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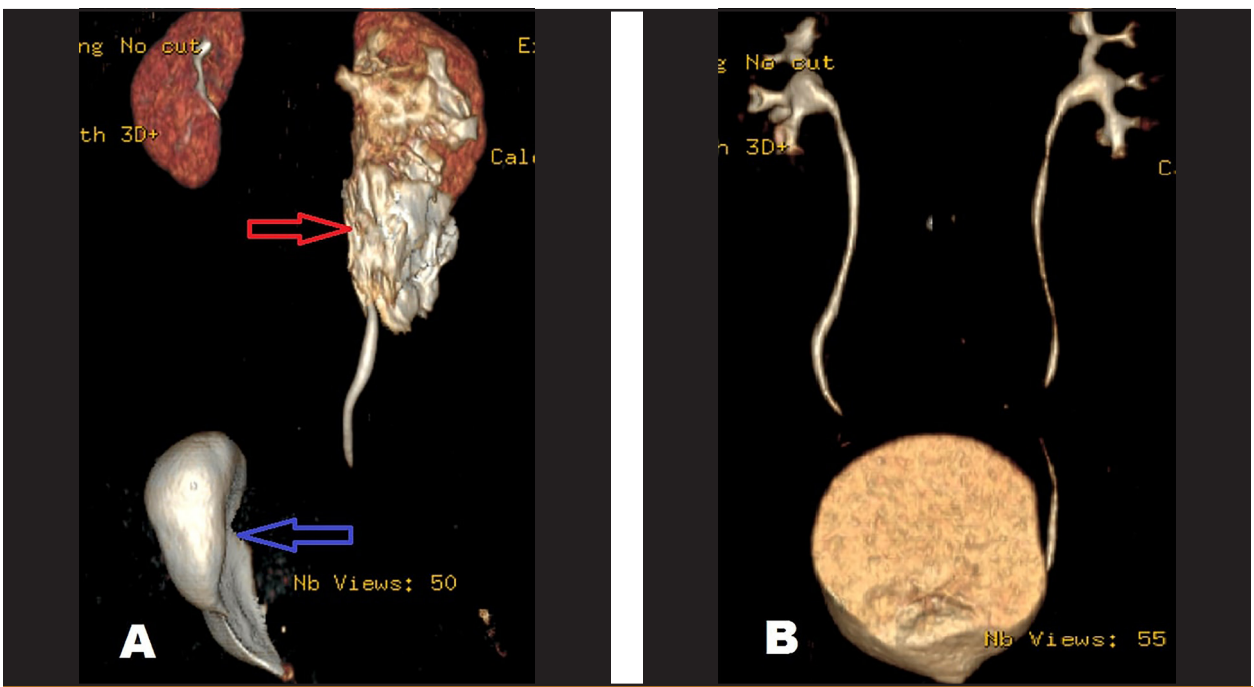

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Dear Colleagues,

We are pleased to have published the secend issue of The New Journal of Urology for 2022. This issue includes 4 original articles, 2 case reports and 2 review. Published articles consist of andrology, endourology, transplantation, general urology, pediatric urology and urooncology. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies.

The New Urology Journal has been indexed in the TUBİTAK-ULAKBİM TR Index since the first issue of 2011. The indexing process of our journal in ESCI, Pubmed and EMBASE continues. Our goal is to increase the visibility of our journal both nationally and internationally with articles of high scientific quality and to become one of the most read urology journals. We would like to inform you that as of 2021 only articles in English will be considered for publication.

The editorial team is very grateful to all the authors and reviewers who have contributed to this issue. We are aware that this is a painstaking effort, and we cannot thank you enough for it.

We request that you submit your articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Respectfully yours.

Ali İhsan TAŞÇI
Editor-in-Chief

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CONTENTS

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Original Research / Özgün Araştırma

Micro V Doppler assessment of testicular blood supply in the pediatric age population: may reduce the need for senior guidance in the evaluation of prepubertal torsion

Pediatrik yaş popülasyonunda testiküler kan akımının mikro V Doppler ile değerlendirilmesi: prepubertal torsiyonun değerlendirilmesinde kıdemli rehberlik ihtiyacını azaltabilir

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Özet

Amaç: Pediatrik popülasyonda testis vaskülaritesini MicroV Doppler (MVD) ve Q pack incelemesi ile değerlendirdik ve deneyimsiz ile kıdemli radyologlar arasındaki interobserver variabiliteyi inceledik. Ayrıca çocuklarda testis kanlanmasını göstermede MVD ve Q pack incelemesini renkli ve power Doppler ile karşılaştırdık.

Gereç ve Yöntemler: Çalışmaya 114 testis (4-14 yaş arası) dahil edildi. Testis mikrodamar yapısı renk, power, MicroV Doppler ve Q-pack inceleme teknikleri kullanılarak incelendi. Testis parankiminin vaskülaritesini görsel olarak puanlamak için renk, Power ve MicroV Doppler için bir gruplama sistemi oluşturuldu.

Bulgular: Çalışmamızda tüm çocuklarda MVD ile testis kan akımının varlığını doğruladık. Renkli, power Doppler ve MVD'de gözlemciler arasında anlamlı bir fark olmadığını ve MVD'de tutarlılık değerinin renkli ve power Doppler'e göre daha yüksek olduğunu bulduk. Q-pack değerleri ile hasta yaşı arasında anlamlı bir pozitif korelasyon gözlemledik. Bu çalışmadan elde edilen Q-pac değerleri yaşla birlikte arttı. İstatistiksel olarak anlamlı yanlılığın olmaması, yöntemin yararlı olduğunu gösterir.

Sonuç: MVD, gözlemciler arası önemli bir değişkenlik olmaması ve çalışma hayatının ilk yıllarında daha az deneyimli radyologlar için prepubertal torsiyon gibi akut skrotal patolojileri

Abstract

Objective: We evaluated the testis vascularity in pediatric population with MicroV Doppler (MVD) and Q pack examination and to detect differences between a limited experience and a experienced senior radiologists. The inter-observer agreement in MVD and Q pack examination is evaluated. We also compared MVD and Q pack examination with color and power Doppler in demonstrating testicular blood supply in children.

Material and Methods: 114 testis (between the ages of 4-14) were included in the study. Testicular microvessel structure was examined by using color, power, MicroV Doppler and Q-pack examination techniques. A grouping system was created for color, Power and MicroV Doppler to score the vascularity of the testicular parenchyma visually.

Results: In our study, we confirmed the presence of testicular blood flow with MVD in all children. We found that there was no significant difference between the observers in color, power Doppler and MVD and the consistency value was higher in MVD compared to color and power Doppler. We observed a significant positive correlation between Q-pack values and patient age. Q-pac values obtained from this study increased with age. The lack of statistically significant bias indicates that the method is useful.

Conclusion: MVD is a reproducible method since there is no significant interobserver vari-

The study was approved by Ethical Committee of Bağcılar Training and Research Hospital (Approval No: 2020.01.1.09.009). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

kolaylıkla tespit edebilmesi nedeniyle tekrarlanabilir bir yöntemdir. Böylece çocuklarda acil vakaların değerlendirilmesinde radyoloji asistanına eşlik eden kıdemli rehberliğe duyulan ihtiyaç azalabilir.

Anahtar Kelimeler: mikro V doppler, testis, kan akışı

ability and can easily detect acute scrotal pathologies such as prepubertal torsion for the less experienced radiologists in the early years of working life. Thus, the need for senior guidance accompanying radiology resident in the evaluation of emergency cases in children may decrease.

Keywords: blood supply, micro V doppler, pediatric age population

INTRODUCTION

Ultrasonography (US) and classical Doppler methods are among the most important diagnostic tools in the evaluation of the acute scrotum in the pediatric population (1). It is quite difficult to evaluate blood flow since testicles are small and flow rates are low in children (2, 3). In a significant proportion of healthy children in the pediatric age group, blood flow can not be monitored by classical methods in the testicles. In the testis with torsion, grayscale findings of parenchyma and the reactive increase in the scrotal fluid may not always be observed especially in the early period (4). Unfortunately, conventional methods such as color and power Doppler are insufficient in demonstrating testicular blood flow in the pediatric population, especially in small children. In cases such as the acute scrotum, it is important to evaluate the testicular blood supply quickly and accurately. Currently, the gold standard analysis for testicular blood flow is the color-power Doppler examination (2, 5, 6).

MicroV Doppler ultrasound is a newly developed noninvasive Doppler technique that qualitatively reveals the slow flow dynamics of small vascular structures (7). Conventional Doppler US methods detect small vessel flow as an artifact and therefore it can not demonstrate the slow flow of the microvessels effectively (7).

Recently, several researchers reported exploring testis vascularity in children by using microvascular imaging techniques. However, there is no study investigating the reliability and reproducibility of Micro V Doppler and Q pack in pediatric patients. Micro V Doppler can visualize the vascularity of microvessels within small organs. However, there is no data available about the interobserver agreement of this method and whether there is any change in the results obtained after the examination of an experienced radiologist (8).

In this prospective study, we evaluated the testis vascularity in the pediatric population with MicroV Doppler US and Q pack examination. And we aimed to detect differences between limited experienced and experienced senior radiologists. The inter-observer agreement in MicroV Doppler US and Q pack examination was evaluated. We also compared MicroV Doppler US and Q pack examination with color and power Doppler in demonstrating testicular blood supply in children.

MATERIAL AND METHODS

General Data

Fifty-seven boys with varying ages from 5 to 15 who applied to the outpatient clinic between 01.07.2019 and 01.12.2019 and were referred to our department with the request for scrotal Doppler ultrasound were included in the study. Our inclusion criteria for boys aged 3-14 years-old, are pre-pubertal and obtaining an informed consent form from their parents. Ethical approval was obtained from the scientific research ethics committee of our hospital (Approval number: 2020.01.1.09.009). Our exclusion criteria were being older than 14 years of age, having a history of previous testicular surgery, a history of undescended testicles, and the patient's mental disability.

