimal duration is unclear and that the use of a minimum three-day voiding diary may prevent variations in the daily activities of patients. However, the NICE guideline does not routinely recommend the use of voiding diary in the evaluation of patients with UI (14). The AUA/SUFU guideline is less insistent on the use of voiding diary than other guidelines; it does not provide a general recommendation concerning the use of a voiding diary in all patients, but it states that a three- to seven-day diary can be used to determine baseline symptoms and response to treatment (12).

Initial Diagnostic Tests

All guidelines agree on the necessity of a urine analysis (UA) to determine the presence of UTI in the diagnosis or prior to the treatment decision. Similar to other guidelines, the EAU guideline states that every patient should undergo UA in the presence of UTI because UI may worsen, or UI may be a sign of UTI. However, it has been determined that nursing home patients with asymptomatic bacteriuria do not benefit from antibiotic therapy in terms of UI (Evidence Level 2) (17). For dipstick UA, a clean midstream or catheterized urine sample should be taken, and if UA is negative, uncomplicated SUI should be considered (19). According to the NICE guideline, every patient with UI should undergo UA to screen for erythrocytes, glucose, protein, leukocytes, and nitrites in the urine. In order to prevent unnecessary testing and reduce the burden on the healthcare system, a routine urine culture analysis is not indicated in patients with SUI who have negative UA (14).

In addition to the guidelines' consensus on UA being the first diagnostic test, it is also recommended that if the patient has a complaint of incomplete emptying or a distended bladder, the PVR should be examined. However, this value should be interpreted with caution since there is no consensus on abnormal PVR (22). Based on the Value of Urodynamic Evaluation (ValUE) trial, ACOG accepts PVR < 150 mL as normal and states that further testing before SUI surgery is unnecessary for patients with this value (11, 23). However, according to the EAU and NICE guidelines, patients with recurrent UTI receiving treatments that may cause or worsen voiding dysfunction, including SUI surgery should be monitored for PVR using ultrasound or catheterization (14, 17). Furthermore, the ACOG (Level A), AUA/SUFU SUI (Clinical Principle) and AUGS guidelines state that PVR assessment should be performed in cases where surgery is considered to evaluate overflow UI (3, 11, 12).

The guidelines' recommendations concerning the use of the pad test in UI assessment vary. The EAU guideline states that the pad test provides Level 2 evidence in the diagnosis of UI (16). The use of the pad test for the quantification of UI is recommended by the EAU (Weak) and AUA (Recommendation) guidelines (12, 17). The 24-hour pad test to be performed at home is sufficient in terms of accuracy (17). On the other hand, the ICI guideline states that the use of pad test is discretionary during the assessment of the UI, and 24-hour testing should be performed if it is to be undertaken (10). According to the NICE guideline, the evidence supporting the use of the pad test is inconclusive and of low quality, with conflicting findings. This guideline does not recommend the routine use of the pad test in the evaluation of UI in women but considers it to be useful in the evaluation of treatment effect (Evidence Level 4) (14). In addition, the EAU and NICE guidelines indicate that the pad test should be repeated to evaluate treatment, but there is no evidence that the use of this affects results (14, 17).

When evaluating female SUI through physical examination, the majority of guidelines indicate that assessment of urethral mobility can guide treatment decisions. The AUA (Expert Opinion) and ACOG (Level C) guidelines both recommend evaluating urethral mobility during the physical examination of women with SUI (11, 12). The Q-tip, Marshall, Bonney and Fluid-Bridge tests are conventional methods used to evaluate urethral mobility (24). However, due to the lack of evidence supporting their usefulness in clinical evaluation, NICE does not recommend their use (14).

In certain cases such as an indefinite diagnosis, hematuria, OAB symptoms, neurogenic bladder, history of prior pelvic surgery, high-grade POP, and a negative stress test in the presence of SUI symptoms, initial diagnostic tests may be insufficient and there may be a need to use advanced tests; e.g., cystoscopy, UDS, and imaging studies (12). In certain clinical situations, urinary incontinence may be caused by a fistula, and therefore testing with dyes to stain urine may be helpful. The CUA guideline recommends cystoscopy if there is a fistula suspicion (16). In contrast, the AUA guideline states

that cystoscopy plays no role in the evaluation of patients with normal urinalysis and those with no additional lower urinary tract abnormalities, who are planned to undergo surgical treatment for SUI, but intraoperative cystoscopy can be performed during certain surgical procedures (12). In the AUGS and NICE guidelines do not recommend routine endoscopic evaluation of the urethra and bladder in the assessment of UI (3, 14). In addition, according to NICE, ultrasound (only PVR assessment) and additional imaging methods should not be used during the routine evaluation of women with UI (14).

Urodynamic Studies

Urodynamic testing is a general term describing measurements that evaluate the performance and abnormalities of the lower urinary tract. UDS allows making clinical observations, determining the underlying causes of symptoms, and measuring related pathophysiological processes while directly evaluating lower urinary system function through the measurement of relevant physiological parameters (25).

