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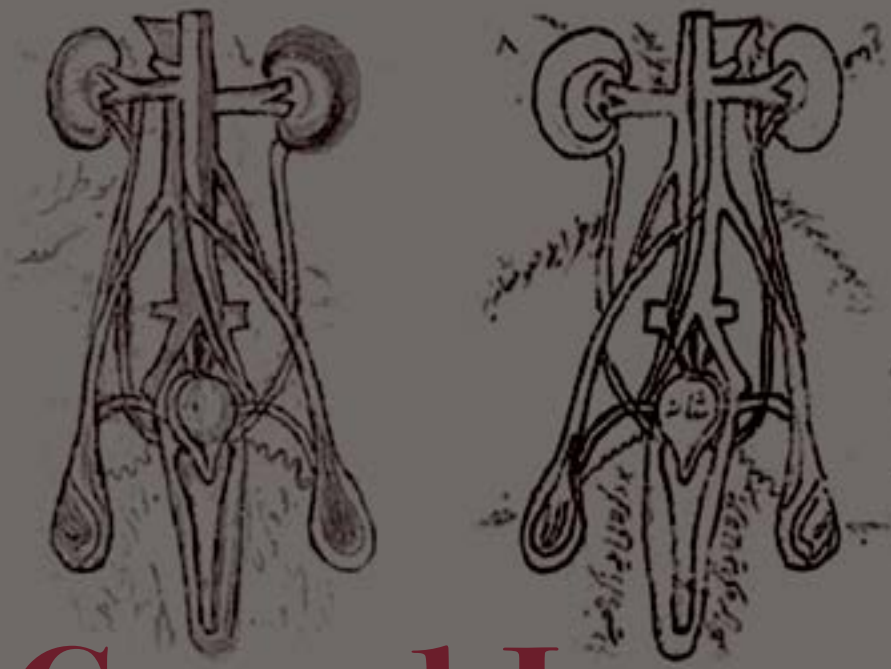

Grand Journal of UROLOGY

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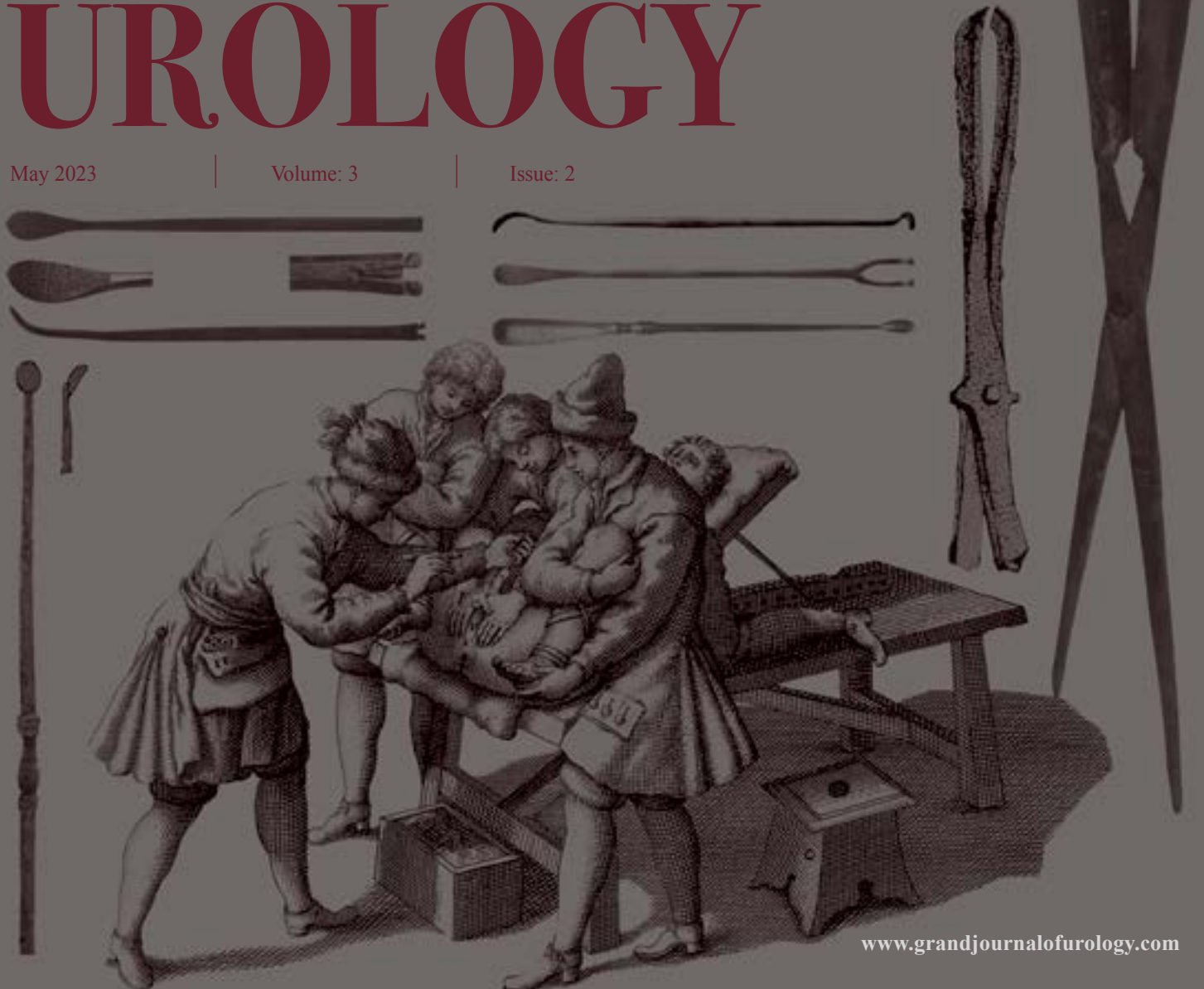

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Grand Journal of UROLOGY

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The target audience of the journal includes, urology specialists, residents in urology and other specialists who are interested in the field of urology. The journal aims to publish original scientific articles, clinical research, reviews, case reports, clinical images, editorial comments, and letters to the editor that are prepared in accordance with the ethical guidelines. Mini reviews, clinical updates, surgical techniques, and a guideline of guidelines that are in the scope of the journal are considered for publication and/or invited by the editor. All manuscripts must be submitted via the online submission system at www.grandjournalofurology.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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Keywords

4 to 6 keywords, can be used for indexing purposes should be provided. Keywords should be selected from Medical Subject Headings (MeSH) databases prepared by the National Library of Medicine (NLM).

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Manuscript

Original Article: It is the most crucial article type since it provides new data based on original research. The main text should be structured with the subtitles of Introduction, Materials and Methods, Results, Discussion, and Conclusion.

Statistical analysis is often required to support the results. It should be done according to international statistical reporting standards. Information on statistical analysis should be given under a separate subtitle under the Material and Methods section, and the statistical methods applied during the process should be specified.

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Acknowledgments (If Available)

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[1], [3-5], [6,9], [8-12,16].

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[1] Guner E, Seker KG, Arikan Y, Huseynov C, Sam E, Ozdal OL. Aktuelle Urol. 2020; 51: 285-289. https://doi.org/10.1055/a-1117-2776.

- Article with more than six authors

[2] Karabulut D, Karabulut U, Caglar FN, Ekşi M, Yenice MG, Guner E, et al. The association between CHA2DS2-VASc score and erectile dysfunction: a cross-sectional study. Int Braz J Urol. 2019; 45: 1204-1208. https://doi.org/10.1590 / S1677-5538. IBJU.2019.0058.

- Book

[3] Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

- Book chapter

[4] McKenna K. Ejaculation. In: Knobil E, Neil J, editors. Encyclopedia of Reproduction, New York: Academic Press; 1999, p. 1002-8.

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Contents

Editorial

Dear colleagues,

I am honored to share with you the second issue of 2023 (volume 3, issue 2) of the Grand Journal of Urology (Grand J Urol) with the contributions of many respected researchers and authors.

Grand Journal of Urology (GJU) aims to carry written and visual scientific urology studies to academic platforms and to make significant contributions to the science of urology.

Our journal has been abstracted/indexed in Tubitak Ulakbim TR Index, DOAJ, EBSCOhost, J-Gate, Index Copernicus International, EuroPub, SciLit, ResearchGate, ScienceGate and Google Scholar international databases. As of these achievements, the Grand Journal of Urology (GJU) has taken its place among the journals indexed by national and international databases.

In this issue of our journal, there are many valuable articles under the subheadings of Andrology, Urological Oncology, Endourology, Urolithiasis, Pediatric Urology and General Urology. I hope that these carefully prepared articles will make important contributions to valuable readers, researchers and the urology literature.

On this occasion, I would like to express my heartfelt gratitude to our authors who have contributed to our journal with their articles, to our reviewers who have meticulously evaluate the articles.

Respectfully yours
May 2023
Assoc. Prof. Ekrem GUNER, MD
Editor-in-Chief

Original Article – Endourology
Grand J Urol 2023;3(2):38-41
DOI: 10.5505/GJU.2023.60362

Bipolar vs Monopolar Transurethral Resection of the Prostate in Iraqi Patients: A Prospective Study

Iraklı Hastalarda Prostatın Bipolar ve Monopolar Transüretral Rezeksiyonu: Bir Prospektif Çalışma

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Abstract

Objective: Bipolar transurethral resection of the prostate (TURP) is a minimally invasive procedure that causes fewer problems, and a faster resection, but requires more expensive equipment. It is the treatment of choice for benign prostatic hyperplasia. In this study, its outcomes will be compared to those of conventional monopolar TURP.

Materials and Methods: Twenty-seven patients aged between 52 and 65 years underwent either monopolar TURP (Group 1, n: 15) or bipolar TURP (Group 2, n: 12). Preoperative and perioperative data were recorded and analyzed, including the maximal flow rate (Qmax), prostate volume, intraoperatively resected tissue volume, resection velocity, and operation time.

Results: Preoperative mean prostate volumes in Groups 1, and 2 were 82.6 ± 21 ml and 78.8 ± 12 ml, respectively (p=0.117). Preoperative mean serum sodium levels were 140.4 ± 2.3 mmol/l in Group 1 and 139.8 ± 2.2 mmol/l in Group 2. Preoperative mean serum hemoglobin values were 15 ± 0.8 g/dl in Group 1, and 14.5 ± 2.2 g/dl in Group 2. Postoperative mean serum sodium levels were 130.6 and 136.7 mmol/l, in Groups 1, and 2, respectively. Eight patients from the monopolar TURP group exhibited a notable drop in serum sodium levels. In the monopolar TURP group, there were 5 occurrences of TUR syndrome and 2 patients needed blood transfusions due to a mean decrease of 5 g/dl in hemoglobin levels. Complications were identified in 7 cases.

Conclusion: Compared to monopolar TURP, bipolar TURP is associated with a shorter hospital stay, and lower transfusion and complication rates.

Keywords: benign prostate hypertrophy, transurethral prostate resection, bipolar, monopolar, saline

Öz

Amaç: Bipolar prostat transüretral rezeksiyonu (TURP), daha az problem ve daha hızlı rezeksiyon oranı sunan, ancak daha pahalı ekipman gerektiren minimal invaziv bir prosedürdür. Benign prostat hipertrofisi için tercih edilen tedavidir. Bu çalışmada, sonuçlar konvansiyonel monopolar TURP ile karşılaştırılacaktır.

Gereçler ve Yöntemler: Yaşları 52-65 arasında değişen 27 hastanın 15'ine monopolar TURP (Grup 1, n: 15) ve 12'sine bipolar TURP (Grup 2, n: 12) uygulandı. Maksimal akış hızı (Qmax), prostat hacmi, intraoperatif rezeke edilen doku hacmi, rezeksiyon hızı ve operasyon süresi dahil olmak üzere preoperative ve perioperatif veriler kaydedildi ve analiz edildi.

Bulgular: Preoperatif ortalama prostat hacimleri Grup 1 ve Grup 2'de sırasıyla 82,6 ± 21 ml ve 78,8 ± 12 ml idi (p=0,117). Grup 1 için preoperatif ortalama serum sodyum aralığı 140.4 ± 2.3 mmol/l ve grup 2 için 139.8± 2.2 mmol/l idi. Preoperatif ortalama serum hemoglobin değerleri Grup 1'de 15 ± 0,8 g/dl, Grup 2'de 14,5 ± 2,2 g/dl idi. Postoperatif ortalama serum sodyum düzeyleri Grup 1 ve Grup 2'de sırasıyla 130,6 ve 136,7 mmol/l idi. Monopolar TURP grubundan sekiz hasta, serum sodyum seviyelerinde dikkate değer bir düşüş sergiledi. Monopolar TURP grubunda 5 kez TUR sendromu görüldü ve 2 hastada hemoglobin düzeyinde ortalama 5 g/dl azalma nedeniyle kan transfüzyonu gerekti. 7 vakada komplikasyon belirlendi.

Sonuç: Monopolar TURP ile karşılaştırıldığında, bipolar TURP daha kısa hastanede kalış süresi ve daha düşük transfüzyon ve komplikasyon oranları ile ilişkilidir.