Micro V Doppler and Q Pack Examination

Testicular microvessel structure was examined by using color, power, and MicroV Doppler ultrasound techniques. Ultrasonographic examinations were begun with color and power Doppler ultrasonography (Esaote MyLab 9, Genoa, Italy) using 12–5 MHz broadband linear array probes. After color and power Doppler, Micro V Doppler and Q pack examination were performed. During the examinations, care was

taken to ensure that probe frequencies and other imaging parameters (general 2D optimization, persistence, etc.) were the same for each patient. The color setting, speed, and filter setings were selected to provide maximum Doppler sensitivity and Doppler angle was kept at between 30-60 degrees. During the Micro V Doppler examination, the scale was 1.5-2.5 cm/s, the mechanical index was 1.5, the wall filter was 50-100 Hz, and the frame rate was>50 Hz. A grouping system was created for color, power, and MicroV Doppler to score the vascularity of the testicular parenchyma visually. Accordingly, Group 1, was determined as testis parenchyma with no blood supply. In group 2, vascularization is detected only within the hilus. Group 3 has moderate vascularization on both testicular hilum and parenchyma. Group 4 was determined as testis with significant vascularization within both testicular hilum and parenchyma. The vascularity of the testis was scored by examining with color, power, and micro V Doppler US.

On Q-pack examination, quantitative values expressing the vascularity numerically were measured from testicular parenchyma. The vascularity was quantitatively measured within the area by placing ROI in the specific region (Region Of Interest) that we will select during the Doppler examination. Three different measurements were taken from the testicular hilum, 1/3 superior, and 1/3 lower part of the testis. Then the average of these 3 measurements was calculated, and the mean value for the testis parenchyma was created.

Image Evaluation

The observers were blinded to patient history and previous ultrasonography. Patients were evaluated by two radiologists with 6 years of experience (M.K) and 6 months of experienced (S. Ş.) in the field of microvascular imaging. Color, power, micro V Doppler and Q pack examinations of testis were first independently assessed by the two radiologists. Parenchymal vascularization was scored according to our grouping system. In the power analysis performed with the G * power 3.1 program related to our study, the effect size for Flow grades SMI in Testicular Masses was determined as 0.54 (Superb microvascular imaging for the detection of parenchymal perfusion in normal and undescended testes in young children) (alpha error probability = 0.05); The total number of samples required to be taken was found to be 38 in the sample size analysis performed with the power value of 0.80.

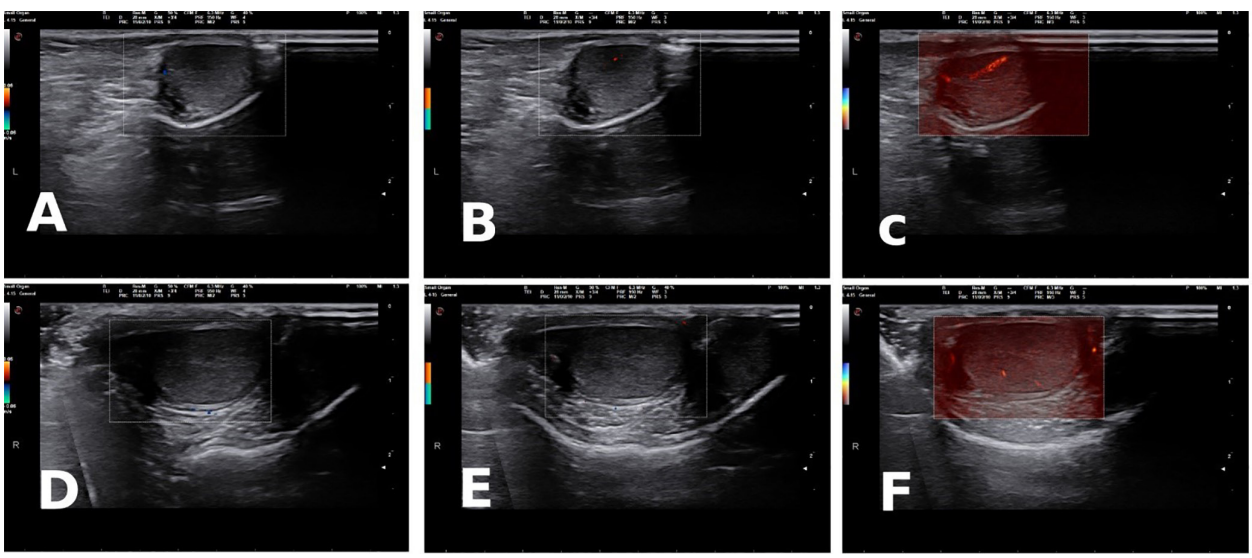

Figure 1. On the color Doppler, power Doppler and MicroV Doppler examination of a 6-year-old boy: vascularization of left testis was grade 0 on color Doppler (A), grade 0 was on power Doppler (B), grade 2 was on micro V Doppler (C). Vascularization of right testis was grade 0 on color Doppler (D), grade 1 was on power Doppler (E), grade 2 was on micro V Doppler (F) according to observer 1. Micro V Doppler imaging was more accurately showed microvascular structure of testis.

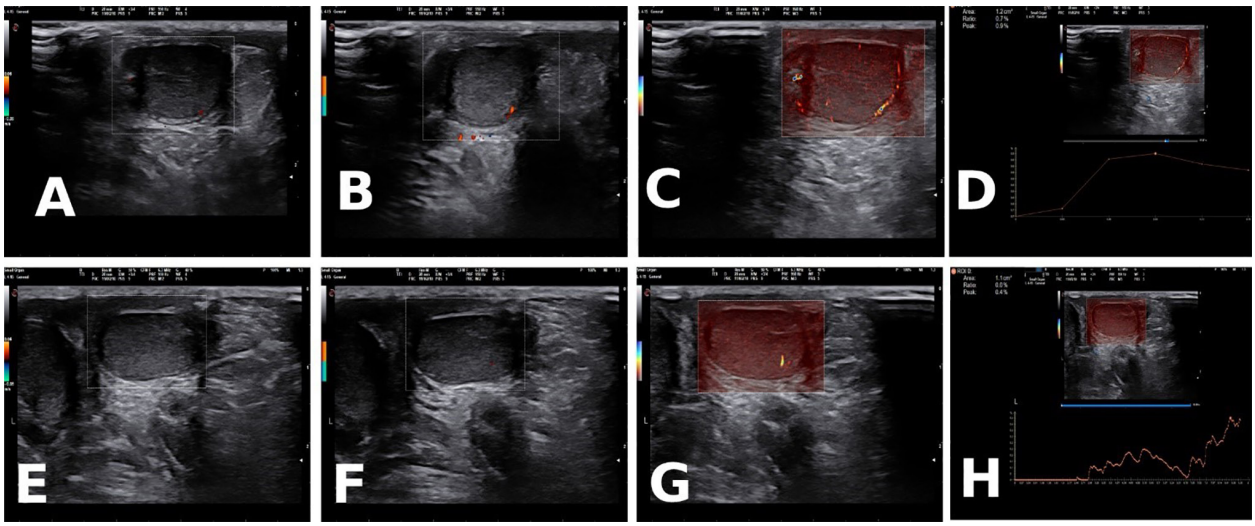

Figure 2. On the color Doppler, power Doppler and MicroV Doppler examination of a 9-year-old boy: vascularization of right testis was grade 1 on color Doppler (A), grade 1 was on power Doppler (B), grade 3 was on micro V Doppler (C). Q pack analysis and quantitative peak value is seen as 0.9 % (D), Vascularization of left testis was grade 0 on color Doppler (E), grade 1 was on power Doppler (F), grade 2 was on micro V Doppler (G) Q pack analysis and quantitative peak value is seen as 0.4 % (H), according to observer 1.

Table 1. Interobserver agreement in right testis color Doppler examination

Color Doppler US findings of right testis	1.Observer		2.Observer		P (Ki square)	Kappa
Group 1	15	26,3%	18	31,6%	0.139	0.812
Group 2	24	42,1%	27	47,4%		
Group 3	15	26,3%	9	15,8%		
Group 4	3	5,3%	3	5,3%		

Ki square test Kappa test

Table 2. Interobserver agreement in left testis color Doppler examination

Color Doppler US findings of left testis	1.Observer		2.Observer		P (Ki square)	Kappa
Group 1	15	26.3%	15	26.3%	0.153	0.809
Group 2	24	42.1%	30	52.6%		
Group 3	9	15.8%	6	10.5%		
Group 4	9	15.8%	6	10.5%		

Ki square test Kappa test

Table 3. Power Doppler US findings of right testis

Power Doppler US findings of right testis	1.Observer		2.Observer		P (Ki square)	Kappa
Group 1	3	5.3%	0	0	0.215	0.825
Group 2	21	36.8%	30	52.6%		
Group 3	21	36.8%	21	36.8%		
Group 4	12	21.1%	6	10.5%		

Ki square test Kappa test

Table 4. Left testis Power Doppler US findings

Power Doppler US findings of left testis	1.Observer		2.Observer		P (Ki square)	Kappa
Group 1	3	5.3%	6	10.5%	0.318	0.832
Group 2	24	42.1%	12	21.1%		
Group 3	21	36.8%	33	57.9%		
Group 4	9	15.8%	6	10.5%		

Table 5. Right testis Micro V Doppler US findings

Right testis Micro V Doppler US findings	1.Observer		2.Observer		P (Ki square)	Kappa
Group 1	0	0	0	0	0.315	0.936
Group 2	0	0	0	0		
Group 3	33	57.9%	30	52.6%		
Group 4	24	42.1%	27	47.4%		

Ki square test Kappa test

Tablo 6. Left testis Micro V Doppler US findings

Left testis Micro V Doppler US findings	1.Observer		2.Observer		P (Ki square)	Kappa
Group 1	0	0	0	0	0.593	0.942
Group 2	0	0	0	0		
Group 3	18	31.6%	16	28.1%		
Group 4	39	68.4%	41	71.9%		

Ki square test Kappa test

Table 7. Correlation analysis between right and left testicular Qpack values and patient ages

		Right testicle Qpack Observer 1	Left testicle Qpack Observer 1	Right testicle Qpack Observer 2	Left testicle Qpack Observer 2	Age
Right testicle Qpack Observer 1 value	rho	1	0.930**	0.659**	0.604**	0.857**
	p		0.000	0.000	0.000	0.000
Left testicle Qpack Observer 1 value	rho	0.930**	1	0.678**	0.677**	0.868**
	p	0.000		0.000	0.000	0.000
Right testicle Qpack Observer 2 value	rho	0.659**	0.678**	1	0.850**	0.786**
	p	0.000	0.000		0.000	0.000
Left testicle Qpack Observer 2 value	rho	0.604**	0.677**	0.850**	1	0.724**
	p	0.000	0.000	0.000		0.000
Age	rho	0.857**	0.868**	0.786**	0.724**	1
	p	0.000	0000	0.000	0.000	

Spearman correlation analysis

Statistical Evaluation

In this study, statistical analyzes is performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In the evaluation of data, in addition to descriptive statistical methods (mean, standard deviation, frequency, and percentage distributions), Shapiro - Wilk normality test will be used to examine the distribution of variables. Independent t-test will be used for comparing normally distributed variables in binary groups, Mann Whitney U test for comparison of variables that do not show normal distribution between binary groups, and chi-square test for comparison of qualitative data. Logistic Regression analysis will be performed to determine the factors affecting the presence of malignancy. The intra-and inter-observer compatibility will be determined by the weighted kappa test, and between power and Micro V Doppler, sensitivity, specificity, positive predictive value, negative predictive value, and test accuracy will be calculated. A p-value less than 0.05 is considered as significant.