There is no consensus about the indications for UDS amongst the guidelines, but all agree that UDS is not required uncomplicated SUI in the index patient after exclusion of urge incontinence) and that it will not change the outcomes of conservative or drug treatment (26). In addition, there is no association between the outcomes of urethral function tests and success or failure after SUI surgery (17). However, women with complicated SUI might find it advantageous to undergo multichannel urodynamic testing and other diagnostic tests before considering of treatment, particularly surgery (3, 18). These recommendations are based on the ValUE trial, in which 630 patients with uncomplicated SUI were included and the addition of UDS during the examination was reported not to affect surgical results (23). The EAU guideline states that, when indicated, UDS should be performed in accordance with the 'Good Urodynamic Practice' standards defined by the International Continence Society (17). While the AUA/SUFU guideline recommends considering the option of performing UDS in patients with UI who are planned to undergo invasive treatment, the ICI and EAU (Weak) guidelines indicate UDS should be considered if its results are expected to change treatment advice and management (10, 12, 17). The AUA/SUFU SUI guideline states that UDS can be disregarded in index patients with clear signs of SUI who accept treatment (Conditional Recommendation, Evidence Level B) and undertaken in non-index patients (Expert Opinion) (12). The AUA/SUFU guideline includes a total of 19 statements on four disease states related to UDS: SUI/POP, OAB, urge UI (UUI) + mixed UI (MUI), and neurogenic bladder + lower urinary tract symptoms. Almost all of the statements on UI in the AUA/SUFU guideline are based on Grade C evidence or expert opinion. However, the AUA/SUFU UDS recommendations have remained unchanged since their publication in 2012 (12). The ACOG and NICE guidelines do not recommend UDS in patients with uncomplicated SUI detected during clinical examination. However, they suggest that UDS should be performed in patients scheduled for surgery, who have predominant UUI or MUI, anterior or apical POP, voiding dysfunction, and a history of previous surgery for SUI (11, 14). In addition, according to the NICE guideline, preoperative multichannel filling and voiding cystometry should not be performed in cases where SUI or stress-predominant MUI can be identified based on examination findings and clinical history. UDS is recommended in such cases if there is urge-predominant MUI or the type of UI cannot be determined, a history suggesting voiding dysfunction, a history of previous SUI surgery, or anterior or apical prolapse (14).

Treatments

Conservative Management

In patients seeking treatment for SUI, treatment decisions should take into account the degree of discomfort their symptoms cause. Since SUI can significantly impact quality of life, the treatment decision should be made considering its capacity to relieve discomfort caused by the symptoms. Treatment options for SUI range from conservative management to surgery. When a patient experiences minimal subjective discomfort resulting from SUI, it is recommended to conduct a thorough evaluation to explore non-surgical conservative treatment options (Expert Opinion) (12). All guidelines recommend that conservative treatment be tried before invasive treatment as it has the least risk of harm. Conservative treatment options include behavioral modification, PFMT (with or without biofeedback), support pessaries for continence, scheduled voiding, urethral inserts, and pharmacotherapy. There is substantial evidence supporting the positive effects of weight loss in improving UI among obese patients, and the EAU, ICI, NICE and AUGS guidelines all present weight loss as a recommendation in overweight patients with UI (3, 10, 14, 17). Weight loss and its maintenance is included as a 'Grade A' recommendation in the CUA guideline and 'Strong' recommendation in the EAU guideline (16, 17). According to the NICE guideline, patients with UI whose body mass index is >30 kg/m^2 should

lose weight (14).

The EAU makes a 'Strong' recommendation of bladder training as the primary therapy in patients with SUI and endorses scheduled voiding for adults with UI (17). Bladder training (regulation of fluid intake, caffeine restriction, keeping healthy bowel habits, and scheduled voiding) is included as a first-line treatment option for patients with UI in the CUA guideline, as well as the EAU guidelines (16). The NICE guideline recommends six weeks of bladder training in the treatment of UI (14). Reduced caffeine intake, which is a part of bladder training and behavioral modification, is recommended by all guidelines in the management of UI. The EAU guideline states that caffeine restriction does not reduce UI but decreases urgency and frequency in patients (17). Suggested modifications, such as scheduled voiding and regulation of excessive fluid intake, are included as 'Grade B' recommendations in the CUA guideline in order to reduce UI symptoms, while they are well-validated recommendations in the guidelines of other groups, such as NICE (14, 16). However, the EAU guideline states that there is conflicting information concerning the efficacy of fluid modification in improving UI symptoms (17). Smoking cessation receives a 'Grade C' recommendation from CUA, while EAU emphasizes the lack of evidence on UI symptom improvement with smoking cessation (16, 17). There is no consistent evidence indicating that the treatment of constipation alone, which is considered a conservative approach, improves UI (Evidence Level 4), but the EAU guideline has the 'Strong' recommendation that patients with the coexistence of constipation and UI should be informed about bowel management (17).