Anahtar kelimeler: benign prostat hipertrofisi, transüretral prostat rezeksiyonu, bipolar, monopolar, salin

ORCID ID: **A.H. Essa** 0000-0001-8706-5357

Introduction

One of the most prevalent issues in older men is benign prostatic hyperplasia (BPH), which causes lower urinary tract symptoms (LUTS). With the aim of reducing side effects and improving quality of life (QoL) of the patients, numerous treatment methods are being used [1]. The gold standard for treating symptomatic BPH associated with prostate volumes ranging between 30 and 80 cc is monopolar transurethral resection of the prostate (TURP) [2]. It is approved as a treatment for LUTS secondary to BPH, but despite numerous technical advancements, it has drawbacks. Considering that it still has a morbidity rate of 11% and a death rate of 0.1%, we are looking for a new procedure that will produce the best possible functional outcomes [3]. The bipolar TURP is now being compared to the traditional monopolar TURP, with efficacy similar to the monopolar procedure but with reduced perioperative problems, insignificant TUR symptoms, lesser blood loss, and shorter catheter dwell time [4-6]. As a lengthy procedure a large prostate can be safely removed under normal saline irrigation [7]. We planned a three-arm trial with a focus on perioperative and postoperative complications as well as immediate functional outcomes because there was a lack of prospective randomized studies comparing monopolar and bipolar TURP. The aim of this study is to compare the outcomes of bipolar and monopolar TURP. To our knowledge, this two-part study is the first prospective randomized trial to compare monopolar TURP versus bipolar TURP [8-12].

Materials and Methods

The study was conducted prospectively on patients who underwent TURP from December 2020 to December 2022. BPH patients with normal PSA, and a prostate volume not exceeding 100 cm^3 were included in the study. The patients with an abnormal PSA, any malignancy, stones or prostate volume exceeding 100 cm^3 were not included in the study.

Surgical indications were retention of urine, failure of medical therapy, and presence of hematuria. Monopolar TURP (Group 1) was applied to fifteen and bipolar TURP (Group 2) to twelve patients. Karl Storz brand 24 F cystoscopes were used for both groups. The irrigation fluid was distilled water in monopolar TURP, and normal saline in bipolar TURP. Twenty-one patients had been on an alpha-1-adrenoreceptor blocker and fifteen patients on a combination of an alpha-1-adrenoreceptor blocker and 5-alpha-reductase inhibitors for an average duration of 9 months before the surgery. At the end of the monopolar and bipolar TURP, a 22 or 24 Fr 3-way urethral Foley catheter was inserted and normal saline irrigation was used. Continuous saline irrigation was done until the urine drained from the urethral Foley catheter became clear with time. The catheters were removed when the urine became clear without continuous saline irrigation within postoperative 3-5 days. Preoperative and perioperative data were recorded and analyzed, including International Prostate Symptom Score (IPSS), maximal flow rate (Qmax), prostate volume, intraoperatively resected prostatic tissue volume, resection velocity, operative time, changes in the serum levels of hemoglobin, and sodium, length of postoperative hospital stay.

Statistical Analysis

All statistical analyzes were performed with SPSS (version 25, Armonk, US). Continuous variables were defined as mean and standart deviation (SD), and cathegorical variables as frequencies (n) and percentages (%). Continuous variables were compared with Mann- Whitney U test and categorical variables with Pearson chi-squared test. P-values of less than 0.05 were deemed statistically significant.

Results

Preoperative prostate volumes were 82.6 ± 21 ml in Group 1 and 78.8 ± 12 ml in Group 2 (p=0.117) (**Table 1**). The preoperative mean serum sodium, and hemoglobin values were 140.4 ± 2.3 mmol/l vs 15 ± 0.8 g/dl in Group 1, and 139.8 ± 2.2 mmol/l vs 14.5 ± 2.2 g/dl, in Group 2, respectively. The postoperative mean serum sodium levels in Groups 1, and 2 were 130.6 and 136.7 mmol/l, respectively. Eight patients from the monopolar TURP group exhibited a notable drop in serum sodium levels. In these patients, the average decrease in serum sodium was 9 ± 1.22 mmol/l. Significant reduction in postoperative serum sodium levels below 125 mmol/l causing the TUR syndrome. The mean operative time was 55 ± 18.4 min in Group 1 and 63 ± 29.8 min in Group 2, (p=0.001). The mean resected prostate volumes were 40.6 ± 12.2 ml in Group 1 and 45.4 ± 10.9 ml in Group 2 (p<0.001). Seven patients in the monopolar TURP group had complications. There were five cases of TUR syndrome in the monopolar group where patients presented with blurred vision and disturbed consciousness. These patients were treated with IV furosemide and hypertonic saline, and 2 patients needed blood transfusions because their hemoglobin levels had decreased on average by 5 g/dl. The alterations in hemoglobin levels are statistically significant, and the bipolar group did not require blood transfusions as a result of postoperative changes in hemoglobin levels.

Postoperatively mean duration of hospital stays were 3 ± 2.3 days in Group 1 and 1 ± 1.3 days in Group 2 (p<0.001). The length of hospital stays for patients in the bipolar TURP group was less than those in the other group. Postoperative 6-month IPSS results revealed statistically significant improvement. In none of the TURP groups any urethral or meatal strictures were not noted during the 6-month follow-up period.

Table 1. The clinical outcome comparison between monopolar vs bipolar TURP

	Group 1 (monopolar, n=15)	**Group 2 (bipolar, n=12)**	**P value**
Age of patients, years	52-65	52-65	0.783
Prostate volume, ml	82.6±21	78.8±12	0.117
Resected volume, ml	40.6±12.2	45.4±10.9	**<0.001**
Operative time, min	55±18.4	63±29.8	**0.001**
Hospitalization, days	3±2.3	1±1.3	**<0.001**
Transfusion rate, n (%)	2 (13.3)	0	0.03

Discussion

Treatment-refractory urinary retention, hematuria, bladder stones, recurrent infections, failure of drug therapy, or patient preference are the main indications for surgical treatment in BPH. In the 1920s and 1930s, conventional TURP underwent its initial development in the United States. TURP is acknowledged as the gold standard for the surgical treatment of BPH as more improvements in surgical instruments and techniques have been made with time [13]. IPSS and Qmax scores improve in about 80% of patients who undergo TURP [14].

Throughout the past three decades, TURP-related morbidities have decreased [15]. Perioperative bleeding and TUR syndrome, a result of excessive absorption of hypotonic solution, are still serious complicaions, and 2% of patients experience TUR syndrome. If the gland is larger than 45 ml and the excision takes more than 90 minutes, the risk is higher. If it occurs, abort the procedure and give diuretics and hypertonic saline [16]. According to our findings, bipolar TURP reduced the chance of developing TUR syndrome compared to monopolar TURP due to a lesser amount of change in serum sodium levels. Compared to monopolar TURP, bipolar TURP allows surgeons to perform the procedure more slowly and to remove more prostate tissue. Also, compared to monopolar TURP, bipolar TURP appears to be more effective at removing tissue and controlling bleeding [17]. In contrast to the need for blood transfusion in two cases in the monopolar TURP group, no transfusions were necessary in the bipolar TURP group. At this point, we should consider the fact that the use of 5-alpha reductase inhibitors such as dutasteride decreases the bleeding because of a decrease in gland vascularity.

Bipolar TURP also required shorter postoperative hospital stay than the other group. According to Starkman et al., individuals who underwent Gyrus bipolar TURP had their catheters withdrawn on average 1.4 days sooner than those who underwent monopolar TURP [18]. Eaton and Francis found that with the Gyrus method, 32 out of 40 patients could be discharged on the same day of the operation. Operators preferred bipolar TURP over monopolar TURP in multicenter research of the procedure due to cleaner resection surfaces (64%) and greater efficacy when resecting the apex of the prostate glands (93%) [19]. The utilization of monopolar TURP in large prostate glands is limited, Bhansali et al. compared bipolar TURP with monopolar TURP in their series of 70 patients with prostate glands >60 ml and reported that bipolar TURP showed excellent results in terms of perioperative blood loss, change in serum sodium levels, and duration of catheterization [20].

The main limitation of our study is very limited number of patients who were included in the study. However, due to the lack of prospectively designed studies on this subject, we think that our current study will contribute to the literature.

Conclusions

Shorter hospital stays, alow rate of transfusions, and fewer complications like TUR syndrome were advantages of bipolar TURP that were comparable to those of monopolar TURP in terms of alleviating voiding symptoms. However, there is a need for multicenter, prospective randomized studies with a higher number of patients to support our results.

Ethics Committee Approval: The study was approved by the Ethics Committee of Al-Iraqia University College of Medicine (Approval date, and registration number: 05.03.2023-FM.SA /36).
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Individualized Management of 1-2 cm Kidney Stones in the Lower Pole Calyces

Alt Pol Kalikslerinde Olan 1-2 cm'lik Böbrek Taşlarının Kişiye Özel Yönetimi

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Abstract

Objective: We aimed to determine the individualized management of middle-sized kidney stones in the lower pole calyces that can be removed using shock wave lithotripsy (SWL) (Group A), flexible ureteroscopic retrograde intrarenal surgery (RIRS) (Group B) and micro-percutaneous lithotomy (micro-PNL) (Group C).

Materials and Methods: Patients who had 1-2 cm kidney stones in the lower pole calyces whose calyceal necks (length: <10 cm, and width: > 5mm), pelvicalyceal angle (>30º) and relatively shorter stone-skin distance as determined based on tomographic urography results were included in the study. Patients with renal cystine, whewellite stones or stones with a hardness above 1000 Hounsfield units were excluded. The groups were not formed randomly. Contarily, treatment methods were explained to the patients and let them decide the treatment method for themselves. Each group consisted of 34 patients.

Results: After excluding nine patients who were lost to follow-up, the study was completed with 93 patients at the final analysis. Stone-free rate was lower in Group A (47%) than Groups B (80.5%) and C (77%) (p<0.001). The mean number of sessions was 2.1 for Group A, 1.55 for Group B and 1 for Group C (p<0.001). Average procedure costs were $169, $1427, and $947 for Groups A, B, and C, respectively (p<0.001). Median length of hospital stay for Groups A, B, and C was 1, 20, and 48 hours (p<0.001), respectively, and 2, 3.9 and 5.5 working days were lost, respectively (p<0.001).

Conclusion: RIRS and micro-PNL had more stone-free rate, but number of working days were lost with lower medical expenditures in the SWL group. The priority of the patients should be determined, and the choice of treatment should be decided in collaboration with them.

Keywords: lower calyx, middle sized kidney stone, shock wave lithotripsy, retrograde intrarenal surgery, micro-percutaneous nephrolithotomy, cost-efficiency

Öz

Amaç: Alt pol kalikslerinde şok dalga litotripsi (SWL) (Grup A), fleksibl üreteroskopik retrograd intrarenal cerrahi (RIRS) (Grup B) ve mikroperkütan litotomi (micro-PNL) (Grup C) ile çıkarılabilen orta büyüklükteki böbrek taşlarının bireyselleştirilmiş yönetimini belirlemeyi amaçladık.

Gereçler ve Yöntemler: Alt kaliks grubunda 1-2 cm arası taşı olan, çekilen tomografik ürografide kaliks boynu uzun yada dar olmayan (uzunluk: <10 cm ve genişlik: > 5 mm), kaliks-pelvis arasındaki açısı dar olmayan (>30º) ve cilt-taş mesafesi uzak olmayan hastalar çalışmaya alındı. Taşın sertliği 1000 Hounsfield ünitesi üzerinde olan, bilinen sistin yada whewellite taşlı hastalar çalışmadan hariç tutuldu. Gruplar randomize değildi. Aksine, tedavi yöntemleri hastalara anlatılarak kendilerinin karar vermeleri istendi. Her grup 34 hastadan oluşuyordu.

Bulgular: Takipten çıkan dokuz hasta hariç tutulduktan sonra son analizde 93 hasta ile çalışma tamamlandı. Taşsızlık oranı Grup A'da (%47) Grup B'ye (%80,5) ve C'ye (%77) göre daha düşüktü (p<0.001). Ortalama seans sayısı Grup A için 2,1, Grup B için 1,55 ve Grup C için 1 idi (p<0.001). Ortalama prosedür maliyetleri Grup A, B ve C için sırasıyla 169$, 1427$ ve 947$'dı (p<0,001). Medyan hastanede kalış saati Grup A, B ve C için sırasıyla 1, 20 ve 48 saat idi (p<0,001) ve çalışma günü kayıpları sırasıyla 2, 3,9 ve 5,5 gün idi (p<0,001).

Sonuç: RIRS ve mikro-PNL'de taşsızlık oranı daha yüksekti, ancak SWL'de iş günü kaybı ve maliyet daha düşüktü. Hastanın önceliğinin ne olduğu belirlenip, tedavi seçimine birlikte karar verilmelidir.

Anahtar kelimeler: alt kaliks, böbrek orta boy taşları, şok dalga tedavisi, böbrek içi cerrahi, mikro perkütan nefrolitotomi, maliyet-etkinlik

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Introduction

Urinary stone disease affects roughly 15% of the population [1]. Kidney stones are most seen in the lower pole calyces [2]. Retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PNL), and shock wave lithotripsy (SWL) are all minimally invasive methods used to treat kidney stones. Patients with stones in the lower pole calyces are treated differently from those with stones in the upper and middle pole calyces. Because lower pole calyceal stones must ascend the infundibulum of the lower pole, reach the renal pelvis, and then depart the kidney into the ureter, making their removal extremely difficult [3].

Many urologists choose SWL as a low-morbidity outpatient option, and many patients tolerate it. PNL is recommended as the primary choice by the European Association of Urology (EAU) for stones bigger than 2 cm and SWL or RIRS for stones smaller than 1 cm. However, the optimal treatment choice for medium-sized lower pole calyceal stones measuring 1 to 2 cm is still up for debate [4]. Furthermore, it is known that SWL is linked to insufficient fragment clearance from the lower pole [5].

Because it has a high success rate regardless of stone size, PNL is currently the standard treatment of choice for large stones (> 2 cm) and is also preferred by many urologists for the treatment of multiple renal stones or stones in the dependent parts of the kidney, such as the lower pole. However, the substantial risk of morbidity outweighs the advantage of high stone-free rate [6]. Miniaturized PNLs with smaller nephroscopes can reduce surgical morbidity. In the removal of renal stones, its efficiency is comparable to that of normal PNL. Miniaturized nephroscopes have calibers ranging from 4.8 to 22 F, with mini-PNL (14-22 F), ultramini-PNL (13 F), and micro-PNL (4.8 F) being the most used ones [7].