RESULTS

A total of 114 testicles were examined in the study. The mean age was 8.7 ± 3.7. Right and left testicular blood flows of each child were evaluated by two radiology physicians with color, power and Micro V Doppler. The agreement value for both observers is shown as the kappa (k) value. Table 2 shows the right testis color Doppler results. There was no statistically significant difference between the results of both observers (between the experienced and inexperienced observers). The agreement between observers was significantly higher (p= 0.139, k: 0.812) (Table 1).

Table 2 shows color doppler results of left testicles evaluated. There was no statistically significant difference between the results of both observers. Interobserver agreement was significantly higher (p= 0.153, k: 0.809) (Table 2). Table 3 shows right testis power Doppler US results. There was no statistically significant difference between the results of both observers. Interobserver agreement was significantly higher (p= 0.215, k: 0.825) (Table 3). Left testis power Doppler US findings are shown in Table 4. There was no statistically significant difference between the results of both observers. Interobserver agreement was significantly higher (p= 0.318, k: 0.832) (Table 4). On the color Doppler examination; no blood flow signal was observed within the parenchyma in 26.3% of the right testes for the first observer, and 31.6% for the second observer. No vascularization detected in 28.9% of all cases. Equally, no blood flow signal was observed within the parenchyma in 26.3% of the left testes for both observers. On the power Doppler examination; no blood flow signal was observed within the parenchyma in 5.3% of the right testes for the first observer, vascularization is detected all of the cases for the second observer. When all cases were evaluated jointly, it was seen that there was no flow in 2.6% of the right testes. On the power Doppler examination; no blood flow signal was observed within the parenchyma in 5.3% of the right testes for the first observer, and 10.5% for the second observer. There was no blood flow visualized in 7.9% overall of the cases. Right testis Micro V Doppler findings are demonsrated in Table 5. There was no statistically significant difference between the results of both observers.Inter-observer agreement was significantly higher (p= 0.315, k: 0.936) (Table 5).

The left testis Micro V Doppler findings are shown in Table 6. There was no statistically significant difference between the results of both observers. Inter-observer agreement was significantly higher (p= 0.593, k: 0.946) (Table 6). Table 7 shows correlation analysis between right and left testis Q pack values and patient ages. All Q pack correlations were highly significant for both observers. A significant correlation was observed between patient age and Q pack values ($p < 0.05$) (Table 7). In our study, we confirmed the presence of testicular blood flow with Micro V Doppler in all children. We observed that an average of 28.9% of the blood flow in the right testis and 26.3% of the left testis could not be observed with color Doppler, and it was dependent on age. We determined that blood flow could not be observed with power Doppler in 2.6% of cases, and this was dependent on age. We found that there was no significant difference between the observers in color, power Doppler, and Micro V Doppler methods, and the consistency value was highest in Micro V Doppler

method compared to power and color Doppler method, respectively. We observed a significant positive correlation between Q-pack values and patient age.

DISCUSSION

The acute scrotum is seen most frequently in two different periods of life. Although the reasons are different, newborns and children aged 12-18 are the most common periods for acute scrotum (9-11). The most common clinical findings are scrotal swelling, pain, edema, and redness. However, it is difficult to reach a differential diagnosis since they are seen in almost every acute scrotum clinic (12). Although surgical exploration is a valid method independent of etiology in acute abdominal surgery, unfortunately, this is not the case in acute scrotum pathologies. In the past, emergency surgical exploration was performed especially in pediatric cases with suspicion of testicular torsion, but it was revealed that 60-85% of them were unnecessary surgery (13). In addition to clinical diagnosis difficulties, it creates the need for imaging techniques. In the studies in the literature; False-positive results were obtained with Doppler US in 38% of boys aged between 10 weeks and 13 years (14). The high rate of false positivity in the pediatric population with conventional methods has increased the need for new technological US methods.

Micro V Doppler is a newly developed Doppler imaging method used to detect blood flow, especially within the microvascular structures. In color or power Doppler techniques, the inability to receive the signals from the microvascular network is due to the need for blood flow above a certain speed. In the Micro V Doppler technique, blood flow signals of microvascular structures can be preserved even at a very low speed. Micro V Doppler is a new Doppler imaging method used to detect blood flow in microvascular structures. This new Doppler technique eliminates the complexity of signals from normal tissue and vascular structures and preserves only the signals obtained from vascular structures so that even very low-velocity blood flows can be detected. Micro V Doppler provides detailed information about very slow and very thin vascular structures and allows the visualization of microvascular structures (15). Tao et al. (16) demonstrated the effectiveness of microvascular imaging techniques in retinal pathologies. Ohno et al. (17) stated that Micro V Doppler may be effective in hepatobiliary pathologies. Arslan et al. (18) showed that microimaging Doppler gives correct findings in proportion to cancer diagnosis in breast cancer cases. It can be seen that Micro V Doppler technology will gain importance in any pathology involving the vascular network of microvascular structures. In our study, we investigated whether we could detect testicular blood flow with Micro V Doppler technology, the effectiveness of this technique according to color and power Doppler and whether there is a difference between operators. Thus, in our study, we found that blood flows that could not be detected by color or power Doppler in the testicular parenchyma could be revealed by examining the microvascular circulation with Micro V Doppler in the pediatric population. We observed that there was a significant observer agreement in all Doppler US types including Micro V Doppler, and there was no significant difference for both observers.

The lack of statistically significant bias indicates that the method is useful and suitable for establishing detecting testicular blood flow in the pediatric population with Micro V Doppler. Our study revealed that Micro V Doppler is a reproducible method since there is no significant interobserver variability. The observer agreement also demonstrated that both the experienced and less experienced radiologists had a higher agreement in detecting testicular blood flow in children. Our study shows that it is a method that can easily detect acute scrotal pathologies such as prepubertal torsion for the less experienced radiologists in the early years of working life. Thus, we think that the need for senior guidance accompanying radiology residents in the evaluation of emergency cases in children may decrease. As it is almost a perfect interobserver agreement; years of experience are not necessary any more thanks to microvascular imaging methods.

There was no blood flow in 28.9% of the right testicles and 26.3% of the left testicles in children on the color Doppler. In our study, blood flow could not be detected in 2.6% of the left testicles with power Doppler. Testicular flow visibility on Doppler methods can

be change with the age (20). Since the flow is slower in early childhood, false-negative results are more frequent (21). In our study, it was observed that all children whose color and power Doppler flow could not be detected were between the ages of 5 and 6. Kalfa et al. report that we can accurately distinguish children with testicular torsion and healthy blood flow from each other with Micro V Doppler technology. In our prospective study, right and left testicular blood flows measured by Micro V Doppler method were positive in all cases among both observers. Thus, we think that the newly developed Doppler methods with a high frame rate can show the slow blood flow in all cases in the pediatric population. Lee et al. reported that finer vascular structures could be demonstrated more accurately by using the higher frame rate Doppler method in undescended testis. Karaca et al evaluated testicular flow with power, color, and Micro V Doppler and found that the most powerful method was Micro V Doppler (22). Ayaz et al. reported that blood flow that could not be traced in color and power Doppler can be easily demonstrated with Micro V Doppler in a study evaluating testicular blood flow of newborns (23). Durmaz et al. stated that Micro V Doppler is the most powerful method in testicular flow in children and that it gives clearer information compared to power and color Doppler (24). In another study, they stated that the best imaging and interobserver agreement rates were with Micro V Doppler rather than conventional Doppler methods in the pediatric population (25). In our study, we observed that Micro V Doppler was the most powerful method following the literature, and unlike other studies, the rate of detecting blood flow in the testicle with microvascular imaging methods was 100%.

Evaluation of the presence or absence of testicular flow is of course the most important step in scrotal pathologies. Ingram et al (19). reported that color Doppler in healthy children observed that there was no testicular blood flow in 38% of the cases. In another study, they stated that blood flow was not observed in 12% of the cases in color Doppler and power Doppler examination, while this rate was much lower in power Doppler. In our study, the Q pack software allows us to obtain quantitative values about the vascularity of this area by placing ROI in the area we want to examine specifically in the tissue we evaluate with Doppler US. In our study, the Q Pack values were examined for the first time in the literature. According to our findings, Q-pack values show a strong correlation with age. Due to the lack of any studies in the literature with Q-pack, further studies will be necessary with larger sample scale.

Our study had some limitations, first, we had a small sample size. We also did not evaluate patients with torsion.

CONCLUSION

In conclusion; we observed that the Micro V Doppler examination is more effective than classical Doppler examinations in the slow flow of small organs. Therefore, in patients with suspected prepubertal testicular torsion, the use of Micro V Doppler examination alone or in combination with classical Doppler methods will give more accurate results. It was determined that the testicular parenchyma Q pack values obtained from this study increased with age, and we think that it can be used as a reference value in future studies since there are no studies on this subject in the current literature. The lack of statistically significant bias indicates that the method is useful and suitable for establishing detecting testicular blood flow in the pediatric population with Micro V Doppler. Our study revealed that Micro V Doppler is a reproducible method since there is no significant interobserver variability and can easily detect acute scrotal pathologies such as prepubertal torsion for the less experienced radiologists in the early years of working life. Thus, we think that the need for senior guidance accompanying radiology residents in the evaluation of emergency cases in children may decrease. As it is almost a perfect interobserver agreement; years of experience are not necessary any more thanks to microvascular imaging methods.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethical Committee of Bağcılar Training and Research Hospital (Approval Number: 2020.01.1.09.009) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; SŞ, FZA, Data acquisition; MK, Data analysis and interpretation; FZA, Drafting the manuscript; FZA, Critical revision of the manuscript for scientific and factual content; SÖ, Statistical analysis; MÖ, Supervision; ATC.