PFMT stabilizes the urethra and increases urethral closure pressure. All the guidelines recommend PFMT for the treatment of SUI and agree that a waiting time of three months should elapse to see improvement in patients when applying PFMT. Recent literature also supports the guidelines indicating that PFMT improves UI and quality of life in women with SUI (27). The EAU guideline offers PFMT as the first-line therapy for elderly and postnatal patients with UI (17). The NICE guideline recommends that PFMT is as effective as surgery in half of patients with SUI and should be undertaken as the first-line therapy in this patient group. It also suggests that patients who benefit from at least three months of PFMT treatment should continue the program. However, it does not recommend routinely combining PFMT with electrical stimulation (14). The AUA guideline states, as 'Clinical Principle', that women with SUI or stress predominant MUI should be informed about alternative non-surgical options or vaginal devices (continence pessary, vaginal inserts, and PFMT) (12). According to the EAU guideline, the improvement of SUI with the use of vaginal devices in selected patients is supported by Level 2a evidence, and the use of pads and/or containment devices is included as a 'Strong' recommendation in the treatment of patients with UI (17).

Although the guidelines offer a variety of options for the treatment of SUI, they do not take into account every patient scenario or provide clear timelines for when conservative management should be discontinued to plan definitive treatment (Table 3).

Table 3. Conservative management

Recommendation	EAU	AUA/SUFU	CUA	ICI	ACOG	NICE
Scheduled voiding	+	+	+	+	+	
Restriction of fluid			+		+	+
Smoking cessation	+		+			
Weight loss	+		+	+	+	+
Treatment of constipation	+				+	
PFMT	+	+	+	+	+	+
Counselling women on the availability of non-surgical options		+			+	
Drug Therapy	+			+		+

EAU: European Association of Urology; **AUA:** American Urological Association; **SUFU:** Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction; **CUA:** Canadian Urological Association; **ICI**: International Consultation on Incontinence; **ACOG:** American College of Obstetrics and Gynecology; **NICE:** National Institute for Health and Care Excellence; **PFMT:** pelvic floor muscle training

Drug Therapy

Duloxetine, a serotonin/norepinephrine reuptake inhibitor, has obtained approval for the treatment of SUI in Europe but not by the United States Food and Drug Administration. Duloxetine inhibits presynaptic re-uptake in the sacral spinal cord of the neurotransmitters serotonin and norepinephrine, which are considered to increase the stimulation of the pudendal nerve, and thus the urethral sphincter tone (28). Although duloxetine is superior to PFMT in the treatment of SUI, the usage of this medications often leads to a high discontinuation rate due to notable gastrointestinal and central nervous system side effects. (28). In the EAU guideline, the role of duloxetine 40 mg twice daily in the treatment of SUI is based on Level 1a evidence. It is recommended (Strong) that duloxetine treatment should be considered in selected patients with SUI symptoms for whom surgery is not considered and that withdrawal should be achieved with dose titration in cases where necessary due to its high side-effect profile (17). The ICI guideline indicates duloxetine therapy for the temporary treatment of UI (10). Similar to other guidelines, the NICE guideline also recommends duloxetine in patients with predominant SUI who prefer pharmacological management and do not agree to surgery (14).

CONCLUSION

The issue of SUI must be addressed in a multifaceted manner and requires a multifaceted perspective on diagnosis, treatment, diverse patient populations, and disease states. This paper summarized the current approaches in the diagnosis and treatment of patients with SUI in light of the current guidelines. This study did not provide a comprehensive analysis of every guideline, but it highlighted notable similarities and differences among them.

Most of the guidelines discussed in this review have similar recommendations for the initial evaluation of patients and the use of conservative treatments. During the initial assessment of these patients, a detailed history should be taken and the degree of SUI and its impact on quality of life should be questioned. Invasive tests and imaging methods should not be preferred during the initial evaluation in patients with uncomplicated SUI, and UDS should be performed only in cases in which the results might alter the diagnosis and treatment decisions. Conservative treatment options include behavioral modifications, PFMT, support pessaries for continence, scheduled voiding, urethral inserts, and pharmacotherapy. Among these options, PFMT and pharmacotherapy stand out in the treatment of SUI and have higher recommendation ratings. Although the reviewed guidelines have similar recommendations concerning the management of SUI, the conclusions of organizations establishing these guidelines can vary due to the differences in available facilities and regulatory agencies across countries, dissimilar expectations of patient populations, limitation of national expenditures and costs, and evidence on which they based their recommendation levels.

Key Points:

1- The reviewed guidelines are not comprehensive in answering all questions but can provide practical evidence-based information on 'index patients'.

2- The initial evaluation of SUI should include taking a detailed history and performing a physical examination.