Flexible ureteroscopy, which was originally used to treat lower pole calyceal stones that were resistant to SWL, may be a less intrusive option to percutaneous treatments [8]. RIRS is becoming more popular as a main treatment for these stones, with greater stone-free rates than SWL and lower patient morbidity than PNL.

Medical expenditures for treating stone disease involve direct and indirect costs. All medical expenses (e.g., prescriptions, hospitalization charges, all consumables and non-consumables required during surgery) are considered direct costs, whereas indirect costs include the patient's lost working days [9]. Health-care systems and individuals nowadays desire shorter hospital stays, speedier return to work, maximum cost efficiency, and higher surgical success rates [10,11].

We compared the safety, efficacy, and cost-effectiveness of SWL, RIRS, and micro-PNL in this study to determine an individualized management for 1-2-cm stones in the lower pole calyces.

Materials and Methods

Study Population and Design

This study had a prospective, non-randomized design. Patients who had 1-2 cm kidney stones in the lower pole calyces with calyceal necks (length: <10 cm, and width: > 5mm), pelvicalyceal angle (>30°) and relatively shorter stone-skin distance, and stone hardness lower than 1000 Hounsfield units as determined based on tomographic urography results were included in the study. The groups were not randomized. The treatment methods were explained to the patients and requested them to decide their treatment preferences by themselves. All patients were included in the study by selecting the appropriate treatment modality. When each group had 34 patients, participation in the study was terminated. In all, 102 patients were divided into three groups (34 patients to each): Group A was managed by SWL, Group B by RIRS, and Group C by micro-PNL. The study was carried out between February 2021 and February 2022 in a single center. Presence of a solitary or abnormal (horseshoe or pelvic kidney) kidney, renal insufficiency, pregnancy, urinary tract infection, radiolucent stone, calyceal diverticular stone, pre-existing metabolic stone disease (whewellite stone, cystinuria, renal tubular acidosis, etc.), a double-j or a nephrostomy tube inserted before surgery, and patients younger than 18 or older than 75 years were excluded from the study. Patients who used antithrombotic drugs were not treated, even with RIRS, to prevent bias.

All procedures were performed by the same surgical team. The urologist who performed the operations was experienced in all these procedures. All patients' urine cultures were sterile before operation. The stone surface was calculated using the formula: height x width x 0.25 x π).

Informed, written consent was obtained from all patients. Ethical approval was granted by University of Health Sciences Sancaktepe Training and Research Hospital Ethics Committee (date: 27.01.2021; decision #: 88).

Surgical Procedure

The endoscopic instruments used had a caliber of 4.8 Fr for micro-PNL (PolyDiagnost, Pfaffenhofen, Germany). Flexible cystoscopes or ureteroscopes were not used, and only a laser lithotripsy was employed in micro-PNL (**Figure 1**). Nephrostomy tubes were not inserted in any patient who underwent micro-PNL. A double-J ureteral stent was placed when required in the presence of pelvic perforation, residual stone, and intraureteral stone migration. For RIRS, diagnostic ureteroscopy was performed with a semi-rigid 6/7.5 Fr ureteroscope (Richard Wolf, Knittlingen, Germany). A 7.5 Fr flexible ureteroscope (Flex X2, Karl Storz, Tuttlingen, Germany) was utilized for the primary operation. A holmium: YAG laser was used to fragment the stones down to the size of 272 microns. The stones were dusted rather than removed using a basket or other equipment. For SWL therapy, an Argemet A1000 device (Turkey) was employed at a frequency of 90 shocks per minute**.** The starting voltage for SWL was 14 kV for 500 SWs, then raised in 2 kV increments every 500 shock waves (SWs) until stone fragmentation started, or up to a maximum value of 24 kV. Stone disintegration was confirmed both by the SWL operator and the surgeon in charge by radiographic control.

The cost of procedure per case included the money spent to purchase disposable materials (e.g., guide, urethral catheter, cover set, gloves), special materials (access sheath for RIRS, dilator set for micro-PNL), drugs (e.g., antibiotics, IV fluids for replacement, analgesics), in addition to hospitalization cost per day, and fees charged for stent removal and endoscopy. The daily bed cost (approximately 20 USD) is standard for patients operated on in

Turkey. The daily bed cost in the National Health Care System of Turkey is approximately 10% of the monthly minimum wage and was calculated as a reference guide for other physicians who are working in different health insurance systems. The average costs of the instruments used per procedure were calculated using the data obtained from the relevant records of the previous five years. Instrument costs encompass money spent for purchase and repair of the instrument. The case number of lifetime cycles were 70 for micro-PNL and 35 for flexible ureteroscope. Total costs include the costs of the procedure plus the mean cost of endoscopy per case. The Argemet A1000 SWL device (Turkey) has a 200-case maintenance cycle, and the maintenance fee is $3000.

Figure 1. Micro-PNL surgical equipment

Outcome Assessment

The primary outcome measures were the stone-free rate and cost, while the time to return to daily activities and length of hospital stay were the secondary outcome measures. Since SWL was conducted in an outpatient environment, hospitalization was measured by the number of hours spent in the hospital. Every SWL session lasted at least one hour, including premedication. The time to return to daily activities was determined by patient self-report. Daily life activity was defined as the patient being able to work at full capacity at the same level as preoperatively, without moderate or severe pain and limitation of movement. In addition, the total period elapsed till return to daily life activities increased by the number of working days lost owing to severe lower urinary tract symptoms before starting to work. Operative time was not assessed because SWL was not performed under anesthesia in an operation room and fluoroscopy time was assessed instead. Stone-free status was defined as lack of any residual stone or a clinically insignificant 3 mm- residual stone on non-contrast computed tomographic examination performed three months following the last procedure. Secondary procedures involved a semi-rigid ureteroscopy performed for ureter stones. Clavien-Dindo classification was used to categorize the complications. Clavien-Dindo grade ≥ 2 complications were included in the statistical analysis.

Statistical Analysis

The mean age, body-mass index (BMI), stone surface area, fluoroscopy time, length of hospital stay, time to return to normal daily activities, treatment cost, stone-free rate (SFR), and complication rates were compared between groups. Statistical analysis showed that the patients in each treatment group were normally distributed, with a standard deviation of 10. The expected true difference in the success rate of surgery was 10%. The type I error probability associated with this null hypothesis test was 0.05. To reject the null hypothesis that the surgical success rates of the two groups were the same, we needed to investigate 30 individuals in each group with a probability of 0.8. The estimated rate of patient loss to follow-up was 10%. All participants were stratified by computer-generated pseudorandom numbers according to surgical procedures. The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 17 for Windows was used for statistical analysis. To compare groups, one-tailed ANOVA and Pearson chi-square tests were performed. A Tukey test was used for post-hoc analysis. Level of statistical significance was defined as a p value of less than 0.05.

Results

After nine patients were excluded due to lack of follow-up information, the final study contained 93 individuals. Mean age, BMI, and stone surface area were comparable between groups (**Table 1**). Patients were monitored for at least three months. Group A had a lower SFR (47%) than Groups B (80.5%) and C (77%) ($p<0.001$) (**Table 2**).

Median hospital stay was shorter in Group A (1 hour) than in Groups B (20 hours) and C (48 hours) ($p<0.001$). Each SWL session lasted one hour, including premedication. Thus, the minimum hospitalization time was one hour in the SWL group. In the SWL group, three patients were hospitalized for seven, and three patients for one day. Subcapsular hematomas developed in two patients hospitalized for seven days were resolved with only bed rest. One patient was hospitalized for three days because of fever, and three patients were interned for one day due to renal colic unresponsive to medication. Hence, the maximum hospital stay was 168 hours (7 days) in Group A. Patients who underwent RIRS and micro-PNL were routinely discharged the next day. However, some of them had longer hospitalization periods due to the presence of pain, fever, gross hematuria, and sepsis. Thus, the maximum hospital stays were 144 hours (6 days) in the micro-PNL and 192 hours (8 days) in the RIRS group. Sepsis occurred in two patients in the RIRS group, and gross hematuria in one patient in the micro-PNL group.

The mean number of sessions was 2.1 in Group A, 1.55 in Group B, and 1 in Group C ($p<0.001$). The mean number of working days lost was lower in Group A (2 days) than in Groups B (3.9 days) and C (5.5 days) ($p<0.001$). In the SWL group, the total working time lost was calculated as four hours (half of a working day), including time spent for coming to the hospital, evaluation, and treatment processes, and return to work or home.

In other words, each SWL session means a loss of half a working day. The mean number of sessions was 2.1 in the SWL group, so the mean number of working days lost should have been about one day, but it increased to two days due to complications developed in patients. In the RIRS group, removal of a double-j stent resulted in loss of a working day as well as the need for a control or emergency visit in an extra session in more than half of the patients, and prolonged hospitalization due to complications, all of which increased the mean number of working days lost approximately four-fold. In the micro-PNL group, the median hospitalization time was two days, along with the half-day spent for the control visit resulted in an exact loss of 2.5 working days. However, we recommended bed rest for at least two days for our patients. Taking into account urinary tract infections, hematuria, and the prolonged hospitalization required for some patients, on an average, 5.5 working days were lost.

The mean cost of procedures was $169, $1427, and $947 for Groups A, B, and C, respectively ($p<0.001$). The cost of all materials used throughout the procedure was also documented (**Table 3**). These were the direct costs, that is, the money that the health system rather than the patients spent. Complication rates were similar between groups (**Table 2**). The most severe complication was sepsis, and none of the patients received blood transfusions or were transferred to the intensive care unit. Sepsis occurred in two patients, one in the SWL group and one in the RIRS group.

Table 1. The detail of the groups

	SWL (Group A)	**RIRS (Group B)**	**Micro-PNL (Group C)**	**P value**
Patient number (n)	30	31	32	
Mean Age (years) ± sd	45±11.2	48.1±13.1	42.8±13.5	0.237
Gender (male/female)	21/9	20/13	19/16	0.430
Mean BMI (kg/m²) ± sd	25.8±3	25.4±2.8	25.1±3	0.582
Side (right/left)	13/15	16/17	20/15	0.655
Mean stone surface area (mm²) ± sd	190.6±77	201±42.5	212±82	0.852

Table 2. Outcomes of the procedures

	SWL (Group A)	**RIRS (Group B)**	**Micro-PNL (Group C)**	**P value**
Patient number (n)	30	31	32	
Mean fluoroscopy time (second) ± sd	46.1±30.3	34.3±22.4	127.8±59	**<0.001**
Stone-free rate (%)	47.7%	80.5%	77%	**<0.001**
Median hospital staying (hours) ± (min-max)	1 (1-168)	20 (16-192)	48 (12-144)	**<0.001**
Mean loss of working day (day) ± sd	2±3.7	3.9±2.5	5.5±3.6	**<0.001**
Mean number of sessions ± sd	2.1±0.9	1.55±0.75	1±0	**<0.001**
Mean cost of procedures ($) ± sd	169±193	1427±501	947±344	**<0.001**
Complication rate	6.7%	12.9%	9.4%	0.438

Table 3. Costs for each spend unit ($) (N.A.: Not applicable)

	SWL	**RIRS**	**Micro PNL**
Prophylaxis, premedication or anesthesia	25	65	35
Disposable materials	25	270.5	219.4
Special materials	34	367.3	194.3
Lithotripter (laser fiber, pneumatic or ultrasonic tip)	N.A.	125	125
Post-procedure drugs	40	37	39.3
Total bed cost	20	82.2	114
Double-j extraction cost	N.A.	130	N.A.
Cost of tool per case	15	350	200
Total	169	1427	947

Discussion

In recent years, many technological developments, such as advanced optical system technologies, have been used in the management of upper urinary tract stones. In the majority of published studies comparing different treatment options for urinary stone disease, the most common parameters were SFR and complications of each technique. However, when selecting an option, the cost-effectiveness of the technique to be used should also be considered. In addition, when calculating the cost of the surgical procedure applied, it is necessary to evaluate the indirect cost parameters such as the total number of working days lost as well as the cost of the materials used.

Because of the high recurrence rate and the possibility of reoperation after treatment of 1-2 cm stones in a lower pole calyx, a rational treatment approach that provides maximum SFR which is a key parameter in evaluating the efficacy of a stone management procedure with minimal morbidity is needed, [12]. Although SWL has been the preferred option for lower pole calyceal stones for many years, its low SFRs have prompted clinicians to seek alternatives. Because of the disadvantages of SWL for this group of stones, RIRS and PNL are now the preferred treatment options [13].

Based on the available literature data, the SFR for the first session of SWL is around 46-64% [14,15]. Similar to these data, our SFR was 47.7% which was statistically significantly lower compared to the other groups. The SFR of the first session of RIRS has been reported as approximately 60-65% [13,16]. In this study, it was 80.5%. The SFR for micro-PNL has been reported as 83% [17,18], while in our study it was 77%.