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Original Research / Özgün Araştırma

The effects of social isolation measures taken against the COVID-19 pandemic on erectile functions of healthcare professionals: a prospective comparative study

COVID-19 pandemisine karşı alınan sosyal izolasyon önlemlerinin sağlık çalışanlarının erektil fonksiyonları üzerine etkileri: prospektif karşılaştırmalı bir çalışma

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Özet

Amaç: Bu çalışmada, COVID-19 pandemisinin doktor, hemşire, tıbbi sekreter, hastane personeli gibi farklı görevlerde bulunan sağlık çalışanları üzerinde yarattığı kaygının erektil disfonksiyona (ED) neden olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntemler: 1 Mayıs-1 Ağustos 2020 tarihleri arasında, son altı aydır haftada en az bir kez düzenli cinsel ilişkide bulunan ve daha önce COVID-19 kliniklerinde çalışmamış gönüllü erkek sağlık çalışanları çalışmaya dahil edildi. COVID-19 kliniklerinde çalışmadan önce ve çalışmaya başladıktan 4 hafta sonra, erektil fonksiyon Uluslararası Erektil Fonksiyon İndeksi-5 (IIEF-5) formu ile belirlendi. Anksiyete bozukluklarını ve şiddetini değerlendirmek için ise Hamilton Anksiyete Derecelendirme Ölçeği (HAM-A) kullanıldı.

Bulgular: Çalışmaya toplam 218 erkek sağlık çalışanı dahil edildi. Bunların 56'sı (%25,7) doktor, 81'i (%37,2) hemşire, 46'sı (%21,1) tıbbi sekreter ve 35'i (%16,1) sağlık personeliydi. Doktorların, COVID-19 servislerinde çalıştıktan 4 hafta sonra ölçülen HAM-A puanının (3,32±4,68), COVID-19 servislerinde çalışmadan önce ölçülen ortalama HAM-A puanına (28,43±14,05) göre anlamlı düzeyde yüksek olduğunu tespit ettik (p<0.001). Doktorların, COVID-19 servislerinde çalıştıktan 4 hafta sonra ölçülen ortalama IEEF-

Abstract

Objective: In this study, we aimed to investigate whether the anxiety caused by the COVID-19 pandemic on healthcare professionals with different duties, such as doctors, nurses, medical secretaries, and medical staff, causes erectile dysfunction (ED).

Material and Methods: In between 1 May 2020 and 1 August 2020, volunteering male health workers who had regular sexual intercourse at least once a week for the last six months and who had not previously worked in COVID-19 clinics were included in the study. Before and 4 weeks after working in COVID-19 clinics, erectile function was determined by the International Index of Erectile Function-5 (IIEF-5) form. The Hamilton Anxiety Rating Scale (HAS) was used to evaluate anxiety disorders and their severity.

Results: A total of 218 male health caregivers were included in the study. Among these, 56 (25.7%) were doctors, 81 (37.2%) were nurses, 46 (21.1%) were medical secretaries and 35 (16.1%) were the medical staff. The mean HAM-A score of the doctors measured 4 weeks after having worked in a COVID-19 clinic (3,32±4,68) was observed to be significantly higher compared to that measured before working (28,43±14,05) (p<0.001). The mean IIEF-5 scores of the doctors measured 4 weeks after having worked in a COVID-19 clin-

The study was approved by Ethical Committee of Erzurum Regional Training and Research Hospital (Approval No: 2020/08-93, Date: 20 April, 2020).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

5 puanlarının (16,34±4,11), COVID-19 servislerinde çalışmadan önce ölçülen ortalama IEFF-5 puanına (22,29±2,35) göre anlamlı düzeyde düşük olduğunu tespit ettik (p<0.001).

Sonuç: Sonuçlarımız COVID-19 kliniklerinde çalışan sağlık çalışanlarının anksiyete ve ED düzeylerinin arttığını ve bu durumdan doktorların diğer sağlık çalışanlarına göre daha fazla etkilendiğini göstermektedir.

Anahtar Kelimeler: COVID-19, sağlık çalışanları, erektil disfonksiyon, anksiyete, hamilton anksiyete ölçeği

ic (16,34±4,11) was observed to be significantly lower compared to that measured before working (22,29±2,35) (p<0.001).

Conclusion: Our results indicate that healthcare professionals working in COVID-19 clinics have increased anxiety and ED, and physicians are affected more than the other healthcare professionals.

Keywords: COVID-19, health professionals, erectile dysfunction, anxiety, hamilton anxiety scale

INTRODUCTION

A series of pneumonia cases were observed in December 2019 in the city of Wuhan, China, and a new type of coronavirus was shown to cause this pneumonia (SARS-CoV-2), and the disease was named coronavirus-2019 (COVID-19) (1,2). The World Health Organization (WHO) reported the COVID-19 infection as a pandemic in March 2020 (3,4). By 5 May 2022, a total of 516.111.527 cases with COVID-19 and 6.273.115 deaths were reported worldwide, depending on the case definitions and test strategies within the affected countries (5). The COVID-19 pandemic is a lot more than a health crisis and has the potential to cause destructive problems with serious effects within societies (6).

ED is defined as permanent insufficiency in reaching and continuing a sufficient erection to provide a satisfactory sexual performance (7). ED affects more than half of the male population aged 40-70 years (8). In addition to psychogenic factors, neurogenic, vasculogenic and hormonal factors play a role in the pathophysiology of ED (9). Studies demonstrate a significant relation of ED with depression and anxiety (10,11). There are studies reporting that some individuals in the general population experienced psychological abnormalities such as anxiety and depression during the COVID-19 pandemic. (12–14). It is an expected situation that health caregivers that struggle actively against the COVID-19 pandemic perceive it at even a stronger extent. Likewise, a recent meta-analysis has reported early-evidence of major anxiety, depression, and insomnia in health caregivers subsequent to the COVID-19 pandemic (15).

We hypothesized that anxiety caused by the COVID-19 pandemic may lead to or exacerbate ED in health caregivers who actively struggle against the disease.

In this study, we aimed to determine the prevalence and severity of anxiety-related ED among healthcare professionals working in COVID-19 clinics and to contribute to the related literature.

MATERIAL AND METHODS

This study was approved by the local ethics committee (Approval Number: 2020/08-93) and designed prospectively. During the COVID-19 pandemic, our hospital has given health services to patients both with and without COVID-19 infection. Meanwhile and especially during the periods with increased number of infected cases, the healthcare professionals who work in departments other than COVID-19 clinics (doctors, nurses, medical secretaries, and other staff) were assigned to COVID-19 clinics. In our hospital, a total of 2577 healthcare staff has been working, and these included 456 doctors, 1115 nurses, 115 medical secretaries and 891 staff (cleaning, patient care). Among these, 1417 (55%) were female 1160 (45%) were male.

In between 1 May 2020 and 1 August 2020, male health caregivers who had a regular sexual relationship for the last six months, which was a minimum of once a week, and who were not assigned to a COVID-19-related department prior to the study, were included in the study. Age, body mass index (BMI), history of a chronic or psychiatric disease and history of medication of the participants were questioned and recorded. Female health caregivers, males with a history or fami-

ly history of COVID-19 infection, those with an IIEF-5 score of <17 prior to the study (with severe, moderate, mild to moderate ED), those with a history of a disease or medication that may have a role in the etiology of ED and those who smoked were excluded from the study. The study included a total of 218 male health caregiver who fulfilled the inclusion criteria. The participants were classified into 4 groups as doctors, nurses, medical secretaries, and other staff. The monthly working hours of each group was between 140-160.

The erectile function of the health caregivers before and 4 weeks after working in COVID-19 clinics were determined using the International Index of Erectile Function-5 (IIEF-5) form that had been translated to Turkish and validated (16). According to the IIEF-5 scoring system, the severity of ED was classified as severe (1-7), moderate (8-11), mild-moderate (12-16), mild (17-21), and no ED (22-25). Evaluation of anxiety disorders and their severity were carried out using the Turkish version of the Hamilton Anxiety Rating Scale (HAM-A), the reliability and validity of which were confirmed. HAM-A is a 14-article scale designed to evaluate and measure the severity of anxiety. It includes items that evaluate both psychiatric and somatic symptoms of anxiety. Each article is graded by a Likert-type scale that is between 0 (absent) and 4 (very severe); higher scores indicate more severe anxiety (17). Classification of the severity of anxiety according to the HAS scores: 0–7=no/minimal anxiety; 8–14=mild anxiety; 15–23=moderate anxiety, and 24 or higher=-severe anxiety (18). The IIEF-5 and the HAM-A forms were fulfilled by the same urologist and psychiatrist by meeting the participants face-to-face before and 4 weeks after working in COVID-19 clinics, and the results of the survey were compared statistically.

Statistical Analysis

Statistical analysis was performed with the IBM SPSS v17.0 software package (SPSS Inc., Chicago, Illinois, USA). Descriptive data were expressed as mean ± standard deviation (SD), numbers, and percentages. The normal distribution of the variables was checked with the Shapiro-Wilk test. The mean differences between the respective groups of data that were not normally distributed were compared with the Wilcoxon test. Categorical variables were analyzed using Pearson Chi-Square and Fisher Exact tests. Intragroup comparisons for occupational groups were made using the Paired Sample T-test, and for intergroup comparisons using the One-Way ANOVA test. Post-Hoc Bonferroni Correction test was conducted to find out which occupational group caused the difference. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 218 male healthcare professionals were included in the study. Among these, 56 (25.7%) were doctors, 81 (37.2%) were nurses, 46 (21.1%) were medical secretaries and 35 (16.1%) were other medical staff. The demographic characteristics of the participants according to their occupational groups have been demonstrated in Table 1.

The mean HAM-A score of the doctors measured 4 weeks after having worked in a COVID-19 clinic (3,32±4,68) was observed to be significantly higher compared to that measured before working (28,43±14,05) ($p<0.001$). The mean IIEF-5 scores of the doctors measured 4 weeks after having worked in a COVID-19 clinic (16,34±4,11) was observed to be significantly lower compared to that measured before working (22,29±2,35) ($p<0.001$). Comparison of the survey outcomes according to occupational groups before and 4 weeks after working in COVID-19 clinics have been demonstrated in Table 2.