3- UDS should be used in the presence of recurrent SUI after complicated SUI or failure of invasive treatments.

4- The reviewed guidelines recommend a gradual approach to the treatment of SUI, starting with conservative treatment and progressing to more invasive procedures as needed.

5- There was little agreement about the initial evaluation except that all guideline panels recommended performing urinalysis, history and physical exam – no other diagnostic modalities were recommended by more than half of the panels.

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Author Contribution

B M Kaynar : Data collection or management, Manuscript writing/editing.

S Kalkan : Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing.

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REVIEW

Urogenital Complications that Decrease Quality of Life in Transgender Surgery

Zeki Bayraktar
Department of Urology, Sancaktepe Sehit Prof Dr. Ilhan Varank Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye

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Correspondence
Zeki Bayraktar, MD, Prof.Dr.
Çamlık Mah. Piri Reis St.
No:4, Papatya Sitesi 48
34890, Pendik-Istanbul, Türkiye
E-mail: dr.zekibay@gmail.com

ORCID
Z.B. 0000-0002-2493-2457

Abstract
Gender reassignment surgeries are performed not to treat a congenital or anatomical anomaly, but to treat the psychological problems of transsexuals. In fact, there is no definitive evidence showing that psychological problems in transsexuals are cured by hormonal and/or surgical treatments for gender reassignment. On the contrary, there is evidence that these psychological problems persist after medical and surgical interventions, and even increase in some transsexuals, and a new form of body dysphoria occurs in a quarter of cases. Psychological problems in transgender people are not cured by surgery, and additional surgery-related complications develop in three-quarters of the cases. The vast majority of these are urogenital complications, and more than half require reoperations. However, in a significant proportion of cases, the outcome is unsuccessful and these urogenital complications significantly reduce the quality of life of transsexuals. Data also show that the life expectancy of transsexuals who undergo surgery is shortened by an average of 25-28 years due to psychological problems, suicides, surgical complications, reoperations and diseases related to hormone use. These results have led to an increase in the number of detransitioners who regret their medical and surgical transition and want to return in recent years, and have increased ethical debates on this issue. In this article, urogenital complications that develop after transgender surgery, which reduce the quality of life and possibly play a role in regrets are summarized.

Keywords: Gender Dysphoria; Transgender surgery; Transsexual; Complication; Quality of life; Urogenital

INTRODUCTION

Gender-reassignment surgery(GRS), which can also be referred to as transgender surgery, is performed not to treat a congenital or anatomical anomaly, but to treat the psychological problems of transsexuals (1,2). In fact, there is no definitive evidence showing that psychological problems in transsexuals with gender dysphoria (GD) are improved by gender-affirming hormonal and/or surgical treatment (2-5). On the contrary, there are studies showing that these psychological problems continue after medical and surgical

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interventions (2), and even increase in some transsexuals after surgery (6), and that a new form of body dysphoria occurs in a quarter of the cases; these people are extremely disturbed with their new physical appearance after medical and/or surgical transition (7).

Transsexuals not only have GD, but are often accompanied by other psychiatric comorbidities (8). Although there is a partial decrease in GD, almost all of these psychopathologies are also observed after GRS. Psychological problems such as depression, post-traumatic stress disorder, personality disorders, problems with work and social life, criminal or violent events and related convictions, partner problems, feeling of loneliness and suicide are common in transgender people after GRS; In other words, psychological problems in transsexuals continue after surgery-throughout life (2). Even regret and detransition are seen; In recent years, there have been many detrans/detransitioners who regretted medical and surgical transition and shared their experiences with regret, there is a serious literature that is beginning to accumulate on the subject of regret and detransition (2,9-19). This situation increases debates and professional disagreements about what is the most appropriate medical approach, especially for young people with GD (20).

GRS is also debated due to surgical complications (21–23) and bioethical dilemmas; the most common bioethical issues in transgender medicine are what the optimal treatment is (there is no consensus on this issue), sterilization as a requirement of legal recognition (permanent infertility), the role of fertility and parenthood, and regrets and detransition after gender reassignment (11,24-26).

Another important issue regarding gender-affirming surgery is urogenital complications, which add to mental problems after surgery and reduce the quality of life. In a study conducted by Kuhn et al., the quality of life and patient satisfaction of a total of 55 transgender individuals who underwent transsexual surgery (52 from male to female, 3 from female to male) were found to be significantly lower 15 years after the transgender surgery (21,22). Urinary and sexual problems were shown as the most common reasons for dissatisfaction. Fifteen years after the operation, the general health status of these individuals was worse and their quality of life was lower due to role limitations, physical limitations and personal limitations (21).