Post-procedural complications are among the main reasons for long hospital stays and delays in patients' return to daily life. Further, the cost of the procedures increases when complications occur [19]. The mean hospital stay for RIRS has been reported as 1-2 days, compared to 1.1-2.4 days for micro-PNL [11,17]. Usually, uncomplicated SWL is an outpatient procedure, but it may still result in the loss of a working day. Similar to literature, the mean hospital stay in our study was shorter in Group A (1 hour) than in Groups B (20 hours) and C (48 hours). Our results showed that the greater the degree of invasiveness, the longer the hospital stay. The daily hospital bed cost was $20, which is approximately 6% of the monthly minimum wage in Turkey. Although it is cheaper than in other countries, other hospital, and medical expenses are comparable because disposable materials and endoscopes are imported. This phenomenon may seem to be an advantage favoring invasive procedures in terms of direct costs. However, there are conflicting data in the literature regarding the length of time it takes a urolithiasis patient to return to daily activities. For example, Demirbas et al. [20] reported length of hospital stay as 11.26 days for ultra-mini PNL, while Xun et al., [21] indicated 5.76 days for standard PNL. In a study from Spain, although the direct costs of URS/RIRS were higher than those of ESWL, no statistically significant difference was found between them in terms of indirect costs [22]. We think that the length of hospital stay differs dependent on local conditions. In our clinic, we encouraged patients to return to daily activities as soon as possible. The mean number of working days lost for SWL (2 ± 3.7 days), RIRS (3.9 ± 2.5 days), and micro-PNL (5.5 ± 3.6 days) were as indicated ($p<0.001$). Although the highest average number of working days lost was detected in Group C, the number of working days lost was in the narrowest range in this group due to lower contingency. We cannot calculate a net amount of financial loss for a working day lost because each patient's daily earnings are different. However, if we accept that the daily earnings are similar for each patient group, we can say that the cost of the procedure increases in line with the degree of invasiveness of the treatment method used. The costs of each procedure may vary by country and by healthcare system [23]. There are few studies on the cost of SWL, but many studies report that the procedure cost was lower for patients with lower stone burden, decreased Hounsfield unit of stone density (<1000), and more favorable renal anatomy [3,24]. Perez et al. reported the direct cost of one session of ESWL as $1690.5 [22]. Regarding the other methods, the mean cost of RIRS in Germany is $951, while in England it is $1398. A miniaturized PCNL in Germany costs $562, while the same procedure in England costs $749 (11). In a Turkish study, the total medical expenditures for RIRS and micro-PNL were reported to be $1250 and $962, respectively [25]. In this study, the mean procedure costs were $169, $1427, and $947 for Groups A, B, and C, respectively. As mentioned before, our RIRS cost was higher than that of the micro-PNL procedure in consideration of the use of a routine access sheath and the insertion, and then removal of a double-j stent**.**

In summary, our study offered a detailed analysis of the safety, efficacy, and cost-effectiveness of these three procedures used for stone extraction. Like all medical problems, management of urinary stone disease imposes a significant socio-economic burden. Moreover, there are financial and social costs related to the working days lost, and the direct costs of the procedures may actually convey greater importance. On the other hand, failure both to determine the Hounsfield units of the stones and also to perfom stone analysis are potential limitations of the study.

Conclusion

The stone-free rates were relatively higher in RIRS and micro-PNL, but the number of working days lost, and medical expenditures were lower in SWL. SWL can thus be attempted first, and if it is unsuccessful, RIRS or micro-PNL can be performed with comparable efficiency and medical procedure cost. Before making a treatment decision, it is necessary to give patients detailed information about the pros and cons of each of the three procedures and consider their decision. In addition, treatment options should be reviewed with patients in consideration of their socioeconomic status.

Ethics Committee Approval: Ethical approval was granted by University of Health Sciences Sancaktepe Martyr Prof. Dr. Ilhan Varank Training and Research Hospital Ethics Committee (date: 27.01.2021; decision #: 88).
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Relationship Between Triglyceride-Glucose Index and Erectile Dysfunction in Subjects Without Cardiovascular Disease

Kardiyovasküler Hastalığı Olmayan Kişilerde Trigliserid-Glukoz İndeksi ve Erektil Disfonsiyon Arasındaki İlişki

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Abstract

Objective: Studies have shown that insulin resistance (IR) plays a role in the pathogenesis of erectile dysfunction (ED). Triglyceride-glucose (TyG) index has been found as a reliable marker of IR. In this study, our aim was to investigate the role of TyG index in patients with ED.
Materials and Methods: One hundred six patients with ED (study group) and 54 subjects with normal sexual function (control group) constituted our study population. Erectile function was assessed by using International Index of Erectile Function-5 (IIEF-5) questionnaire. TyG index was calculated for each participant.
Results: ED patient were older, had higher total cholesterol (TC), low- density lipoprotein cholesterol (LDL-C), glucose and triglyceride concentrations and TyG indexes ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.036$, $p=0.026$ and $p=0.003$, respectively). IIEF-5 scores showed a negative correlation with TyG indexes ($r= -0.273$, $p=0.001$). Receiver operating characteristic (ROC) curve analysis showed that TyG index cut-off value of 9.03 had 70.3% sensitivity and 65% specificity in predicting mild-to-moderate, moderate, and severe ED. Univariate logistic regression analysis showed that age, TC, LDL-C, and TyG index had predictive values for the identification of the patients who had mild-to-moderate, moderate, and severe ED.
Conclusion: TyG index might be a valuable diagnostic tool for ED, and it might be used in clinical practice for the evaluation of patients.
Keywords: erectile dysfunction, triglyceride, glucose

Öz

Amaç: Çalışmalar insulin direncinin (İD) erektil disfonksiyon (ED) patogenezinde rol oynadığını göstermiştir. Trigliserid-glukoz (TG) indeksi İD için güvenilir bir belirteçtir. Bu çalışmada amacımız ED'li hastalarda TG indeksinin rolünü araştırmaktır.
Gereçler ve Yöntemler: Yüz altı ED hastası (çalışma grubu) ile normal cinsel fonksiyonlu 54 kisi (kontrol grubu) çalışma popülasyonumuzu oluşturdu. Erektil Fonksiyon, Uluslararası Erektil İşlev Formu-5 (IIEF-5) ile değerlendirildi. Her katılımcı için TG indeksi hesaplandı.
Bulgular: ED olan hastalar daha yaşlı, daha yüksek total kolesterol (TK), düşük yoğunluklu lipoprotein-kolesterol (LDL-K), glukoz ve trigliserid konsantrasyonları ile TG indeks değerlerine sahip idi (sırası ile ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.036$, $p=0.026$ and $p=0.003$). IIEF-5 skoru, TG indeks değerleri ile negatif bir korelasyon gösterdi ($r= -0.273$, $p=0.001$). ROC eğrisi analizi; 9.03 TG indeksi değerinin hafif-orta, orta ve ciddi ED'yi öngörmede %70.3 duyarlılık ve %65 özgüllüğe sahip olduğunu gösterdi. Univaryant lojistik regresyon analizi; yaş, TK, LDL-K ve TG indeksinin hafif-orta, orta ve ciddi ED'ye sahip hastaların belirlenmesinde prediktif değere sahip olduğunu gösterdi.
Sonuç: TG indeksi, ED tanısında yararlı bir araç olabilir. Hastaların klinik değerlendirmesinde kullanılabilir.
Anahtar kelimeler: erektil disfonksiyon, trigliserid, glukoz

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Introduction

Erectile dysfunction (ED) has a negative influence on the quality of life of patients. Its prevalence shows an association with age, surpassing over 80% in men who are older than 80 years [1]. Although this disorder might have organic or psychological causes, the most common underlying pathology is abnormalities of the penile blood vessels. ED shares the same risk factors for cardiovascular disease (CVD) with similar underlying pathophysiological mechanisms [2]. The relationship between ED and CVD is bidirectional. Studies have shown ED as a predictor of CVD and the presence of CVD has been found to be associated with more severe forms of ED [3]. As such, current guidelines have recommended a detailed examination of ED patients in terms of CVD and risk factors [2]. This approach gives physicians a chance for risk mitigation, early diagnosis, and management of CVD.

Insulin resistance (IR) coexists with the proatherogenic milieu and is a part of the atherogenic process [4]. By affecting systemic factors as well as intimal cells that are involved in atherosclerosis, IR seems to have an important role in plaque formation and progression of ED [5]. IR has been related to decreased nitric oxide production and vasodilatation both of which play a role in the pathogenesis of ED [6]. Men with ED have been shown to have higher levels of homeostatic model assessment insulin resistance (HOMA-IR) index which is the most popular method for the assessment of IR [7]. However, this test is relatively expensive and requires measurement of both serum insulin and glucose levels, which has led researchers to search for alternative methods. Triglyceride-glucose index (TyG index), the calculation of which is based on the measurements of serum triglyceride (TG) and glucose levels, is an easily obtainable and reliable marker for IR. The prognostic utility of the TyG index has been shown in acute coronary syndrome, lower extremity peripheral artery disease, heart failure, fatty liver disease, and stable coronary artery disease [8-12]. In the present study, we aimed to evaluate the TyG indexes of the ED patients and to find whether the TyG index has any predictive value in diagnosing ED.

Material and Methods

We retrospectively screened data files of the patients who were referred from the urology clinic to the cardiology outpatient clinic of a tertiary hospital between January 2022 and January 2023. One hundred sixty patients constituted our study population. Patients who had a history of percutaneous coronary artery intervention, coronary artery bypass graft operation, diabetes mellitus, peripheral arterial disease, liver failure, renal failure, malignancy, thyroid abnormalities, and hypertension were excluded. Patients were referred from the urology department for the purpose of cardiovascular evaluation. All patients gave informed consent for study participation. The study was approved by the local ethics committee (date: 06.03.2023, decision #: 2023-05-15) and conducted in compliance with The World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Diagnosis of ED was made by using the International Index of Erectile Function-5 (IIEF-5) questionnaire. The questionnaire consists of five Likert-type questions which are scored from one to five, while one point represents severe disease whereas five points indicate normal sexual function. According to the scores obtained by the patients in this questionnaire, the severity of ED was classified into groups of severe (5-7 pts), moderate (8-11 pts), mild-to-moderate (11-16 pts), and mild ED (17-21 pts), while scores ≥22 points indicated normal erectile function. Turkish validation of this questionnaire was made by Turunç et al [13]. Patients who had IIEF-5 scores between 1 and 21 constituted the study group (n=106) and the participants who had IIEF-5 scores between 22 and 25 constituted the control group (n=54).

For fasting blood tests blood samples were taken from the antecubital vein in a sitting position. Collected samples were analyzed for biochemical (AU 2700, Beckman Coulter Inc., California, USA) and complete blood count parameters (Sysmex XE 5000, Sysmex Medical Int., Kobe, Japan). TyG index of each patient was calculated as the natural logarithm of the product of plasma glucose and TG using the following formula: fasting glucose value (mg/dL) x fasting triglyceride value (mg/dL)/2. Cardiovascular status of the patients was evaluated based on the results of physical examinations, electrocardiograms, and treadmill exercise tests. Medications that influenced heart rate were stopped two days before the exercise test which was performed by using Schiller CS-200, Switzerland device.

Statistical Analysis

Normality of the data was assessed by examining skewness, kurtosis of the data and by use of Kolmogorov-Smirnov test. Since all data showed nonparametric distribution, comparison of two groups was done using Mann-Whitney U test. Categorical data were compared by chi-square test. Quade ANCOVA test was used to compare TyG values of the two groups where age was used as a covariate. Correlations between TyG indexes and IIEF-5 scores were performed using Spearman correlation analysis. ROC curve analysis was conducted to find the cut-off value of TyG index in predicting patients who had mild-to-moderate, moderate, and severe ED. Univariate logistic regression analysis was conducted to determine the variables that have a predictive value in diagnosing ED. A p value of less than 0.05 was considered statistically significant. All statistical analyses were conducted by using SPSS Statistics for Windows, Version 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM, USA).

Results

The mean age of the study population was 44.24±7.29 years including 70 (43.8%) smokers, and 41 (25.6%) alcohol users. There were no differences between the two groups in terms of the prevalence of smoking, alcohol consumption, high-density lipoprotein-cholesterol (HDL-C), hemoglobin, creatinine concentrations, leukocyte, and platelet counts. ED patients were older and had higher total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), glucose and triglyceride concentrations, and TyG indexes. According to Quade ANCOVA

results, the TyG indexes were higher in ED patients when age was used as a covariate (t=-1.876, p=0.045). The clinical characteristics of the two groups are shown in **Table 1**. IIEF-5 scores showed a negative correlation with TyG indexes (r= -0.273, p=0.001).

A total of 37 patients had IIEF-5 scores under 17 points indicating the presence of mild-to-moderate, moderate, and severe ED. ROC curve analysis showed that cut-off value of 9.03 for TyG index had 70.3% sensitivity and 65% specificity in predicting mild-to-moderate, moderate, and severe ED (AUC: 0.729, p<0.001, 95% CI: 0.634-0.856) **(Figure 1**). Univariate logistic regression analysis showed that age, TC, LDL-C, and TyG index were the variables that had predictive values for the identification of patients who had mild-to-moderate, moderate, and severe ED (**Table 2**).