No significant difference was observed in the severity of anxiety and erectile dysfunction between the occupational groups before working in a COVID-19 clinic ($p=0.172$ and $p=0.729$, respectively), whereas a significant difference was observed 4 weeks after having worked in a COVID-19 clinic ($p<0.001$ and $p<0.001$, respectively) (Table 3).

The multiple comparison test was performed to determine the group that led to this difference. The results revealed doctors as the group that led to difference for the HAM-A scores and the IEEF-5 scores (Table 4).

According to the post-hoc test, the total HAM-A scores of the doctors were significantly higher compared to nurses, medical secretaries, and other medical staff 4 weeks after they had worked in a COVID-19 clinic ($p<0.05$), whereas the IEEF-5 scores were significantly lower compared to medical secretaries and other medical staff ($p<0.05$) (Table 5).

Table 1. Comparative results of demographic data of occupational groups

	Doctor	Nurse	Secretary	Staff	p
	n=56	n=81	n=46	n=35	
Age (year)	30,1±5,3	28,1±5,2	32,1±4,6	33,0±5,0	0.814*
BMI (kg/m^2)	26.4 ± 3.1	25.9 ± 3.8	24.9 ± 2.8	25.4 ± 2.1	0.110*

*Values were expressed as mean ± standard deviation. BMI: body mass index, * One Way ANOVA,*

Table 2. Comparison of the survey outcomes according to occupational groups before and 4 weeks after working in COVID-19 clinics

	Doctor n=56 (%16)			Nurse n=81 (%21,1)			Secretary n=46 (%37,2)			Staff n=35 (%25,7)		
	BW	AW	P*	BW	AW	P*	BW	AW	P*	BW	AW	P*
HAM-A Score	3,3±4,6	28,4±14,0	**<0,0001***	3,1±4,8	17,3±8,8	**<0,0001***	3,4±4,9	12,4±8,3	**<0,0001***	5,1±6,8	19,3±13,6	**<0,001***
IEFF-5 Score	22,2±2,3	16,3±4,1	**<0,0001***	22,4±2,3	17,7±3,7	**<0,0001***	21,7±3,2	19,4±3,8	**<0,0001***	21,3±3,2	19,5±3,6	**<0,001***

Values were expressed as mean ± standard deviation. ***HAM-A:*** *Hamilton Anxiety Rating Scale,* ***IEEF-5:*** *International Index of Erectile Function-5,* ***BW:*** *Before working in COVID-19 clinics,* ***AW:*** *4 weeks after working in COVID-19 clinics, * Paired Sample t-Test*

Table 3. Comparison of the anxiety and ED severity according to occupational groups before and 4 weeks after working in COVID-19 clinics

		Doctor n (%)	Nurse n (%)	Secretary n (%)	Staff n (%)	Total n (%)	p
BW							
Anxiety severity (score)	No/minimal anxiety (0-7)	53 (94,6)	76 (93,8)	41 (89,1)	30 (85,7)	200 (91,7)	0.172*
	Mild (8-14)	1 (1,8)	3 (3,7)	4 (8,7)	1 (2,9)	9 (4,1)	
	Moderate (15-23)	2 (3,6)	2 (2,5)	1 (1,8)	4 (2,2)	9 (11,4)	
	Severe (>23)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Total		56 (100)	81 (100)	46 (100)	35 (100)	218 (100)	
AW							
Anxiety severity (score)	No/minimal anxiety (0-7)	6 (10,7)	22 (27,2)	23 (50,0)	12 (34,3)	63 (28,9)	**0.001***
	Mild (8-14)	7 (12,5)	14 (17,3)	12 (26,1)	2 (5,7)	35 (16,1)	
	Moderate (15-23)	15 (26,8)	30 (37,0)	6 (13,0)	11 (31,4)	62 (28,4)	
	Severe (>23)	28 (50,0)	15 (18,5)	5 (10,9)	10 (28,6)	58 (26,6)	
Total		56 (100)	81 (100)	46 (100)	35 (100)	218 (100)	
BW							
ED severity (score)	No ED (22-25)	33 (58,9)	52 (64,2)	31 (67,4)	20 (57,1)	136 (62,4)	0.729*
	Mild (17-21)	23 (41,1)	29 (35,8)	15 (32,6)	15 (42,9)	82 (37,6)	
	Mild-moderate (12-16)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	Moderate (8-11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	Severe (5-7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Total		56 (100)	81 (100)	46 (100)	35 (100)	218 (100)	
AW							
ED severity (score)	No ED (22-25)	5 (8,9)	14 (17,3)	18 (39,1)	13 (37,1)	50 (22,9)	**0.001***
	Mild (17-21)	18 (32,1)	39 (48,1)	20 (43,5)	13 (37,1)	90 (41,3)	
	Mild-moderate (12-16)	26 (46,4)	23 (28,4)	8 (17,4)	9 (25,7)	66 (30,3)	
	Moderate (8-11)	7 (12,5)	5 (6,2)	0 (0)	0 (0)	12 (5,5)	
	Severe (5-7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Total		56 (100)	81 (100)	46 (100)	35 (100)	218 (100)	

*ED: Erectile dysfunction, BW: Before working in COVID-19 clinics, AW: 4 weeks after working in COVID-19 clinics, * Pearson chi square*

Table 4. Comparative results of HAM-A and IIEF-5 scores of health professionals before and 4 weeks after working in COVID-19 clinics

	Mean ± Standard Deviation (n:218)	95% Confidence Interval Lower Limit-Upper Limit	p
BW			
HAM-A score	3,6±5,1	2,9-4,3	0,259
IEFF Score	22,0±2,7	21,7-22,4	0,138
AW			
HAM-A score	19,4±12,4	17,4-21,0	**<0,0001***
IEFF Score	18,0±4,0	17,4-18,5	**<0,0001***

Values were expressed as mean ± standard deviation. ***HAM-A:*** *Hamilton Anxiety Rating Scale,* ***IEFF-5:*** *International Index of Erectile Function-5,* ***BW:*** *Before working in COVID-19 clinics, AW: 4 weeks after working in COVID-19 clinics,* **** One Way ANOVA***

Table 5. Post-hoc comparative results of HAM-A and IEFF-5 scores of health caregivers

	Profession		95% Confidence Interval		p
			Lower Limit	Upper Limit	
HAM-A Score	Doctor	Nurse	5,9	16,2	
		Secretary	10,0	21,9	
		Staff	2,9	15,7	
IEFF-5 Score	Doctor	Secretary	-5,1	-1,1	
		Staff	-5,3	-0,9	

*Values were expressed as mean ± standard deviation. HAM-A: Hamilton Anxiety Rating Scale, IEFF-5: International Index of Erectile Function-5, * One Way ANOVA, Post Hoc*

DISCUSSION

We have established the hypothesis that there may be a relationship between anxiety and ED in healthcare workers who play an active role in the COVID-19 pandemic, and we have determined that both anxiety and the ED severity increase in healthcare professionals working in the COVID-19 clinics. Furthermore, this study demonstrated that the severity of ED was different among different occupational groups of health caregivers in the COVID-19 pandemic.

ED affects the quality of life of the individual to an important extent. Clearing the etiology of ED in order to develop effective preventive and therapeutic strategies against it, is one of the subjects of priority in the field of health (11). The organic causes and depression are those investigated widely, whereas the correlation between anxiety and ED has encountered less interest (19). However, there are a few studies showing the relationship between anxiety and ED (11,20). This study was conducted on young and healthy individuals with no history of chronic disease or smoking habit, which eliminated the other possible causes of ED. In our study, a significant reduction was observed in the IIEF-5 scores of the participants after they had worked in the COVID-19 clinic (<0.001) and a significant increase was observed in the severity of ED (<0.001). This suggests psychogenic causes of the situation and indicates the negative effects of the COVID-19 pandemic on health caregivers.

In order to prevent the spread of COVID-19, different types of public health measures (social isolation, quarantine and curfews) have been implemented by governments. Although these precautions are important in order to place the infection under control, it is not a good experience for those who are exposed. These people may have concerns and fears regarding their own health and that of the people around them through anger and disappointment about the uncer-

tainty of the return of life to "normal". Some people may experience post-traumatic psychological problems due to high levels of stress or loneliness (6). It is even complicated for health caregivers. Health caregivers who interfere with the pandemic, may be exposed to physical and psychological stress factors that may lead to serious health problems (21). In the study of Bai et al. conducted on the health caregivers during the SARS pandemic, acute stress disorder was observed in 5% of the staff, anxiety was observed in 17% and insomnia was observed in 14%. Furthermore, in 22% of the health caregivers, the feeling of being labelled and rejection were observed since they have worked in a hospital (22). In another study on health caregivers, more traumatic stress was observed in those who had worked in a COVID-19 clinic than those who had not (23). Our hospital continues to provide health services throughout the period of the COVID-19 pandemic actively with all branches. As expected, a significant increase was observed in the mean HAS scores (<0.001) and the severity of anxiety (<0.001) in the staff of our hospital after they had worked in a COVID-19 clinic.

The COVID-19 pandemic appears to have affected the whole world to a higher extent than any other pandemic. In the study of Lai et al. on health caregivers treating COVID-19 patients, anxiety was reported in 44,6% of the participants (24). In the study of Koksal et al. conducted on health caregivers during the pandemic, 36.9% and 57.5% of the participants were reported to have a score higher than the defined cut-off value for depression and anxiety, respectively, although no psychiatric disease was observed in 90% of the operational room staff (25). Symptoms of stress (29.8%), anxiety (24.1%) and depression (13.5%) were reported in the study of Lu et al. investigating the effects of the COVID-19 pandemic on health professionals (26).

Limited studies are available in the literature investigating the influence of the COVID-19 pandemic on the sexual functions of healthcare workers (27-32). In the cross-sectional study by Culha et al. Conducted with 232 healthcare professionals fighting COVID-19 in pandemic hospitals, the authors have reported that during the pandemic, libido, duration of foreplay, coitus frequency decreased, and positions of coitus have changed. The fact that the participants had not been evaluated for anxiety, depression, and sexual functions before the pandemic and the study was conducted when the pandemic had begun to lose its velocity are the limitations of the study (27). Güzel et al. Have reported that compared to pre-pandemic period, health workers' sexual desire level, weekly sexual intercourse frequency, foreplay duration and coitus duration decreased during the ongoing pandemic period. (28). Similarly, in the study by derose et al., 264 healthcare professionals were evaluated by using IIEF-15 and Female Sexual Function Index (FSFI), and sexual desire was reported to decrease in more than 40 % of females and more than 80 % of males (29). Bulut et al. Have detected that post-traumatic stress disorder and ED were significantly higher among actively working healthcare professionals as compared to controls during the pandemic. In addition, being a nurse was reported to be a risk factor for severe ED (30). In the study by Eroglu et al. Evaluating the changes in anxiety among healthcare workers during the pandemic and the effect of anxiety on sexual functions, the scores of IIEF-15 and State Anxiety Inventory-I (STAI-I) were compared at the beginning and the 6th month of the pandemic. The authors have reported that the COVID-19 pandemic negatively affected the sexual life of healthcare workers and sexual function decreased in both sexes, and anxiety severity significantly increased (31). In a systematic review by Bakr et al. Evaluating the changes in erectile functions in healthy controls and health care providers during the pandemic, the COVID-19 pandemic was concluded to be related to increasing ED rates, anxiety and depression increased the severity of ED more particularly in health care providers (32).