Gender-affirming surgeries include facial surgery, chest surgery and genital surgery procedures (27). Each of these surgeries has its own complications, but since the subject of our article is limited to urogenital complications, we will mainly focus on genital surgery and will only describe the urogenital complications associated with these surgical procedures. For this purpose, PubMed was screened with the terms "transgender surgery", "gender affirming surgery", "vaginoplasty", "phalloplasty", "metoidioplasty", and "urological complications". A total of 194 articles were listed; 61 articles with the terms "gender affirming surgery," "urological complications," and "vaginoplasty," 92 articles when the term "phalloplasty" was added instead of vaginoplasty, and 41 articles when the term "metoidioplasty" was added. Duplicate articles were removed. And ultimately, 26 articles that were suitable for our review - focusing on and/or transplanting urogenital complications - were examined.

In this article, early and late urogenital complications that develop after gender-affirming (or transgender) genital surgery and reduce the quality of life are summarized.

Male-to-Female (MtF) Surgical Procedures and Complications:

Approximately three-quarters of transsexuals who request gender reassignment are in this group (73.4%) (28). Male-to-female gender-affirming surgeries include the following surgical procedures; 1) Facial surgery: brow reduction, hairline advancement, laser hair removal, feminizing rhinoplasty, malar augmentation, mandibular recontouring, chondrolaryngoplasty; 2) Chest surgery: augmentation mammoplasty and fat grafting; 3) Genital surgery: vaginoplasty (penile-inversion vaginoplasty or intestinal vaginoplasty) and vulvaplasty (27). Each of these surgeries has its own complications, but we will mainly focus on MtF genital surgery (penile-inversion vaginoplasty and intestinal vaginoplasty) and will only describe the urogenital complications associated with these surgical procedures.

The most commonly performed technique for primary male-to-female transgender vaginoplasty is penile inversion vaginoplasty (29,31,33). Penile-inversion vaginoplasty is the gold standard of feminizing genital surgery; it uses penile skin to form the neovagina, the glans for a neo-clitoris, and the scrotum and skin for labia majora and minora (27). However, in cases where the penis/phallus is not sufficiently developed, for example in cases where puberty blockade is applied [pubertal supression with hormon use also blocks penis-phallus development (30)], vaginoplasty can be performed using ileum and sigmoid colon segments as an alternative method. However, both of these methods have complications such as bleeding, hematoma, infection, delayed wound healing, neovaginal stenosis, flap necrosis, urethral stenosis, urethral fistula, incontinence, rectal injury, rectal fistula, internal organ injury and pelvic floor disorders. Some of these

are serious complications that require constant care and/or intervention (29,31).

Urogenital problems detected by *Kuhn et al.* 16 years after vaginoplasty are as follows; urination dysfunction 47%, urge 25%, stress incontinence 23%, never being sexually satisfied 23%, urge incontinence 17%, stool urgency/incontinence 9.4%, inability to empty the bowels/incomplete evacuation 7.6%, neovaginal prolapsus 7.5% and the need for reoperation for prolapsus 3.4% (23). *Kuhn et al.* in another study, they reported the urological problems experienced after transgender surgery as follows; change in urine flow direction 50%, feeling of insufficient emptying 22%, recurrent urinary tract infection 22%, stress urinary incontinence 16% and overactive bladder 6%. A diverted stream, overactive bladder and stress urinary incontinence were common problem (22).

Similarly, complications after transgender surgery reported by Papadopoulos et al. were as follows; delayed wound healing 25%, decentralized urine flow 22.5%, genital pain 15%, bladder infection 15%, bleeding 12.5%, decreased vaginal sensitivity 12.5%, impaired bladder function 10%, decreased chitoral sensitivity 10%, wound infection/abscess% 7.5, colon damage 7.5%, breast hardness 5.3%, vaginal stenosis 2.5%, short vagina 2.5%, genital odor 2.5%, clitoral asymmetry 2.5%, clitoral necrosis 2.5% and defecation problem 2.5%; Emergency surgery or re-operation was performed in one quarter of the cases in this study [in cases where wound infection/abscess colon damage, breast hardness, vaginal stenosis, short vagina and clitoris necrosis developed] (32).

According to a systematic review conducted by *Horbach et al.* (26 studies with a total of 1,563 cases were examined in this meta-analysis), the urogenital complications following transsexual surgery were as follows (penile skin inversion vaginoplasty was performed in 1,461 of the cases, ileal or colonic vaginoplasty was performed in 102); Neovaginal stricture or stenosis was the most commonly reported adverse outcome with an incidence of 12.0% (4.2-15.0%). Other complications included partial necrosis of the vagina (2.7–4.2%), clitoral necrosis (1–3%), genital pain (3–9%), rectal injury (2–4.2%), rectovaginal fistula (0.8–17.0%), neovaginal prolapse (1–2%), urethral meatal stenosis (1–6%), change in voiding function (32%), urinary incontinence (19%), wound dehiscence (12–33%), local abscesses (5%), and hematoma (3%) (33).