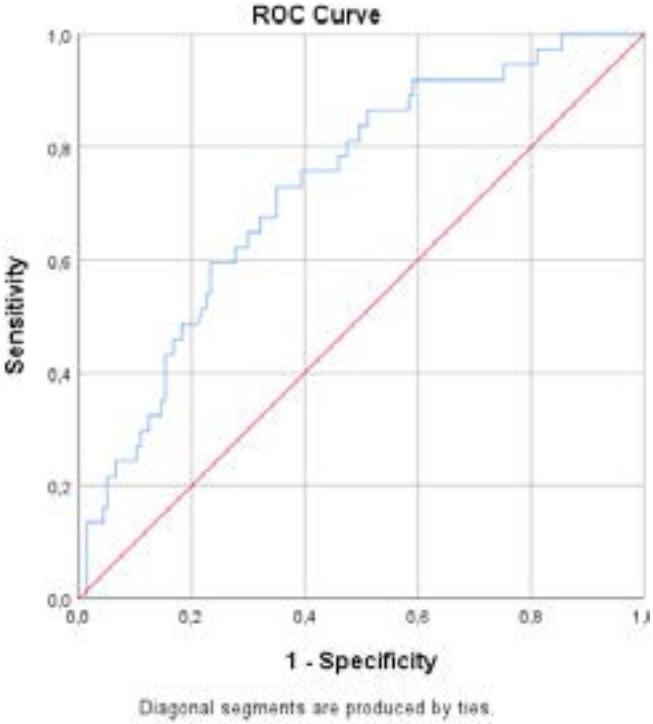

Figure 1. ROC curve analysis of TyG index for predicting mild-moderate, moderate and severe ED

Table 1. Clinical and demographic characteristics of the study and control groups

	Study group (n=106) (IIEF-5 score ≤21)	**Control group (n=54) (IIEF-5 score ≥22)**	**P value**
Age (years)	46.35±6.95 46 (42-51.25)	40.11±6.12 39 (35.75-44)	**<0.001**
Smoking (n, %)	44 (41.5)	26 (48.1)	0.423
Alcohol (n, %)	24 (22.6)	17 (31.5)	0.231
Total cholesterol (mg/dL)	206.92±92 207 (177-234)	173.19±36.28 162 (148-198.25)	**<0.001**
HDL-C (mg/dL)	47.26±19.45 44 (38-49)	50.04±23.09 42 (37-54)	0.937
LDL-C (mg/dL)	130.11±37.24 131.9 (101.25-154.25)	102.74±33.07 96 (80.25-119.3)	**<0.001**
Triglyceride (mg/dL)	163.85±87.95 143 (99.5-200.25)	137.12±77.79 101 (78.5-189.25)	**0.026**
Glucose (mg/dL)	109.39±12.35 111.5 (104-117)	103.41±5.93 103 (99.75-105)	**0.036**
Hemoglobin (g/dL)	14.73±1.26 15 (14-15)	14.40±2.20 15.4 (12.2-16)	0.956
Leukocyte count (10^9/L)	9.99±4.83 8.5 (6-14.25)	8.27±3.67 9 (4-11)	**0.244**
Platelet count (10^9/L)	247.49±71.16 235 (197-294)	234.61±71.20 241 (210.75-276)	0.973
Creatinine (mg/dL)	1.13±0.4 1.0 (0.72-0.99)	1.02±0.5 1.0 (0.8-1.00)	0.769
TyG index	8.95±0.56 9.00 (8.55-9.30)	8.52±0.53 8.61 (8.25-9.16)	**0.003**

HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; TyG index: triglyceride-glucose index

Table 2. Univariate logistic regression for prediction of mild-to-moderate, moderate and severe disease

	P value	OR	95% CI
Age	**<0.001**	1.168	1.098-1.231
Total cholesterol	**<0.001**	1.027	1.013-1.043
LDL-C	**<0.001**	1.045	1.014-1.039
TyG index	**<0.001**	1.829	1.012-3.281

LDL-C: low density lipoprotein-cholesterol; TyG index; triglyceride-glucose index

Discussion

Our study has shown that the TyG index is an independent predictor for the presence of ED. Moreover, it had a negative correlation with IIEF-5 scores, with higher values indicating lower IIEF-5 scores. Besides TyG index, parameters of age, TC, and LDL-C were predictors for ED.

Although the HOMA-IR index is widely used in clinical practice, its calculation is based on the measurement of glucose and insulin concentrations. In contrast, the TyG index is calculated as the natural logarithm of the product of fasting plasma glucose and and TG concentrations, both of which can be easily measured and evaluated [14]. Studies have shown that the TyG index is a valuable tool for measuring IR, making it a good alternative to the HOMA-IR index [15,16].

Previous studies evaluated the role of IR in ED and found that IR was associated with ED. Chen et al. demonstrated that insulin resistance correlated with the severity of ED. In that study, patients who had IR had decreased testosterone concentrations and deteriorated endothelial functions emphasizing the pathophysiological link between IR and ED [17]. Similarly, Rey-Valzacchi et al. showed that the addition of metformin treatment to sildenafil decreased the IR and ameliorated the ED in patients with IR [18]. Yilmaz et al. investigated the value of the TyG index in ED patients and found that the cut-off value of 8.88 for the TyG index predicted ED with sensitivity and specificity of 67% and 68.8%, respectively [19]. Li et al. evaluated National Health and Nutrition Examination Survey database to expose the link between the TyG index and ED in general population. They found that the prevalence of ED was increased in subjects who had higher TyG indexes [20]. IR is considered a predictor of prediabetes, and progression to diabetes is associated with the atherosclerotic process [17]. It has been shown that patients with IR had increased levels of sympathetic activity, endothelin-1 concentration, oxidative stress, inflammatory activity, and impaired endothelial function; all of which are thought to play a role in ED [21,22]. Our study was in line with the aforementioned studies in that we also detected higher TyG indexes in ED patients supporting the role of IR in the pathogenesis of ED. In our study, cut-off value of 9.03 for TyG index had 70.3% sensitivity and 65% specificity in predicting the presence of ED. In our study, no patient had a history of ischemic heart disease and all of them had negative treadmill exercise tests.

Although no patient in the current study had a history of ischemic heart disease and cardiovascular risk factors, patients with ED had unfavorable metabolic profiles including increased levels of LDL-C, TC, glucose, triglyceride concentrations, and TyG index values, all of which have been shown to be related to endothelial dysfunction [23]. Patients with ED were older, however, age-adjusted TyG indexes have remained at a higher level in ED patients.

As the limitations of the sudy; our study was a single-center, retrospective study and the sample size was relatively small.

Long-term follow-up of the patients was not done and the effect of lifestyle and medical interventions on TyG index and ED was not assessed.

Conclusion

TyG index, an easily calculable and effective method for assessing IR, had a predictive role in patients with ED. It could be used in clinical practice to evaluate the cardiovascular status of ED patients.

Ethics Committee Approval: The protocol of the present study was reviewed and approved by the Institutional Review Board of University of Health Sciences Dr. Sadi Konuk Training and Research Hospital (date: 06.03.2023, decision #: 2023-05-15).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
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Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.O., C.Y., H. P.; Design – E.O., C.Y., H. P.; Supervision – E.O., C.Y., H. P.; Resources – A. K., D. K., M. P.; Materials – A. K., D. K., M. P.; Data Collection and/or Processing – A. K., D. K., M. P.; Analysis and/or Interpretation – E.O., C.Y., H. P.; Literature Search – A. K., D. K., M. P.; Writing Manuscript – E.O., C.Y., F. N. T. C.; Critical Review – E.O., C.Y., F. N. T. C., H. P.
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Comparison of Pre-COVID-19, COVID-19, and Post-COVID-19 Urinalysis Parameters and Assessment of Their Relationships with Renal Functions

Pre-COVID-19, COVID-19 ve Post-COVID-19 Ürinanaliz Parametrelerinin Karşılaştırılması ve Böbrek Fonksiyonları ile İlişkilerinin Değerlendirilmesi

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Abstract

Objective: This study compared the pre-COVID-19, COVID-19, and post-COVID-19 periods of the patients in terms of urinalysis parameters and assessed the relationships between the changes in these parameters and renal functions.

Materials and Methods: Four-hundred-eighty-two moderate and severe COVID-19 patients who had the data of urinalysis performed in the pre-COVID-19 period at most three months before the onset of COVID-19 diagnosis, during COVID-19 disease, and 15 days after they completely recovered from the COVID-19 disease were included in the study. Parameters of bilirubin, erythrocyte, leukocyte, protein, glucose, acidity (pH), and density were analyzed in urine samples, and the results were recorded.

Results: CRP, e-GFR, fibrinogen and D-dimer values were found to be significantly different between the three groups (for all parameters $p<0.05$). A negative correlation was found between e-GFR and both CRP ($p<0.001$, r:-0.289) and D-dimer (p:0.02, r:-0.129) values of the patients during COVID-19. Urine pH, presence of leukocyturia, presence of microscopic hematuria and presence of proteinuria were found to be significantly different between the three groups (for all parameters $p<0.05$). It was determined that these four parameters increased significantly during the COVID-19 period and decreased in the post-COVID-19 period. A negative correlation between urine density and e-GFR (p:0.04, r:-0.175) and a positive (p:0.02, r:0.195) correlation between urine density and CRP were detected during COVID-19.

Conclusion: The significant presence of hematuria and proteinuria during COVID-19 disease in line with the literature data supports the opinion that the disease causes renal involvement. The tendency of the parameters on the post-COVID 15th day to return to normal ranges shows that the effects of the inflammation are reversible after the patients recover from the disease.

Keywords: COVID-19, e-GFR, hematuria, proteinuria, urinalysis

Öz

Amaç: Bu çalışmada hastaların Pre-COVID-19, COVID-19 ve Post-COVID-19 dönemlerinde idrar parametrelerinin karşılaştırılması ve bu değişimin böbrek fonksiyonları ile ilişkisi değerlendirilmiştir.

Gereçler ve Yöntemler: Pre-COVID-19 dönemde 3 ay öncesine kadar, COVID-19 hastalık döneminde ve COVID-19 hastalığından tamamen iyileştikten 15 gün sonra ürinanaliz yapılmış olan 482 orta ve şiddetli COVID-19 hastası çalışmaya dahil edilmiştir. İdrar örneklerinde bilirubin, eritrosit, lökosit, protein, glukoz, asidite (pH) ve dansite parametreleri incelendi ve sonuçlar kaydedildi.

Bulgular: CRP, e-GFR, fibrinojen ve D-dimer değerleri üç grup arasında anlamlı olarak farklı bulundu (tüm parametreler için $p<0,05$). COVID-19 döneminde e-GFR'nin CRP ($p<0.001$, r:-0,289) ve D-dimer (p:0.02, r:-0,129) ile negatif korelasyona sahip olduğu bulundu. İdrar pH'ı, lökositüri varlığı, mikroskobik hematüri varlığı ve proteinüri varlığı üç grup arasında anlamlı olarak farklı bulundu (tüm parametreler için $p<0.05$). Bu dört parametrenin de COVID-19 döneminde anlamlı artış gösterdiği, post-COVID-19 dönemde de azalma gösterdiği saptandı. COVID-19 döneminde idrar dansitesinin e-GFR ile negatif (p:0.04, r:-0,175) CRP ile pozitif (p:0.02, r:0,195) korelasyona sahip olduğu tespit edildi.

Sonuçlar: Literatür verileri ile uyumlu olarak COVID-19 hastalığı sırasında anlamlı hematüri ve proteinüri varlığı, hastalığın böbrek tutulumuna neden olduğu görüşünü desteklemektedir. Post-COVID-19 15. günde ölçülen parametrelerinin normale dönme eğilimi göstermesi enfeksiyon dönemi geçtikten sonra inflamasyonun etkilerinin geri dönüşümlü olabileceğini göstermektedir.

Anahtar kelimeler: COVID-19, e-GFR, hematüri, proteinüri, ürinanaliz

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Introduction

Coronaviruses mainly cause respiratory tract infections and gastrointestinal infections in humans [1]. World Health Organization (WHO) named the infectious pneumonia disease caused by SARS-CoV-2 virus as coronavirus disease 2019 (COVID-19) [2]. Hypoxia, dyspnea, acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure can also be seen in severe and critically ill COVID-19 cases [3]. But most of the SARS-CoV-2 cases remain asymptomatic after vaccination [4]. Many studies revealed that urinary system involvement is prevalent in patients infected with SARS-COV-2. Only limited number of studies showing a correlation between urinary biochemical parameters and SARS-COV-2 are available in the literature [5,6].

Urinalysis covers quick, economical, useful, and noninvasive tests which provide detailed information on urine. These data can aid in the diagnosis of many diseases including urinary tract infections and can also be used in the monitorization of the outcomes of the treatment used for these diseases [7,8].

The effects of SARS-CoV-2 on urinary biochemical parameters were analyzed through comparing patient and control groups or based on the severity of the disease in previous studies but no research has yet been made both on the effect and change in urinary parameters in periods before, during, and 15 days after recovery from COVID-19 disease and also on the relationship between the change in these parameters and renal function tests and inflammatory markers. This study compared the parameters of urinalysis in periods before, during, and after recovery from pre-COVID-19 disease, and assessed the relationships between the changes in these parameters and renal functions.

Material and Methods

The protocol of the study was approved by the Institutional Ethics Committee of Necmettin Erbakan University (NEU: 2020/2835). Nine hundred ninety-seven patients hospitalized due to COVID-19 disease between January 2020 and January 2022 were evaluated. Demographic data and comorbid conditions of the patients were recorded. Four hundred eighty-two moderate and severe COVID-19 inpatients who complied with the inclusion criteria and had the data of urinalysis performed in a maximum of three months before the diagnosis of COVID-19 disease, during the course of COVID-19 disease, on the 1st day of hospitalization, and on the 15th day of their discharge were included in the study.

RT-PCR-positive oropharyngeal and nasopharyngeal swabs prepared for the detection of SARS-CoV-2 infection revaled the diagnosis of COVID-19. Following the diagnosis of Sars-Cov-2 infection, 15-30 mL clean, middle-flow urine samples were collected for the patients. After the recovery, once the first negative RT-PCR result of these patients was obtained, urinalysis was re-taken on the post-discharge 15th day. Urine samples were drawn from the urinary catheters of the critically ill patients. Urinary parameters of bilirubin, erythrocyte, protein, glucose, acidity (pH), and urine density were analyzed semi-quantitatively on Dirui- H800 FUS-2000 (Dirui Industrial Co. Ltd., China) urine biochemical analysis device, digital imaging and automatic particle definition method microscopically and the results were recorded.