Similar to these studies, we have found a significant increase in anxiety and ED levels 4 weeks after beginning to work in COVID-19 clinics. Besides, the increase in anxiety and ED was higher in physicians than in other healthcare professionals (nurses, secretaries, staff). Although our results are similar to those of Culha et al., we consider that evaluating healthcare professionals' erectile functions and anxiety levels before and

after working in COVID-19 clinics made our results more valuable. We also consider that in the study of Bulut et al., it is difficult to determine whether working in COVID-19 clinics or the pandemic itself has led to ED. It may be expected that healthcare professionals may have been affected more by the pandemic as they are more conscious of the pandemic. Showing that anxiety and ED severity increased after beginning to work at COVID-19 clinics makes the results of our study more meaningful. Besides, differently from the study by Bulut et al., we have detected that physicians' anxiety and ED levels increased more than other Healthcare Professionals. We suggest that this results from their having more information about the disease than other healthcare professionals.

The limitations of our study include the small number of participants, not evaluating the sexual quality of life of the partners, and the absence of long-term outcomes.

CONCLUSION

Our results show that anxiety and ED levels of healthcare professionals working at COVID-19 clinics have increased and physicians are affected more than the other healthcare professionals. Healthcare professionals who are affected by this should be given psychological and sexual consultancy with a multi-disciplinary approach.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethical Committee of Erzurum Regional Training and Research Hospital (Approval Number: 2020/08-93, Date: 20 April, 2020) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; AEC, ES, SOD, IK, EO, IHT, IO, Data acquisition; SOD, IK, Data analysis and interpretation; NC, FA, IHT, Drafting the manuscript; AEC, ES, NC, IK, EO, Critical revision of the manuscript for scientific and factual content; AEC, ES, FA, EO, IHT, IO, Statistical analysis; NC, FA, IHT, Supervision; IK, IO.

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Original Research / Özgün Araştırma

Does bladder wall thickness have a place in the evaluation of male patients with lower urinary tract symptoms?

Alt üriner sistem semptomları olan erkek hastaların değerlendirilmesinde mesane duvar kalınlığının yeri var mıdır?

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Özet

Amaç: Mesane duvar kalınlığının (MDK), alt üriner sistem semptomları (AÜSS) olan erkek hastalarda, Uluslararası prostat semptom skoru (IPSS) ve üroflowmetri parametreleri ile ilişkisinin olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Üroloji polikliniğine Haziran 2021- Ocak 2022 tarihleri arasında AÜSS ile başvuran erkek hastaların prostat spesifik antijen (PSA), prostat volümü, işeme sonrası rezidü idrar (PVR), IPSS, Maksimum akış hızı (Qmax), Ortalama akış hızı (Qort), üroflowmetri, MDK değerleri ve intravezikal prostatik protrüzyon dereceleri (İPP) kaydedildi. Hastalar MDK açısından 2 gruba ayrıldı (Grup: 1 MDK < 5 mm; Grup 2: MDK ≥ 5 mm). Bu iki grup arasındaki başlangıçta kaydedilen değerler arasındaki fark analiz edildi.

Bulgular: Dahil edilen 110 hastanın (Grup 1:65, Grup 1:45) ortanca yaşı 56.5(15); ortanca MDK 4.25(3.60) idi. Her iki grup arasında PSA, prostat volümü, üroflow toplam akım miktarı, Qmax, Qort, IPSS ve IPP değerleri istatistiksel anlamlı farklı bulundu. Her iki grup arasında yaş ve PVR değerleri benzer bulunmuştur. Mesane duvar kalınlığı ile IPSS ve Qort değerleri arasında güçlü, Qmax değeri arasında çok güçlü korelasyonel ilişki tespit edilmiştir.

Sonuç: Mesane duvar kalınlığı, üroloji pratiğinde IPSS ve üroflowmetri değerlerinin tahmini için kullanılabilen basit bir sonografik ölçümdür.

Anahtar Kelimeler: mesane duvar kalınlığı, alt üriner sistem semptomları, ultrasonografi

Abstract

Objective: To investigate whether bladder wall thickness (BWT) is associated with The International Prostatic Symptom Score (IPSS) and uroflowmetry parameters in male patients with lower urinary tract symptoms (LUTS).

Material and Methods: Prostate volume, prostate specific antigen (PSA), post-void residual (PVR) urine volume, IPSS, maximum and average urinary flow rates (Qmax, Qave), BWT and intravesical prostatic protrusion (IPP) grades of male patients who applied to the urology outpatient clinic with LUTS between June 2021 and January 2022 were recorded. .Patients were divided into 2 groups in terms of BWT (Group: 1 BWT < 5 mm; Group 2: BWT ≥ 5 mm). We compared IPSS, PVR, PSA, Qmax, Qave, prostat volume and IPP grades between two groups.

Results: A total of 110 patients were included in the study (Group 1: n= 65, Group 2: n=45). Median(IQR) age, and median BWT values of the patients were 56.5(15) years, and 4.25(3.60) mm, respectively. PSA, prostate volume, total urine volume, Qmax, Qave, IPSS and IPP values were found to be statistically different, while age and PVR were similar between two groups. In addition, a strong correlation was found between BWT and IPSS- Qave, and a very strong correlation between BWT and Qmax.

Conclusion: BWT is a simple sonographic measurement that can be used to estimate IPSS and uroflowmetry parameters in urology practice.

Keywords: bladder wall thickness, lower urinary tract symptoms, ultrasonography

The study was approved by Ethical Committee of Bursa Yüksek İhtisas Training and Research Hospital (Approval No: 2011-KAEK-25 2021/11-03 Date: 2021.11.17). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Lower urinary tract symptoms are a dynamic process that worsens with age. Although benign prostate enlargement is blamed for LUTS, disruption of bladder dynamics is responsible for most of the symptoms. Unless the bladder outlet obstruction is relieved, compensatory detrusor hypertrophy develops initially(1). If this compensatory mechanism is forced above its limits, renal decompensation and eventually renal insufficiency ensue.

Bladder outlet obstruction prevents voiding and is diagnosed by synchronized measurement of detrusor pressure and urine flow rate. The measurement of these dynamic parameters is made by urodynamic tests. However, since they are invasive, urodynamic investigations are avoided as much as possible and its application is recommended when conservative treatment methods fail. Since they cannot distinguish between detrusor hypoactivity and bladder outlet obstruction as is the case with urodynamic studies, uroflowmetry is one of the non-invasive tests frequently used in evaluating obstruction. When the threshold value is taken as 10 ml/sec, it has 70% specificity, 47% sensitivity, and 70% positive predictive value(2).

The idea of estimating bladder outlet obstruction with non-invasive imaging methods has been the subject of many studies. Prostatic configuration, intravesical prostatic protrusion, BWT, and ultrasonographically estimated bladder weight are the predictive parameters for obstruction as recommended in the European Association of Urology Guidelines to predict obstruction (1). Studies have shown that both BWT (3, 4) and IPP (5, 6) are associated with LUTS and bladder outlet obstruction. However, the level of evidence remains low due to the lack of standardization in threshold values.

In our study, we aimed to investigate whether BWT is associated with LUTS and uroflowmetry parameters in patients with LUTS.

MATERIAL AND METHODS

Ethics committee approval numbered 2011-KAEK-25 2021/11-03 was obtained for our study from the Ethics Committee of the University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital. The study was conducted in two centers (University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital and Nusaybin State Hospital). The study included male patients aged 40-90 years who applied to the Nusaybin State Hospital urology outpatient clinic between June 2021 and January 2022 with complaints of non-neurogenic LUTS. The study was conducted prospectively. Patients with a diagnosis of a bladder tumor, prostate cancer, history of bladder and prostate surgery or urethral stricture and a neurological disease were excluded from the study.

Age, medical treatment status, digital rectal examination findings, IPSS, PSA (ng/mL), uroflowmetry findings (Qmax (mL/sec), Qave (mL/sec)), ultrasonographically measured PVR (mL), BWT values (mm) and grades of IPP were recorded. All patients were using α-blockers, anticholinergics, 5-alpha reductase inhibitors, or a combination of these. The patients were divided into three groups according to IPSS as mild, moderate and severe LUTS.

Bladder wall thickness was measured transabdominally from the suprapubic region using a ultrasonograph with a convex 5–7 Mhz probe. Before uroflowmetry, measurements were made by a single clinician from the anterior wall when the patients felt urgent desire to pass urine. The thickness between the bladder mucosa and adventitia, which appears hyperechogenic, was measured(Figure 1,a-b). Calculation of the IPP grade was done by measuring the distance between the tip of the prostate median lobe and the bladder neck in the midsagittal plane by transabdominal USG while the bladder remained at the same level of distensio (Figure 1-c). The IPP was divided into 3 groups (< 5 mm grade 1, 5-10 mm grade 2, and >10 mm grade 3).

Patients were divided into two groups as having BWT<5 mm and ≥5 mm. The difference between LUTS and uroflowmetry parameters of the two groups was analyzed. In addition, the correlation between BWT and data used in the diagnosis of LUTS were analyzed.