The complication rate is also high in ileal or colonic vaginoplasty, which is performed as an alternative method. *Morrison et al.* reported the overall complication rate after vaginoplasty performed with the ileal or colonic segment as 58% (34). The most common complications in this study were mucorea 29%, neovaginal strictures/stenosis 20%, protrusion 6.1%, rectovaginal fistula 2.4%, urethrovaginal fistula 1.2% and intestinal obstruction 1.2%. The long-term complications identified in this study were as follows; neovaginal stenosis 22.5%, protrusion 15.6%, intestinal obstruction 3.6%, colitis 2.5% and prolapse 2.4% (34).

Complications such as rectal-urethral fistulas, urinary incontinence and vaginal stenosis that develop after vaginoplasty surgery are complications that limit the patient's daily life and cause serious problems. These patients have to perform vaginal dilation with dilators of different sizes several times every day after surgery (at home and at work) to prevent vaginal stenosis. This is a painful procedure, especially at first. However, neovaginal stenosis is inevitable in some cases and cannot be treated with dilatation. In cases of stenosis where dilator treatment fails, it may be necessary to recreate the neovaginal space with revision surgery and re-cover the space with a new graft (29).

Female-to-Male (FtM) Surgical Procedures and Complications:

Approximately one quarter of transsexuals who request gender reassignment are in this group (28). Female-to-memale gender-affirming surgeries include the following surgical procedures; 1)Facial surgery: Brow augmentation, hair transplant, masculinizing rhinoplasty, malar modification, maxillary augmentation, mandibular recontouring, cenioplasty, thyroid cartilage augmentation; 2)Chest surgery: Periareolar mastectomy, double-incision mastectomy, free nipple grafting; 3) Genital surgery; phalloplasty and metoidioplasty (27). Each of these surgical procedures has its own complications, but due to the subject of the article, but due to the subject of the article, only urogenital complications due to phalloplasty and metoidioplasty will be summarized here.

The most common early complications in FtM gender-affirming genital surgical procedures which includes phalloplasty (creating a penis-phallus with tissues taken from the hand or arm) and metoidioplasty (creating a penis-phallus using the clitoris and vaginal walls), are wound dehiscence, infections, total and partial flap necrosis and urethral loss. Late complications of FtM genital surgical procedures include urethral stenosis, persistent vaginal cavity, penile prosthesis problems and urethrocutaneous fistulas (35-38). While *Morrison et al.* reported total flap loss after phalloplasty as 1.7% and partial flap loss as 5.43% (39), *Monstery et al.* reported partial flap loss as 7.3% (40).

The most common urological complications after

phalloplasty are urethral strictures, fistulas and associated urination problems. In a meta-analysis conducted by Wang et al., a total of 1,731 patients who underwent phalloplasty (39 articles) were examined and the overall complication rate was reported as 76.5% (in 75.1% of these cases, the radial forearm free flap was used); the urethral fistula rate was 34.1%, and the urethral stricture rate was 25.4% (41). These data show that more than three out of every four patients (>75%) who underwent phalloplasty developed complications -mostly urological.

In a meta-analysis conducted by *Hu et al.* (21 studies, 1566 cases), the rate of urethral fistula or stenosis detected after phalloplasty was found to be 49% [in one in two patients] and penile prosthesis complications were found to be 28% (42).

In a recent study conducted by *Veerman et al.* and published in the American Journal of Urology (J Urol.), the complications in trans men who underwent phalloplasty or metoidioplasty techniques and were followed for an average of 23 months were as follows; Urethral stricture was 63% in both techniques, urethral fistula was reported to be 27% in phalloplasty and 50% in metoidioplasty, and the need for reoperation due to fistula or stenosis was reported to be 73%. Despite this, 30% of cases were unable to urinate from the tip of the phallus. The authors commented in the conclusion that *"Genital gender affirming surgery with urethral lengthening is a complex procedure with a high complication rate. After treating complications no clinically relevant differences in urological functioning were recorded."* (43).

In another systematic review, *Nikolavsky et al.* reported that the rate of urethral fistula as 22-75% and urethral stenosis as 25-58% after phalloplasty and metoidioplasty (37).

Urethrocutaneous fistula is the most common urethral complication after phalloplasty and its incidence varies between 15-70%. This is often accompanied by urethral stricture. There is no standard treatment technique defined for the treatment of urethral fistulas or strictures (44).

In a recent meta-analysis, *Robinson et al.* examined a large and heterogeneous group of transgender men (1,212 patients, 129 genital reconstructions) and identified a total of 281 complications. These results are sourced from a large, heterogeneous group of transgender patients spanning 3 continents and dozens of surgical centers. More than half of the cases (50.5%) required reoperation. The rate of urethrocutaneous fistula was reported as 40%, urethral stenosis was reported as 32%, and worsening mental health was reported as 19%. According to the authors, these results support anecdotal reports that complication rates following gender affirming genital reconstruction are higher than are commonly reported in the surgical literature. In the conclusion section of the meta-analysis, the authors say: *"Complication rates, including urethral compromise and worsened mental health, remain high for gender affirming penile reconstruction."*(45).