Peripheral venous blood samples (5 mL) were drawn into serum separator tubes (Vacuette, Greiner Bio-One, Kremsmuenster, Austria) in the morning between 9:00 am and 10:00 am after 8 hours of fasting. Serum samples were set aside for 30 to 60 minutes to allow the formation of clots prior to centrifugation at 1500G for 10 minutes at room temperature. Results of routine biochemical, hematological, and urine analyzes were obtained by reviewing patients' records. Hematological analyses were performed using XN-1000 Sysmex (Sysmex Corporation, Kobe, Japan) hematology analyzer. All biochemical parameters were analyzed using Abbott kits (Abbott Laboratories, Chicago, IL, USA), which are manufactured for use with an Architect c16000 Auto-Analyzer.

Exclusion Criteria

Patients with underlying chronic diseases such as hypertension, diabetes mellitus, chronic heart failure, patients with urinary system oncological and stone disease, mild COVID-19 that did not require hospitalization, and critically ill COVID-19 patients that required intensive care unit care were excluded from the study.

Statistical Analysis

The data were encrypted and entered SPSS (Version 23) software (IBM, SPSS Inc., Chicago, Illinois, USA). The categorical values of the patients were expressed as numbers and percentages and analyzed with a chi-square test. Continuous variables were presented as mean and standard deviation (SD). Friedman and Cochrane Q-tests were used for the statistical analysis of the three groups. $P < 0.05$ was considered statistically significant.

Results

Mean age of 482 patients included in the study was 51.1 ± 20 years and 54% of the patients were male. A significant difference was found among the three groups in terms of hematological parameters of e-GFR, CRP, fibrinogen, and D-dimer values. (For all parameters: $p<0.05$). There was no difference among the three groups regarding the remaining hematological parameters. In the post-COVID-19 period of the patients, renal function tests such as eGFR, creatinine, and urea had turned back to their baseline values. Details of demographic and hematological parameters are available in **Table 1**. In the correlation analysis a negative correlation was found between e-GFR and both CRP ($p<0.001$, r:-0.289 and D-dimer (p:0.02, r:-0.129) during the course of the COVID-19 disease (**Figure 1**).

Urinalysis parameters of pH value, leukocyturia, microscopic hematuria, and proteinuria differed among the three groups (for all parameters $p<0.05$). These three parameters had a significant increase during the COVID-19 disease and decreased in the post-COVID-19 period. No difference was detected between other urinalysis parameters. Details of urinalysis parameters are available in **Table 2**. The correlation analysis showed a negative correlation between urine density and eGFR (p:0.04, r:-0.175), and a positive (p:0.02, r:0.195) correlation between urine density and CRP (**Figure 2**).

Table 1. Details of pre-COVID-19, COVID-19, and post-COVID-19 15th day demographical and hematological parameters

Parameters n=482	Pre-COVID	COVID	Post-COVID 15th day	P
Demographical parameters				
Age (year) mean ± SD	51.1 ± 20			-
Sex M/F %	54 /46			-
Hematological parameters				
e-GFR (mean± SD)	92.1 ± 33.2	88.69 ± 33.5	90 ± 37.7	**0.03**
Urea (mean± SD)	33.9 ± 21.9	46.9 ± 50	41.08 ± 30.4	0.39
Creatinin (mean± SD)	1.17 ± 0.5	1.36 ± 1.37	1.1 ± 0.3	0.8
CRP (mean± SD)	23 ± 67	69 ± 89	35 ± 57	**0.001**
Fibrinogen (mean± SD)	290 ± 140	373 ± 219	335 ± 151	**<0.001**
D-dimer (mean± SD)	287 ± 600	655 ± 2180	452 ± 798	**<0.001**
Uric acid (mean ± SD)	6.1 ± 3.4	5 ± 1.9	5.5 ± 2.7	0.15
Sodium (mean± SD)	138.4 ± 3.4	138.1 ± 5.2	138.2 ± 5.6	0.06
Potassium (mean± SD)	4.4 ± 0.5	4.32 ± 0.6	4.2 ± 0.7	0.32
Calcium (mean± SD)	9.1 ± 1.2	9.01 ± 0.7	9 ± 1.04	0.2
LDH (mean± SD)	235 ± 112	259 ± 218	250 ± 196	0.31
CPK (mean± SD)	88 ± 61	122 ± 195	85 ± 73	0.7

eGFR: estimated glomerular filtration rate; SD: standard deviation; CRP: C- reactive protein; LDH: lactate dehydrogenase; CPK: creatine phosphokinase

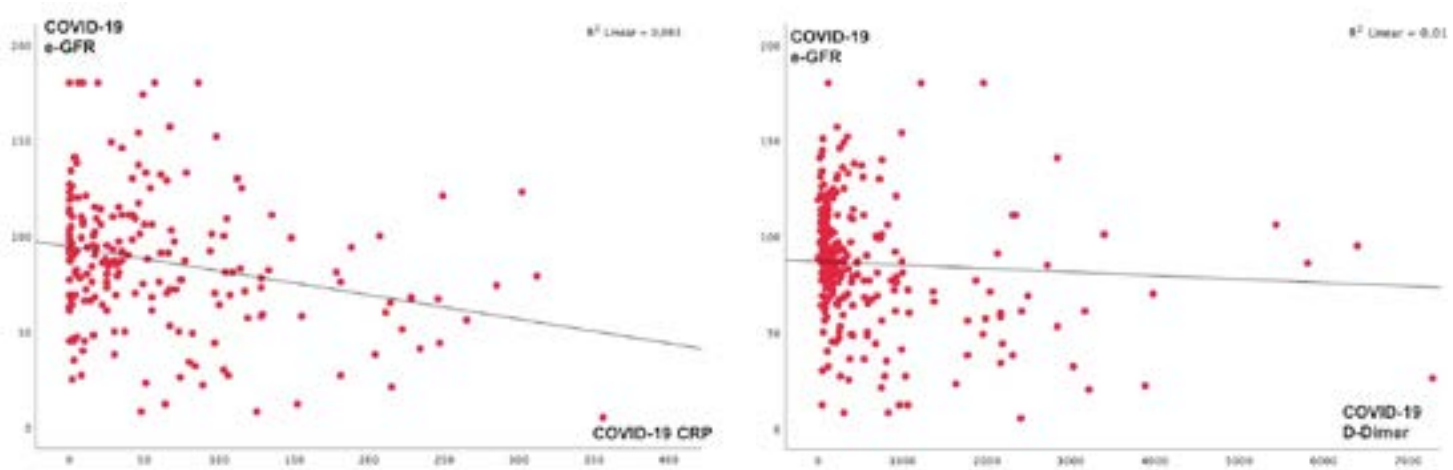

Figure 1. Correlation analysis of e-GFR with CRP and D-dimer

Table 2. Details of pre-COVID-19, COVID-19, and post-COVID-19 15th day urinalysis parameters

	Pre-COVID	COVID	Post-COVID 15th day	P
Urine density (mean± SD)	1016.61 ± 8.4	1017.02 ± 48.7	1015.1 ± 6.4	0.15
Urine pH (mean± SD)	5.88 ± 1.2	6.04 ± 1	6.2 ± 0.7	**0.04**
Urine bacterial microscopy (Number of cells) (mean ±SD)	1.97 (0-10)	2.04 (0-25)	2 (0-20)	0.58
Urine leukocyte microscopy (Number of cells) (mean ±SD)	3.77 (0-5)	9.67 (0-664)	7.67 (0-365)	**0.04**
Urine erythrocyte microscopy (Number of cells) (mean ±SD)	3.15 (0-5)	29.83 (0-488)	7.75 (0-388)	**0.01**
Bilirubinuria + %	5.6	1.5	0.5	0.36
Proteinuria + %	2.2	3.3	0.7	**0.01**
Glucoseuria + %	6.8	8.8	5.6	0.44

SD: sandard deviation

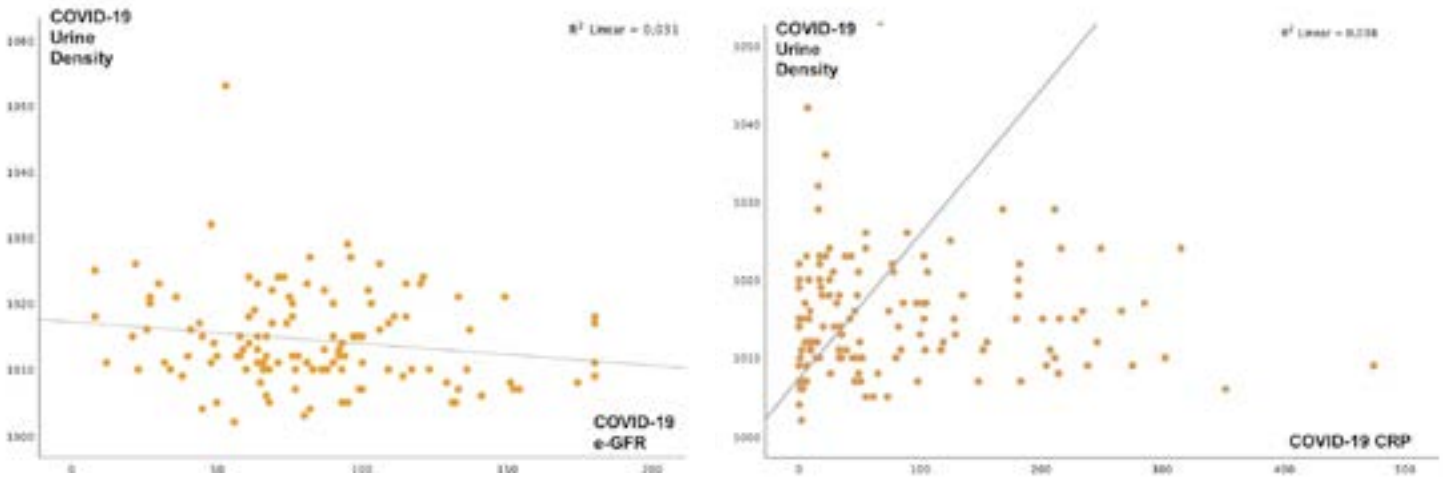

Figure 2. Correlation analysis of urine density with e-GFR and CRP

Discussion

Urine biochemical parameters can be used for the diagnosis of urinary tract infections, and other systemic diseases, and in the follow-up of treatment effects. Urinalysis can reveal these parameters and is also extremely useful as it provides easy sampling, cost efficiency, and quick results [8].

A limited number of studies in the literature have shown the relationship between COVID-19 and urinary parameters. Current studies were conducted through the comparison of Sars-COV-2 positive and negative patients. Our study stands unique as it shows the changes in urine biochemistry in patients before the diagnosis of COVID-19 disease, during, and after recovery from this epidemic. Liu et al. reported higher urine protein, pH values, and erythrocyte counts, but lower urine density in the COVID-19 group compared to the control group [9]. Another study reported kidney involvement in 75% of COVID-19 patients, and 65.8% of these patients had proteinuria and 41.7% had hematuria [10]. Murgod et al. detected a higher rate of hematuria and proteinuria in COVID-19 patients compared to healthy controls and a significant increase in both parameters as the severity of the infection increased [6]. Demirelli et al. assessed 120 COVID-19 patients, and categorized these patients based on the severity of the disease. Respective percentages of these patients had glucosuria (6.7%), proteinuria (13.4%), urobilinogen positivity (5.8%), leukocyturia (8.3%), and hematuria (9.2%) [11].

In our study patients, we detected a significant increase in the rates of proteinuria, hematuria, and leukocyte counts during COVID-19 disease compared to the pre-COVID-19 period and a significant decrease in these parameters after recovery from the disease ($p<0.05$, for all parameters). Additionally, urine pH levels increased in the COVID-19, and post-COVID-19 periods of the patients. As reported in the studies, we think that the presence of proteinuria and hematuria in our study is related to renal involvement in COVID-19. Contrarily, the detection of leukocyturia associated with COVID-19 can be related to the worsening of infection or the change of bladder flora due to the medications used in hospitalized patients.

Pei et al. reported that proteinuria and microscopic hematuria were more significant in critically ill COVID-19 patients and acute kidney injury was seen at a rate of 42% among these patients while at a rate of 4.5% in the COVID-19 population in general [10]. Bonetti et al. studied the urine samples of 226 patients admitted to the emergency department and proteinuria, and microscopic hematuria were detected in 89%, and 72% of the patients, respectively. They reported that high urea and creatinine values were related to increased mortality rates and analysis of urine sediment was regarded as a useful prognostic test [5]. In their logistic regression analysis, Morell-Garcia et al. reported that among urinalysis parameters microscopic hematuria was a risk factor for acute kidney injury (AKI), intensive care requirement, and mortality [12]. Yıldırım et al. reported the presence of AKI in 4.5% of COVID-19 patients and rates of proteinuria and hematuria were 64% and 64% vs 4.8% and 43% in patients with and without AKI, respectively. Additionally, significantly higher creatinine, CRP, fibrinogen, and D-dimer levels were detected in AKI patients [13].

In this study, we aimed to statistically evaluate the change in kidney function tests in our patients during, and after recovery from the COVID-19 disease. As a matter of fact, it was determined that creatinine values increased and eGFR values decreased (1.17 ± 0.5 vs 1.36 ± 1.37, 92.1 ± 33.2 vs 88.69 ± 33.5 respectively) during COVID-19 disease compared to the pre-COVID-19 period. Although creatinine elevation occurred in most of the patients, this increase could not be described as evidence of renal failure. As a matter of fact, it has been determined that the results of kidney function tests such as eGFR, creatinine, and urea tend to return to pre-COVID-19 values after recovery from this disease. While urea, creatinine, and eGFR levels tend to decrease during COVID-19 disease, they tend to normalize in the post-COVID-19 period, but the change is significant only for eGFR ($p:0.03$). Although these findings support the claim that COVID-19 negatively affects renal function, our data has shown lack of any permanent change that can cause permanent kidney failure. This study has also showed a negative correlation between levels of some markers of inflammation including eGFR, CRP, and D-dimer ($p<0.001$, $p=0.02$ respectively). These findings have indicated that the severity of infection and inflammation may aggravate the adverse effects on kidney functions. Additionally, urine density during COVID-19 disease had a negative correlation with eGFR and a positive correlation with CRP. This fact can be an indicator of the relationship between infection and urine parameters.