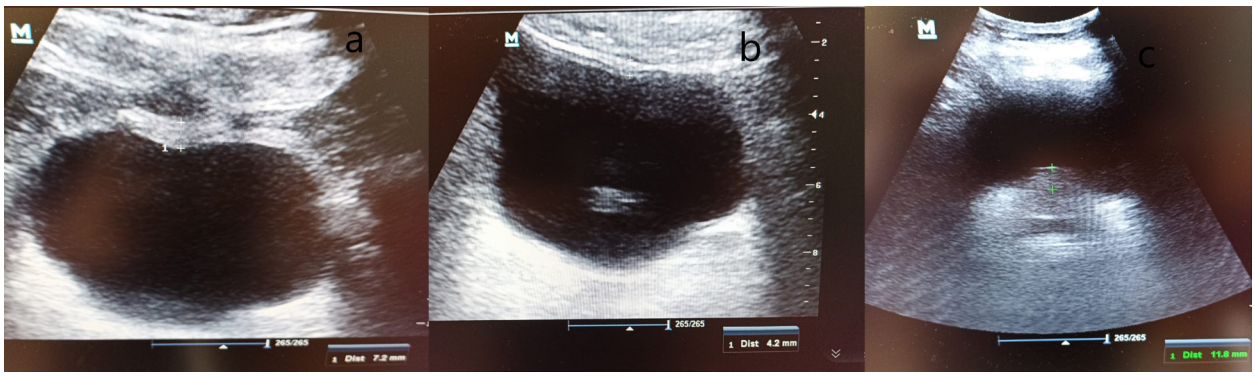

Figure 1. Ultrasonographic measurement of BWT and IPP in the transverse plane from the suprapubic area. a) The thickness of the anterior bladder wall that appears hyperechoic: 7.2 mm b) BWT of a patient with a lower IPSS: 4.2mm c) IPP measurement from the base of bladder: 11.8 mm(grade 3)

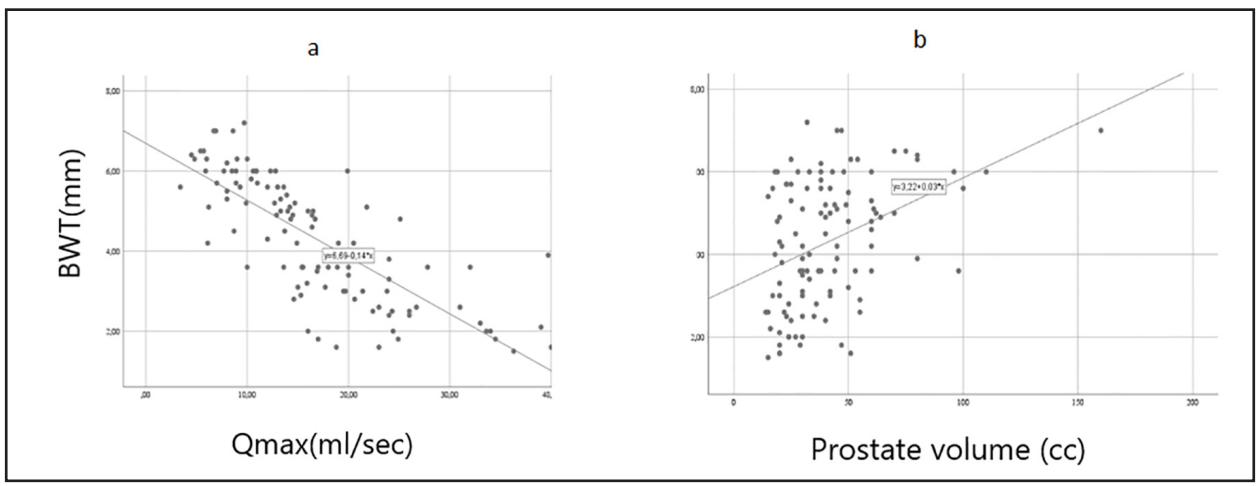

Figure 2. Relationship between bladder wall thickness and Qmax(a) and prostate volume(b)

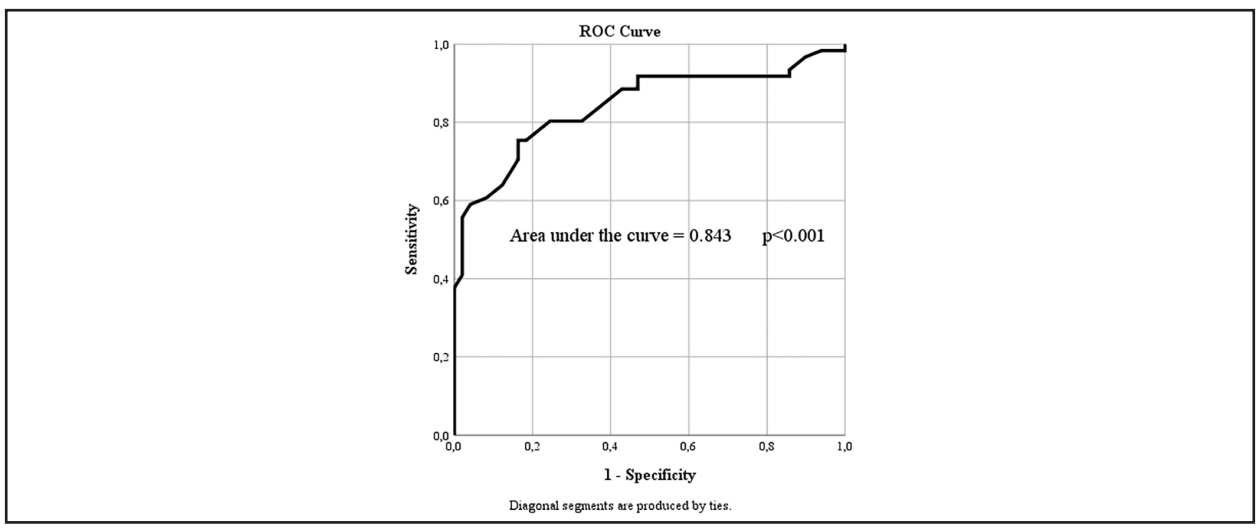

Figure 3. Roc curve analysis comparing bladder wall thickness and IPSS

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of the parameters was determined using analytical (Kolmogorov-Smirnov and Shapiro-Wilks analysis) and visual (histogram and probability graphs) methods. In descriptive statistics continuous variables were expressed as median (min-max) or mean±standard deviation while categorical variables in numbers and percentages. Mann-Whitney U test or Independent sample t test was used to compare the normally distributed continuous variables between the two groups. The difference between the categorical variables was calculated by the Fisher Exact test. Spearman Correlation test was used to investigate the correlation between bladder wall thickness and various parameters. A receiver operating characteristic (ROC) curve was applied to obtain the optimum cut-off value of bladder wall thickness in predicting severe IPSS. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 110 patients were included in our study. The mean age of the patients was 59.2 ± 9.3 years (median: 56.5 (15). Median(IQR) values for BWT 4.25(3.60) mm; total volume of voided urine 250.0(182.3) cc, Qmax 15.45(11.20) mL/sec, prostate volume 37(26) mL and IPSS 20.0(10.0) points were as indicated.

A total of 110 patients were included in Group 1 (n=65 ; 59%) and 2 (n=45 ; 41%) . There was no statistically significant difference between the two groups in terms of age and PVR. In the group with BWT ≥5 mm, PSA, prostate volume and IPSS were found to be significantly higher (p<0.05). Qmax, Qave and total volume of voided urine were found to be statistically significantly lower in the group with BWT 5≥mm compared to the group with BWT <5 mm (p<0.05). A significant difference was found between IPP grade and BWT (p<0.001) and BWT increased in line with IPP. While all of those with mild IPSS had BWT <5 mm, 86.7% of those with moderate and 36.1% of those with high had an BWT less than 5 mm. As IPSS increased, statistically significant increases were noted in BWT (p<0.001)(Table 1).

A statistically significant positive correlation was found between BWT and PSA, moderate correlations were detected between BWT, and prostate volume, BWT, and PVR, while a strong positive correlation was noted between BWT, and IPSS. A moderate correlation was observed between BWT and total volume of voided urine, and urine flow, while a very strong correlation between BWT, and Qmax and a strong negative and statistically significant correlation between BWT, and Qave were detected. There was no statistically significant correlation between age and BWT (p>0.05) (Table 2, Figure 2).

The area under the ROC curve was found to be statistically significant (0.843 with a confidence interval of 0.768-0.918), (p<0.001). When the BWT is 3.95 mm and above, the presence of higher IPSS can be predicted with 80.3% sensitivity, 75.5% specificity, 80.3 PPV and 75.5% NPV. When the BWT is 4.10 mm and above, higher IPSS indicating a severe bladder outlet obstruction can be predicted with a sensitivity of 78.7%, specificity of 77.6%, PPV of 81.4% and NPV of 74.5%. (Table 3) (Figure 3).

DISCUSSION

According to the guidelines, history, physical examination, symptom scores, urinalysis, PSA, and PVR measurement are recommended for diagnostic purposes in male patients with LUTS(1). Uroflowmetry is also recommended before medical or surgical treatment. Although the pressure flow study is thought to be the most useful method in the diagnosis of obstruction, it is recommended only in specific cases due to the lack of randomized controlled studies. Because urodynamic studies are invasive and can lead to various complications, many studies have been conducted to predict obstruction using non-invasive methods(7, 8). In our study, we showed that BWT is associated with LUTS and uroflowmetry parameters.