After phalloplasty, urethral stricture develops in more than half of the cases, and in 94-96% of them, the need for reoperation (urethroplasty) occurs, but despite this, the result is unsuccessful in half of the cases. Reoperations or rescue urethral externalization surgeries are often needed. However, despite all efforts, patients may have to live with perineal urethrostomy for life (35).

Penile implants may also accompany phalloplasties and their complications include infection, erosion, migration, and mechanical failure (46). In a meta-analysis conducted by et al., penile prosthesis complications in phalloplasty were reported as 28% (42).

The data show that complications develop after phalloplasty in at least three quarters of cases and that reoperation is required in approximately half of them, but the outcome is unsuccessful in a significant proportion of cases. Transgender individuals who underwent phalloplasty, despite reoperations, they experience difficulty urinating, incontinence and perineal-genital pain, cannot urinate from the tip of the phallus, and may even have to live with a perineal urethrostomy for life. These urolgical complications significantly reduce the quality of life of transsexuals (21).

Complications that develop after metoidioplasty are similar to phalloplasty. *Waterschoot et al.* reported urethral fistula as 46%, permanent fistula as 36.5%, and urethral stricture as 19% after metoidioplasty (47). They also reported a 4.1% rate of high-grade complications in the first 30 days after surgery.

Are Urogenital Complications of Transgender Surgery Higher Than Reported in the Literature?

The data we have conveyed show that most of the transsexuals who have undergone gender-affirming surgery have to struggle with complaints such as inability to urinate or urinary incontinence throughout their lives. However, there are two more important issues at this point;

First, we know the early and mid-term complications of transgender surgery; Since complications such as urethral stricture, urinary fistula and infections recur at a high rate, transgender individuals who undergo gender-affirming surgery are forced to undergo urological follow-up throughout life and often need urological reoperations. However, we do not know the long-term effects of neourethra on kidney and

bladder functions (37,40).

Second, the rates of urogenital problems following gender-affirming surgery are probably higher than those reported in the literature (45). Because transsexuals are quite shy about expressing their urogenital problems after surgery. *Kuhn et al*. who have studies on this subject, report that urogenital problems after gender-affirming surgery are underreported, probably due to the shyness of transsexuals (22,23). The results of the comprehensive study conducted by *Kamran et al.* also support this interpretation. They examined "patient-reported outcome measures"(PROM) in this comprehensive study (which included 286 studies representing 85.395 transgender cases in more than thirty countries) and found that patient reports were absent or incomplete in most studies (48).

The data suggest that the urogenital complications that develop in transsexuals who undergo gender-affirming surgery are not fully reflected in the literature (more complications develop than the rates reported in the literature and/or may develop in the long term). Moreover, the complication rates reported in the literature are quite high. So why do trans men request phalloplasty, a surgical procedure with a high rate of complications, even though it is not mandatory? They do, because more than 98% of trans men desire to urinate while standing, which is considered a symbol of masculinity (37). This desire is a demand that exists at the level of obsession in trans men. Another possible reason for this high demand is that transgender people are not properly informed by healthcare professionals about surgical complications. Most transsexuals who think that their psychological problems will end with gender-affirming surgery are not subjected to an adequate psychiatric evaluation, nor are they informed as they should be about surgical complications. A recent study conducted by Vandenbussche in Germany, shows that this is the case; more than half (55%) of detransitioners who started the medical and/or surgical transition process (gender-affirming treatment) but later regretted it reported that they were not adequately informed (not adequately evaluated) by a doctor or psychiatrist before starting the transition (19). As we mentioned before, not only GD (and related psychological distress) is observed in transsexuals, but it is often accompanied by other psychiatric comorbidities (8). For this reason, an in-depth psychiatric evaluation and follow-up is essential in transsexuals (11). However, literature data show that in recent years, this has often been neglected and gender-determining medical or surgical treatments have been initiated with brief and superficial evaluations (11,21).