Failure to analyze urinary sediment, urine creatinine, and electrolyte values and non-categorization of the severity of COVID-19 disease in our patients are the main limitations of this study.

Conclusion

This study detected a significant decrease in eGFR, and increase in infection parameters of CRP and D-dimer during the COVID-19 disease. Thus, attention should be paid to kidney failure during the COVID-19 disease, especially in patients with critical kidney function test results and it should be emphasized that the condition may get more severe due to the severity of the infection. The significant presence of hematuria and proteinuria during the COVID-19 disease supports the idea that the disease also affects kidneys in line with the literature data. The tendency of the parameters to return to their normal ranges 15 days after recovery from COVID-19 disease indicates that the effects of the inflammation are reversible after the resolution of the infection. Highly detailed studies including greater number of subgroups investigating changes in urinary findings for a longer period should be conducted.

Ethics Committee Approval: All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Consent according to the Helsinski declaration was taken from local ethics committee before the study (NEU: 2020/2835; date: 27.01.2021; decision #: 88).
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Case Report – Pediatric Urology

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Diphallus: A Rare Urological Anomaly - What to Do Next? Case Report and Literature Review

Difallus: Nadir Bir Ürolojik Anomali - Sırada Ne Yapılmalı? Olgu Sunumu ve Literatür İncelemesi

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Abstract

Diphallus is a very rare congenital anomaly usually accompanied by various congenital anomalies and can be classified according to the anatomical structure in which the anomaly develops. Generally, in cases with diphallus, the surgical approach is preferred, in that, the hypoplastic structure has been excised for esthetic and functional purposes and penile reconstruction is performed. In addition, urethroplasty has been also performed in the presence of any accompanying urethral abnormality. In the current case, we report a two-year-old boy who was diagnosed as having glandular diphallus.

Keywords: diphallus, diphallia, penile duplication, genitourinary anomaly, glans penis, reconstructive surgery

Öz

Difallus oldukça nadir rastlanılan konjenital bir anomalidir. Genellikle çeşitli konjenital anomalilerin eşlik ettiği difallus, anomalinin geliştiği anatomik yapıya göre sınıflandırılabilmektedir. Literatür incelendiğinde, genellikle cerrahi yaklaşım tercih edilen difallusta, estetik ve fonksiyonel amaçlarla hipoplastik yapının eksize edilerek penil rekonstrüksiyon işlemi uygulandığı, eşlik eden üretral anomali varlığında üretroplasti uygulandığı görüldü. Bu vaka sunumunda genitoüriner sistem muayenesi sonrası glans penisle sınırlı difallus tanısı koyulan 2 yaşındaki erkek çocuk sunulmaktadır.

Anahtar kelimeler: difallus, difalya, penis dublikasyonu, genitoüriner anomali, glans penis, rekonstrüktif cerrahi

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Introduction

Diphallus, which is also known as diphallia, is a very rare congenital anomaly encountered nearly one in 5.5 million population. Since the first case was presented by Wecker in 1609, only 120 cases have been reported in the literature so far [1]. Vast majority of cases with diphallus were accompanied by various congenital anomalies mainly genitourinary and anorectal malformations [1,2]. Diphallus can be classified as glandular diphallus, bifid diphallus, and complete diphallia according to the anatomical structure involved [2]. During the 12th week of the fetal development, a circular part originated from ectoderm is seen at the periphery of the glans penis, which gives rise to prepuce (foreskin), a skin part which covers the glans. The corpus cavernosum and corpus spongiosum of the penis develop from the mesenchyme in the phallus. Bilateral labioscrotal swellings elongate toward each other and fuse in the midline to form the scrotum. The fusion site is seen as scrotal raphe [3]. Bilateral urethral folds fuse in the midline to form the corpus spongiosum and cavernous urethra between the 12th and 14th weeks of the fetal development. It is estimated that a fusion defect in genital tubercle during the fetal development period results in the condition termed diphallia [4]. Surgical treatment involves penile reconstruction and restoration of accompanying malformations after excision of the hypoplastic structure, however, the number of patients who have undergone surgical interventions is relatively low. In our case report, we aimed to present a patient with glandular diphallus and the follow-up process.

Case

Urethral meatus was observed during the genitourinary examination of a two-year-old male patient without any complaint, who was admitted to the urology clinic by his parents for circumcision. The penile skin could not be retracted, and glans was wider than the normal size for his age, a finding which suggested the presence of a congenital genitourinary abnormality. Foreskin was retracted using a mosquito forceps **(Figure 1)**. While the corpus penis was single, the glans was distally separated from the midline and a glandular diphallus was observed. Mea was observed in distal parts of both glandes. The patient had been followed up for one year after birth with the diagnosis of patent foramen ovale. Apart from this, no additional pathological finding was detected in physical examination of the patient. In urinary USG examination, both kidneys were normal, bladder contours were smooth, and bladder wall thickness was within normal limits. Both meatuses were catheterized and cystourethrography was planned. A 6F feeding catheter was advanced through the right glans, however it could be inserted through the left glans only 2 cm. In the imaging performed a 1:1 diluted contrast fluid injected through the right meatus moved along the penile structure, reaching and filling the bladder. We have tried to inject the contrast material through the catheter that could be advanced distally only 2 cm through the mea of the left glans, but we failed due to an overwhelming resistance. The feeding tube was withdrawn, and the procedure was repeated, however the contrast material could not be injected further **(Figure 2)**.

We have concluded that the proximal part of the meatus was obliterated. Cavernosography could not be performed, because this infant was not able to cooperate. In physical examination, a connection was found between the glans and the corpus cavernosum. Multidisciplinary approach is very important for the cases with genitourinary abnormalities. For this reason, we have requested additional second opinions from plastic surgery and child psychiatry departments. Due to the complication risks of surgical procedures performed on glans penis and the very young age of the patient, we have decided to plan the operation in the following years upon the consent of the family.

Figure 1. Bifid glans after foreskin retraction

Figure 2. Cystourethrography performed after catheterization of both urethras with 6f feeding catheter

Discussion

Diphallus is a very rare anomaly that can be encountered associated with many other congenital malformations. Embryologically, a diphallus deformity can occur in two forms as pubic symphysis diastasis in which each phallus has the same set of corpora cavernosa and urethras, or cleavage of the pubic tubercle, in which each phallus has a unique set of corpora cavernosa and urethras. Diphallus has been classified in several types. Most cases of diphallus have the same corpora cavernosa in each penis [1,2]. It is important to perform a comprehensive examination in terms of congenital malformations that may present at the same time. It has been mentioned in various case reports that patients might have accompanying colon and bone anomalies, particularly genitourinary and anogenital anomalies [1,5]. Magnetic resonance imaging (MRI) could be performed instead of cavernosography to check the status of corpus cavernosum and external genitalia. But it could also be a challenging procedure considering relatively younger age of the patients and cooperation problems [6]. Multidisciplinary approach has a crucial importance for all cases with genitourinary abnormalities because of psychological impact of this condition on the patient, family, and quality of life in general. Parents should be informed about the process in detail, and should be included in the treatment process. A PubMed search was conducted with "diphallia" and "diphallus". Although 400 years

Table 1. A literature review of preoperative and postoperative datas of diphallus

	Age	Diphallus type	Associated anomaly	Methods of surgery
V. Deshpande- 2020	2 years	-Complete	-Bifid scrotum	-Phalloplasty, Scrotoplasty
Kundal et al- 2013	3 years	-Complete	-Hypospadias	-Phalloplasty, Urethroplasty
A. Tepeler et al- 2007	14 years	-Complete	-Bifid scrotum	-Phalloplasty, Scrotoplasty
Mirshemirani et al- 2010	2 days	-Complete	-Imperforate anus + colon, Bladder duplication, Hypospadias, Bifid scrotum	-Colostomy, Cystoplasty, Urethroplasty, Phalloplasty, Scrotoplasty, Colon resection + anastomosis
	4 years	-Complete	-Bladder duplication, Inguinal hernia	-Cysto-urethroplasty, Phalloplasty, Hernia repair
	12 years	-Complete	-Single kidney, Bifid scrotum, Hemi-vertebra, Bladder exstrophy	-Bladder extrophy repair, Ceco-vesical augmentation, Mitrofanoff
	1 year	-Complete	-Bladder duplication, Bifid scrotum	-Phalloplasty, Scrotoplasty, Cystoplasty
	14 years	-Bifid phallus	-Bifid scrotum, Hypospadias	-Phalloplasty, Scrotoplasty
	9 months	-Complete	-Bifid scrotum, Imperforate anus	-Colostomy, Phalloplasty, Scrotoplasty, PSARP
Elsawy et al- 2012	37 days	-Complete	-Inguinal hernia	-Phalloplasty + Penile anastomosis
Dunn et al- 2019	3 years	-Complete	-Bifid scrotum -Bladder duplication	-Phalloplasty, Scrotoplasty, Cystoplasty
Tirtayasa et al- 2013	12 years	-Complete	-Bifid scrotum	-Phalloplasty, Scrotoplasty
Karagözlü Akgül et al- 2018	4 years	-Complete	-Rectovesical fistula, Bladder duplication, Anal atresia, Colon and Rectum duplication	-Urethroplasty, Phalloplasty, Abdominoperineal pull-through, Colon resection
Zhang et al- 2020	23 years	-Pseudodiphallia	-	-Phalloplasty

have passed since the first case report and about 120 cases have been reported in the publications, there is still not enough information about the surgical procedure to be applied in most of them. After review of the literature, case reports with sufficient preoperative and postoperative data are summarized in **Table 1**.

Many studies apparently have not longer follow-up periods. In a comprehensive study with six cases Mirshemirani et al., stated that additional anomalies were observed in all cases that required additional surgical procedures [1]. In case reports presented by Deshpande [7], Kundal [8], and Tepeler [2], Elsawy [9], Dunn [10], Tirtayasa [11], and Karagözlü Akgül [12], phalloplasty plus scrotoplasty was performed for the correction of an additional anomaly. In only one case presented by Zhang [13], any additional anomaly was not reported. There is not enough information about the long-term complication rates of the surgical procedures performed for accompanying urethral malformations, and there is also no clear data on the effect of surgical procedures on the improvement of erectile dysfunction, which is associated with the congenital defects of corpus cavernosum. More comprehensive and prospective studies with longer follow-up periods are needed to get more insight into diphallus and other associated conditions.

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Case Report – Urological Oncology

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Everolimus Treatment and Selective Artery Embolization Application in a Case of Tuberous Sclerosis-Related Bilateral Renal Angiomyolipoma

Tüberoskleroz İlişkili Bilateral Renal Anjiyomiyolipom Olgusunda Everolimus Tedavisi ve Selektif Arter Embolizasyonu Uygulaması

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Abstract

Angiomyolipomas are the most common benign mesenchymal tumors of the kidney. Although they are often seen sporadically, they can also be observed as a part of the tuberous sclerosis complex (TSC). They occur at an earlier age in cases associated with tuberous sclerosis (TS), bilateral mass and epithelioid formation. There are various treatment approaches such as active surveillance, nephron-sparing surgery, nephrectomy, angioembolization, and use of mammalian target of rapamycin (mTor) inhibitors. Our case was a patient with bilateral multiple renal angiomyolipomas associated with TS. We applied mTOR inhibitor and angioembolization therapy to this patient. In our article, we tried to evaluate our success rate in our treatment and the treatment regimens to be applied in these patients.

Keywords: angiomyolipoma, tuberous sclerosis, everolimus

Öz

Anjiyomyolipomlar böbreğin en sık görülen iyi huylu mezenkimal tümörleridir. Sıklıkla sporadik olarak görülse de tüberoskleroz kompleksinin (TSC) bir parçası olarak da görülebilir. Tüberoskleroz (TS) ilişkili olgularda daha erken yaşta, bilateral kitle ve epiteloid formasyonda karşımıza çıkar. Aktif izlem, nefron koruyucu cerrahi, nefrektomi, anjiyoembolizasyon, rapamisinin memeli hedef (mTOR) inhibitörleri gibi çeşitli tedavi yaklaşımları vardır. Bizim olgumuz tüberoskleroz ile ilişkili bilateral multiple renal anjiyomiyolipomları olan bir hasta idi. Bu hastaya tedavi olarak mTOR inhibitörü ve anjiyoembolizasyon tedavisi uyguladık. Yazımızda tedavimizdeki başarı durumumuzu ve bu hastalarda uygulanacak tedavi rejimlerini yorumlamaya çalıştık.

Anahtar kelimeler: anjiyomiyolipom, tüberoskleroz, everolimus

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Introduction

Angiomyolipomas (AMLs) are the most common benign mesenchymal tumors of the kidney, mainly composed of smooth muscle, dysmorphic vessels and mature adipose tissue, causing regional complications. They are responsible for 1-3% of kidney tumors with an incidence of 0.3-3% in general population and a female-to-male ratio of 2:1 [1]. Fifty to seventy percent of the cases consist of sporadic renal AMLs, characterized by a smaller size (average 1-4 cm), slower growth rate (0.19 cm/year), unilateral presentation, and an average age at disease onset ranging between 43 and 53 years at the time of diagnosis [2,3]. The remaining 30-50% of the cases are associated with genetic syndromes such as sporadic lymphangioleiomyomatosis (LAM) and tuberous sclerosis complex (TSC) [3]. The latter is due to an autosomal dominant mutation of the TSC1 (9q34) or TSC2 (16q13.3) genes, with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway, associated with a multisystemic disease, greater number of lesions, higher growth rate (1.25 cm/year), lower mean age at diagnosis (18 years), and development of considerable complications during follow-up [4].

Factors determining the necessity and type of treatment include the presence of symptoms, an aneurysm >5 mm in the mass, the size of the lesion, its association with a disease complex (TS and LAM), kidney reserve, pregnancy plan, patient compliance, occupation, and activity status. Most (82-94%) of the patients with a mass lesion larger than 4 cm are symptomatic and 50-60% of them may bleed at any time. Major risk factors for bleeding are tumor size, grade of angiogenic component, and synchronous presence of TS [5,6].

Although selective arterial embolization is effective in controlling bleeding in emergency situations, research on its effectiveness in long-term treatment continues [7]. In addition to surgical and embolization treatment options, studies are continuing on drug treatments using mTOR inhibitors, which are thought to play a role in the pathogenesis, especially in the treatment of multiple, unresectable or metastatic AMLs accompanying disease complexes such as TS or LAM. The aim of our study is to evaluate the treatment with everolimus and selective arterial embolization, and subsequent follow-up period of a patient who applied to our clinic, and received the diagnosis of renal AML.

Case

A 38-year-old female patient was admitted to the outpatient clinic due to bilateral flank pain. In the physical examination of the patient, a mass lesion was palpated on the right side of the flank. She was not tachycardic, and her respiratory function test results were within normal limits. The patient had hypopigmented macules widely spread on her face and body, fibromas on her face, without any history of epileptic seizures. Laboratory test results, and hemoglobin levels were within normal limits. She had no hematuria. Histopathological examination of biopsy specimen obtained from the fibromatoid skin lesion revealed the presence of an angiofibroma. No pathological finding was found in brain MRI. The patient received the diagnosis of TS, with bilateral AMLs detected on computed tomography **(Figure 1).**

Since as a result of an aggressive surgical approach of bilateral nephrectomy, the patient may remain anephric, we decided to use less invasive methods by communicating to the patient. In order to reduce the size of bilateral renal masses, mTOR inhibitor (everolimus) treatment was started. To ease the patient's tolerance, treatment was started at daily doses of 5 mg, and then continued with 10 mg everolimus. The treatment was continued for 1 year, and stopped after the decrease in the size of the mass slowed down in the follow-up **(Figure 2)**. Bilateral selective angioembolization was decided because the mass enlarged by 20% as detected in the imaging performed 3 months after the drug was discontinued. Everolimus treatment combined with embolization was started because of the rapid growth tendency of the mass after everolimus treatment was stopped. The patient's recurrent pain decreased after the procedure, and the character of the mass changed as detected on imaging **(Figure 3)**. The drug treatment was continued for 1 more year and then stopped. The mass lesions of the patient did not enlarge during the follow-up period of nearly 18 months, and she is still being monitored every 6 months.

Despite development of complications of everolimus treatment such as oral aphthous lesions and dyspeptic complaints, the patient did not discontinue the treatment. No secondary infections were observed after everolimus treatment. During the follow-up period of the patient, her hemoglobin levels did not decrease, and any signs of bleeding were not observed in the imaging tests performed.

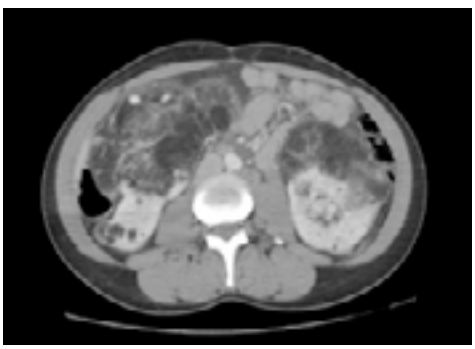

Figure 1. Ct scan image at the time of diagnosis

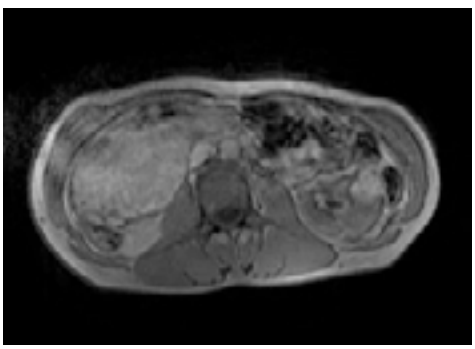

Figure 2. MR image 3 months after treatment with mTOR inhibitor

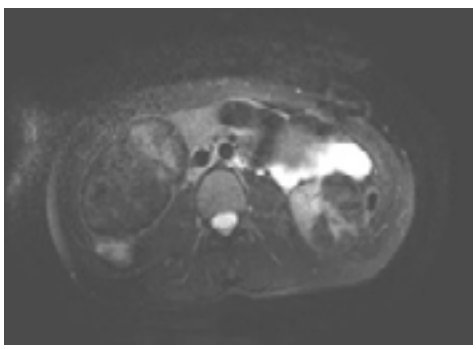

Figure 3. MR image 1 month after arterial embolization

Discussion

AMLs are usually asymptomatic, but they may also present with mass, flank pain, and hematuria, most commonly related to the size of the lesions, and sometimes accompanied with bleeding into the retroperitoneal region. Patients have symptoms such as palpable abdominal mass, hematuria, flank pain (Lenck's triad), and mass lesions may reach large sizes, disrupting the kidney structure and leading to hypertension, renal failure and even death. Tumors with a size of 4 cm and above carry the risk of spontaneous bleeding because of their abnormal vascularity and aneurysmal structures. Symptoms develop in 68-80% of the patients with masses larger than 4 cm, bleeding episodes are observed in approximately 50-60%, and hypovolemic shock develops in 1/3 of the patients presenting with potentially life-threatening hemorrhage. The most important risk factors for bleeding are the size of the tumor, the grade of the vascular component, and the presence of TS. The risk of spontaneous bleeding is observed in 13%, and 51% of the cases with mass lesions measuring <4 and >4 cm, respectively [8].

Although the majority of AMLs are benign, a small number of them may have an aggressive behavior pattern and may cause local invasion. The mass lesions are histologically classified in classical and epithelioid types. Most of the sporadic ones are of the classical type. Epithelioid AML is a rare variant of AML with a tendency to malignant transformation and is mostly associated with the TSC. It is considered a locally aggressive tumor. Epithelioid AMLs can be confused with renal cell carcinoma due to the absence of adipose tissue and the presence of pleomorphic epithelioid cells.

In cases with TS, pathognomonic skin lesions, neurological findings and clinical findings may be associated with the involvement of other organs. Although the natural history of renal AML is not clearly understood, it is known that the number and size of renal AMLs increase with age. Tumors in patients with TS and multiple AMLs grow larger compared to those with isolated lesions [9]. It has been stated that AML cases associated with TS should be closely monitored because of the possibility of their being bilateral, multifocal, and gradual enlargement over time [7]. The goal of treating symptomatic AML is to preserve nephrons and kidney function. Therefore, selective arterial embolization, laparoscopic or open partial nephrectomy, open or laparoscopic cryoablation or radiofrequency ablation should be the priorly preferred treatment modalities, only in case of absolute necessity total nephrectomy should be performed [6]. Although effective treatment is provided by total nephrectomy in large or hemorrhagic masses, nephron-sparing partial nephrectomy is usually an option [10]. In addition, preoperative selective arterial embolization is an option that facilitates surgery in cases of acute bleeding or in the presence of large masses. As a minimally invasive procedure our patient with bilateral renal masses received combined treatment with everolimus and arterial embolization to refrain from the adverse effects of bilateral surgical procedure such as relevant complications and renal dysfunction. Reduction in the size of the mass observed in the follow-up of the patient, also reduced the risk of bleeding.

The European Association of Urology (EAU) guidelines indicate that the most appropriate approach for AML would be active surveillance. Selective arterial embolization is recommended as first-line therapy if active monitoring will no longer be performed. If surgical treatment is to be preferred, the guidelines suggested that many patients can be managed with nephron-sparing surgery, and that some patients require radical nephrectomy. In addition, it is stated that tumor volume can be reduced with mTOR inhibitors (everolimus and sirolimus) and surgery can be delayed with this treatment [1].

The mTOR regulates cell proliferation, autophagy, and apoptosis by participating in multiple signaling pathways in the body. The mTOR signaling pathway, which is often activated in tumors, not only regulates gene transcription and protein synthesis so as to modulate cell proliferation and immune cell differentiation but also plays an important role in tumor metabolism. Therefore, the mTOR signaling pathway is a hot target in anti-tumor therapy research. In recent years, a variety of newly discovered mTOR inhibitors have entered clinical trials, and a variety of drugs have been proven to have higher efficacy in combination with mTOR inhibitors [11].

In a study examining 524 patients who underwent transarterial embolization with the diagnosis of AML, self-limiting postembolization syndrome developed in 35.9% of the patients without any case of mortality. A 38.3% reduction in tumor size (mean 3.4 cm) was detected in an average follow-up period of 39 months after embolization. During the follow-up period, 20.9% of patients required unplanned repeat embolization or surgery. Reasons for reinterventions included: AML revascularization (30%), unchanged or increasing tumor size (22.6%), persistent or recurrent symptoms (16.7%), and acute retroperitoneal hemorrhage (14.3%) [12]. In our patient, while the largest diameter of the mass was 11.5 cm after everolimus treatment, it decreased to 7.5 cm after angioembolization and reoperation was not required.

Although everolimus treatment continues to be used at the conventional dose (10mg), lower doses have been used in some studies. In the study of patients with TS-related AML, Hatano et al. compared treatment with daily doses of 5 mg and 10 mg, and any difference was not seen in the efficacy of the treatment, while less treatment-related side effects were observed in the 5 mg group [13].

There is no definite information about the duration of everolimus treatment, some studies have claimed that intermittent treatment may be more successful in reducing side effects. Hatano et al. had observed that the side effects were observed less frequently when the treatment was started again. In this study with ongoing follow-up, retreatment was not required in 31% of the patients, because lack of growth in the size of the mass, although 1.5 years had passed after the treatment was discontinued [14]. We have observed that our patient could more easily tolerate retreatment. The conditions for stopping and restarting treatment vary in studies, and large series of patient groups are needed to ensure standardization of the retreatment protocol.

Conclusion

Treatment is mostly required for symptomatic, large, multifocal, bilateral masses that are associated with TS and tend to enlarge with age. In the selection of the treatment method, care should be taken to protect the kidney functions to the maximum extent. Combined treatment with everolimus and selective arterial embolization can be used as minimally invasive treatment method, but close follow-up is important, keeping in mind that re-angioembolization may be required due to the growth tendency of the mass

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Giant Penile Fibroepithelial Polyps
Dev Penil Fibroepitelyal Polipler

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Introduction

Patients with penile lesions often delay seeking medical consultation, leading to advanced presentation of penile malignancies and extensive lesions. The main challenge in diagnosing these lesions is distinguishing between benign and malignant conditions, which cannot be defined on clinical evaluation only. The main concern is diagnosing squamous cell carcinoma and its variants. Benign lesions, such as fibroepithelial polyps, are rare and a diagnosis of exclusion.

Fibroepithelial polyps arise from the mesoderm. They can occur anywhere on the skin, more frequently in the groin, axilla, and eyelids. In the urological setting, they are more commonly found in the ureter. There are few reported cases of penile presentation, with the polyps typically appearing on the glans and associated with poor hygiene or urinary catheter use. The possibility of recurrence or malignant transformation has been reported inconsistently in the literature [1,2].

We present a case with a florid manifestation of fibroepithelial polyps.

Case

A 62-year-old man with no relevant medical history presented to the emergency department with symptoms of a urinary tract infection (UTI). During the physical examination, the physician noticed two large masses on the patient's penis, that the patient had not referred to **(Figure 1).** When questioned, he responded that the lesions appeared in the previous year and had gradually increased in size, but they did not cause any pain or discomfort. The lesions were remarkably clean, with no signs of infection or ulceration. One of the masses involved the urethral meatus **(Figure 2),** but did not apparently obstruct urine flow. No other urethral lesions were visible. Laboratory testing revealed any significant biochemical abnormalities besides leukocyturia.

The patient was started on a cephalosporin for the UTI and referred to urology department for an excisional biopsy, to exclude a malignancy or a giant condyloma (Buschke–Löwenstein tumor). The surgery was performed under general anesthesia and the masses were fully excised, circumcision and meatoplasty were performed with resultant favorable cosmetic

Figure 1. Penile lesions

Figure 2. Penile lesion arising from the urethral meatus

Figure 3. Appearance after surgical excision

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outcome **(Figure 3).** The urinary catheter was left in situ for a week and any postoperative complications were not observed.

The histopathological examination of the biopsy specimen revealed benign fibroepithelial polyps without any association with human papillomavirus. The histopathological examination results were reported as: hyperplastic, hyperkeratotic, malpighian tubules lined with polypoid formations without koilocytes or dysplasia; underlying connective tissue proliferation with interlacing collagenous bands in an edematous matrix, characterized with discrete mononuclear inflammatory reinforcement. The largest lesion measured 9 cm in length. One month after surgery, there was residual edema, but there were no recurrences after 6 months of follow-up.

Conclusion

Timely excision of penile lesions is mandatory to exclude malignancy, but benign histology is a possibility despite exuberant manifestations. Upon a diagnosis of fibroepithelial polyps, surveillance should focus on clinical examination to exclude recurrence. If it occurs, repeat excision is feasible.

Keywords: penile neoplasms, fibroepithelial neoplasms, phalloplasty

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