Shortened Lifespan and Unhappy Life in Transsexuals

Since gender reassignment surgery/transgender surgical procedures started in the 1970s, there has been an accumulation of knowledge and literature on this subject for more than 50 years. The main purpose of transgender surgery was not to treat a congenital or anatomical disorder, because there is no such problem, but to treat mental distress. For the treatment of psychological problems, radical surgical interventions -which cause irreversible loss of organs and functions- were recommended and performed (and are still being performed). However, relatively old and current literature showed/shows that psychological problems in transsexuals continue after these radical surgeries. In fact, the quality of life is decreasing even further after the surgery. The old and new literature do not contain any significant differences on this issue, contain similar results. A relatively early study conducted by *Sorensen* in Denmark (1981) reported that transsexual operations were not resocializing, but rather the opposite (49). Approximately 66% of the transgender people in the study lived alone and did not have sexual intercourse. Most of those who had sexual intercourse also had problems. 50% of the cases required additional surgeries due to complications and subjective problems that required reoperation of the vagina. People in the core group required fewer surgical corrections and were more satisfied with the surgical outcome, and they also had a better psychic state than the others. In this group, the advantages of gender reassignment seemed to outweigh the disadvantages, but in individuals outside the core group, subjective and objective problems were so pronounced that Sorensen says; "*But among the persons who do not belong to the core group subjective and objective problems seem so pronounced that operation must be advised against in spite of the often extremely, subjectively unsatisfactory condition of these patients preoperatively.*" (49).

Current studies conducted in Sweden and Denmark show that there is no change in these results. The Swedish cohort, which is the longest follow-up study on this subject, shows that mental problems in transgender people continue after surgery (2). Additionally, a study conducted by *Simonsen* et al. in Denmark shows that the life expectancy of of transsexual who underwent gender reassignment surgery was shortened by approximately 25-28 years. While the average life expectancy in Denmark is 81.9 years for women and 78 years for men, this period is 53.5 years for transsexuals who

have undergone surgery (50). In other words, the lifespan of transsexuals who undergo gender reassignment surgery is shortened by 25-28 years. Because these transsexuals use hormones throughout their lives, accordingly, fatal diseases such as cancer, lung and cardiovascular diseases increase, and when infections, surgery-related complications, reoperations, intense psychiatric problems and suicides are added, the average life expectancy decreases by 25-28 years (50). However, transsexuals who undergo surgery cannot be happy while they are also alive. Relevant studies show that psychological problems in transgender people continue after surgery, and that these problems even increase in some transgender individuals (2,6,49,50). When surgery-related urogenital complications are added to these psychological problems (such as reoperations, genital pain, difficulty in urinating, fistula, urinary incontinence and sexual problems), the quality of life of transsexuals decreases significantly (21,22).

Conclusion and Discussion

The data in the literature show that in gender reassignment surgery/transgender surgery - depending on the technique applied - urogenital complications develop in two-thirds to three-quarters of the cases, more than half of them require reoperation, but despite this, the outcome is unsuccessful in a significant portion of the cases. These complications significantly reduce the quality of life of transgender people. Data also shows that psychological problems in transgender individuals continue after surgery, and in some cases even increase, and that they have to struggle with these problems throughout life. When suicides, complications related to surgery, reoperations and diseases related to hormone use are added to these psychological problems, the lifespan of trans people is shortened by an average of 25-28 years (6,50).

Transsexuals who undergo gender reassignment surgery to get rid of their psychological problems (with this expectation) cannot get rid of these problems, and they also have to deal with surgery-related complications after the surgery. This situation significantly reduces the quality of life of transgender individuals. Mostly, Transsexuals complain about urogenital problems among postoperative complications (22,23). These complications may be one of the important reasons for regret and detransition (14). In recent years, there have been a significant number of detransitioners who regret starting their social, medical, and surgical transition and want to return (9-19). Current research displays that trans people who request gender reassignment treatment are not subjected to an adequate psychiatric evaluation before medical and surgical treatments, are given superficial or brief evaluations instead of in-depth examinations, and also are not sufficiently informed about surgical complications (11,19). This situation is a serious medicolegal and ethical risk for healthcare professionals. This risk increases disagreement among experts regarding the optimal treatment of GD/transsexuality (20,24-26).

It can be concluded that transgender surgery cannot treat the psychological problems of transgender people and also it causes urogenital complications that reduce the quality of life. There are problems in medical practice regarding the treatment of GD or transsexuality. Although there is no definitive evidence showing that transgender surgery treats mental problems in transgender people, and even though there are studies showing the opposite, these surgeries are still widely performed. In-depth evaluations [for indication] are not made before the decision on gender reassigning medical and surgical treatment. Although there is no consensus on what is the most appropriate treatment for GD/transsexuality, transgender surgery is widely performed around the world. Surely, this situation also increases the number of detransitioners who regret their transition and want to return. The data show that, in the context of the search for optimal treatment in GD/transsexuality, new studies are needed, including alternative treatment approaches, prioritizing the ancient principle of medicine "primum non nocere/first do not harm".

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The journal' s financial expenses are covered by the Eurasian Uro-oncological Association. The journal is published quarterly – three times a year- in February, June and October, respectively and the language of the journal are English and Turkish.

The purpose of the New Journal of Urology is to contribute to the literature by publishing urological manuscripts such as scientific articles, reviews, letters to the editor, case reports, reports of surgical techniques, surgical history, ethics, surgical education and articles of forensic medicine.

The target group of the journal consists of academicians working in the field of urology, urologists, residents of urology and all other fields of expertise and practitioners interested in urology.

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