Because of methodological differences in studies and lack of standardization in measurements, the level of evidence for the use of BWT in the diagnosis of BPH is not strong enough for its inclusion in the guidelines. In their study evaluating the bladder neck obstruction using the urodynamic technique, Park et al. showed

Table 1. Comparison of two groups formed according to Bladder Wall Thickness in terms of parameters

	(BWT<5) mean±SD (n=65)	(BWT≥5) mean±SD n=45)	p
Age (year) median (IQR)	55.0(12)	63.0(18)	0.099**
PSA (ng/mL) median (IQR)	1.0(1.38)	2.05(3.1)	**0.002****
Prostate volume (cc) median (IQR)	30.0(24)	43.5(29)	**0.002****
Post voiding residual urine volume (mL) median (IQR)	30.0(50)	36.0(100)	0.204**
Total voiding urine volume (mL) median (IQR)	304.0(191.0)	217(155.0)	**0.001****
Qmax (mL/sec) mean±SD	21.4±7.6	10.3±4.0	**0001***
Qave(mL/sec) mean±SD	8.0±3.7	4.1±1.7	**0.001***
IPSS median (IQR)	16.0(8.0)	25.0(5)	**<0.001****
IPP, n (%)			
Grade 0 (<5mm)	57 (90.5)	6 (9.5)	**<0.001 ¥**
Grade 1 (5-10mm)	8 (30.8)	18 (69.2)	
Grade 2 (>10 mm)	-	21 (100.0)	
IPSS, n (%)			
Lower	4 (100.0)	-	**<0.001 ¥**
Mild	39 (86.7)	6 (13.3)	
High	22 (36.1)	39 (63.9)	

***SD:** Standart deviation *: t test in independent groups ** :Mann Whitney u **¥:** Fisher's Exact Test*
***PSA**: Prostate-specific antigen, **Qmax**: maximum urinary flow rate **Qave**: average urinary flow rate **IPSS**: International Prostatic Symptom Score **IPP**: Intravesical prostatic protrusion*

Table 2. Correlation between parameters and bladder wall thickness

(n=110)	Bladder Wall Thickness (mm)	
	r*	p
Age(year)	0.141	0.142
PSA (ng/mL)	0.332	**<0.001**
Prostate Volume (cc)	0.384	**<0.001**
Post voiding residual urine volume (mL)	0.271	**0.004**
Total voiding urine volume (mL)	-0.444	**<0.001**
Q max (mL/sec)	-0.826	**<0.001**
Q ave (mL/sec)	-0.668	**<0.001**
IPSS	0.733	**<0.001**

**: Spearman Correlation coefficient*
***PSA:** Prostate-specific antigen, **Qmax:** maximum urinary flow rate **Qave:** average urinary flow rate **IPSS:** International Prostatic Symptom Score*

Table 3. IPSS Prediction of Bladder Wall Thickness Evaluation of Strength

BWT (mm) Threshold value	Sensivity	Specifity	Positive Predictive Value	Negative Predictive Value
3.95	80.3	75.5	80.3	75.5
4.1	78.7	77.6	81.4	74.5

***BWT:** Bladder Wall Thickness*

that BWT and detrusor wall thickness (DWT) can be used in predicting bladder outlet obstruction in the patient group over 70 years of age(9). In this study BWT was measured after uroflowmetry. In their study Eze et al, found that mean PVR, IPSS, prostate volume and percentage of bladder emptying were statistically different between groups with BWT below and above 5 mm in symptomatic BPH patients(10). Azab and Elsheikh. evaluated the change in total IPSS, quality of life scoring, symptom scores, Qmax and PVR after 2 months of α-blocker therapy given to the patients in the study group. They found statistically significantly greater improvement in these values in the group with BWT <5 mm. Therefore, it was emphasized that BWT could be evaluated in determining the response to medical treatment (11). In their study, Karaköse et al. reported that BWT was significantly lower after alpha-blocker treatment. In addition, they found a significant difference in Qmax and PVR between the groups with BWT <5mm and ≥5mm, but not in terms of Qave, quality of life, PSA, prostate volume and IPSS(12).

As the bladder outlet resistance increases, the contraction force of the bladder increases. As the contraction force increases, detrusor hypertrophy occurs. Residual urine and increased pressure in the bladder cause edema and congestion in the interstitial space. With the combination of all these, an increase in BWT is observed. Detrusor hypertrophy contributes mostly to the increase in BWT. It may be possible to evaluate the development, progression of the disease and response to treatment of the disease by measuring the BWT with USG(13). Sonographically, hyperechoic mucosa and serosa of the bladder wall, while hypoechoic detrussor are seen. Although we measured all layers of the bladder wall in our study, only DWT was measured in some studies, considering that actually thickness of the detrusor muscle increased. For example, in their study including 102 patients, Kessler et al. measured detrusor wall thicknesses. They divided the patients into urodynamically obstructed, equivocal and non-obstructed groups. The mean detrussor wall thickness in the obstructed group was found to be statistically significantly higher compared to the eqivocal and non-obstructed groups. In addition, they found the cut-off value to be used in the diagnosis of obstruction as 2.9 mm (3). According to the authors, sonographically, the mucosa and serosa of the bladder wall appear hyperechoic which creates difficulties in distinguishing it from the surrounding tissues, and also leads to errors in making precise measurements of BWT.

The relationship between bladder wall thickness and LUTS was also investigated in other patient groups, such as female patients with symptoms of overactive bladder and pediatric patients with spina bifida.(14, 15). Blatt et al. included both genders in their study. According to the results of the study, BWT was not different between patient groups with bladder outlet obstruction, detrusor overactivity and normal urodynamics(16). Panayi et al included 379 female patients with lower urinary tract symptoms in their study. According to the classification of the International Continence Society, patients were divided into overactive bladder, stress urinary incontinence and mixed urinary incontinence groups. According to the analysis, mean BWT were significantly different in the stress urinary incontinence group compared to the mixed urinary incontinence and overactive bladder groups. They also reported that the group with daytime urinary frequency >7 had a greater mean BWT than the group with <7(17).

In similar research studies different ideas have been put forward about from where, and how to measure BWT, the device of the measurement, and the degree of bladder distension during measurements. In some studies, bladder wall thickness was measured when the bladder was not full(9), but the general consensus is that BWT decreases as bladder gradually distends. BWT reaches a plateau when bladder filling reaches 200-300 cc, or 46-60% of bladder capacity. Oelke et al. reported that BWT gradually decreased up to 250 cc of bladder filling, and then remained at the same level (13). Another question is related to the place of measurement BWT on the bladder wall. Although measurements are generally made from the anterior wall through the transabdominal route (18, 19), some authors measure BWT from several places and take their average (20). According to the report of the Incontinence-Research Society, the place where bladder wall

thickness is measured does not matter, entire bladder wall has the same thickness (13). On the contrary, in their study Anzia et al. measured BWT by MRI in both male ,and female patients, and, reported that there were differences in the values of bladder wall thickness depending on the place of measurements(21). Finally, the use of USG probes with higher Mhz is important in terms of detecting small changes. In our study, we made a single measurement with 5-7 Mhz USG from the anterior wall, through transabdominal route, when the patients felt urgent desire to pass urine before uroflowmetry.

Although our study emphasizes that BWT is closely related to IPSS and uroflowmetry parameters, it also has some limitations. First, diagnosis of bladder outlet obstruction of the patients was made with uroflowmetry test instead of pressure flow studies. Second, our study includes a small number of patients. Finally, measuring the bladder wall thickness during the patients' feeling of urgent desire to void urine may have resulted in measurement differences due to subjective nature of this approach.

CONCLUSION

According to the results of our study, BWT was found to be associated with IPSS and uroflowmetry parameters in male patients with LUTS. It can be used in daily urology practice as a non-invasive method for predicting the severity of symptoms and obstruction. Our results should be supported by studies with more patients in which the obstruction is evaluated urodynamically.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethical Committee of Bursa Yüksek İhtisas Training and Research Hospital (Approval No: 2011-KAEK-25 2021/11-03), and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; ÖE, SÇ, Data acquisition; ÖE, SZ, ÇB, Data analysis and interpretation; SZ, ÇB, Drafting the manuscript; ÖE, EB, Critical revision of the manuscript for scientific and factual content; ÖE, EB, Statistical analysis; EB, Supervision; SÇ, AG.

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Original Research / Özgün Araştırma

Assessment of associated factors with nocturia in young and older urinary incontinent

Üriner inkontinansı olan genç ve yaşlı kadınlarda noktüri ile ilişkili faktörlerin değerlendirilmesi

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Özet

Amaç: Üriner inkontinanslı (Üİ) genç ve yaşlı kadınlarda noktüriyi etkileyen faktörleri değerlendirmek.

Gereç ve Yöntemler: Kasım 2021-Mart 2022 tarihleri arasında Üİ şikâyeti ile üroloji polikliniğine başvuran kadınlar çalışmaya dahil edildi. Demografik veriler, antropometrik ölçümler, ilaçlar ve komorbiditeler kaydedildi. Yaşam kalitelerini değerlendirmek için ICIQ-SF testi uygulandı. Geceleri ≥2 idrar yapma ihtiyacı ile uyanan hastalarda noktüri var olarak kabul edildi.

Bulgular: Çalışmaya 92 kadın dahil edildi. Hastalar <60 yaş (n=47) ve ≥60 yaş (n=45) olarak 2 gruba ayrıldı. Bel çevresi ve vücut kitle indeksi ≥60 yaş hastalarda daha yüksekti (sırasıyla; p= <0,001, p= 0,034). Kullanılan ilaç sayısı yaşlı grupta daha fazlaydı (p= <0,001). Diüretik ve antikolinerjik ilaç kullanımı yaşlı grupta genç gruba göre daha yüksekti (sırasıyla; p= <0,001, p= 0,006). Tip 2 Diabetes Mellitus'lu (DM) hasta sayısı ve komorbidite sayısı yaşlı grupta daha fazlaydı (sırasıyla; p= 0,002, p= 0,025). Noktürisi olan ve olmayan genç grupta antropometrik ölçümler, kullanılan ilaçlar ve komorbiditeler açısından fark bulunmadı. Noktürisi olan yaşlı grupta ilaç sayısı ve Tip 2 DM olan hasta sayısı noktürisi olmayan yaşlı gruba göre anlamlı olarak daha yüksekti (sırasıyla; p= 0.04, p= 0.036).

Sonuç: Tip 2 DM ve çoklu ilaç kullanımı, Üİ›li yaşlı kadınlarda noktüri için risk faktörleridir. Bu risk faktörlerinin değerlendirilmesi ve yönetimi daha iyi klinik sonuçlara katkıda bulunabilir.

Anahtar Kelimeler: yaşlı, noktüri, risk faktörleri, üriner inkontinans, kadın

Abstract

Objective: To assess the factors affecting nocturia in young and older women with urinary incontinence (UI).

Material and Methods: Women who applied to the urology outpatient clinic with the UI complaint between November 2021-March 2022 were included. Demographic data, anthropometric measurements, medications and comorbidities were recorded. The ICIQ-SF test was applied to evaluate their quality of life. Patients who have been waking up at night with the need to urinate ≥2 were considered to have nocturia.

Results: Ninety-two women were included. Two groups were created as patients <60 years (n=47) and ≥60 years (n=45). The body mass index and waist circumference were higher in patients ≥60 years (respectively; p= 0.034, p= <0.001). Using of diuretic and anticholinergic medications was higher than in the younger group (respectively; p= <0.001, p= 0.006). The total number of medications was higher in the older group (p= <0.001). The number of comorbidities and the number of patients with Type 2 Diabetes Mellitus (DM) were higher in the older group (respectively; p= 0.002, p= 0.025). No difference was found in the young group with and without nocturia in terms of anthropometric measurements, medications used, and comorbidities. The number of medications and the number of Type 2 DM patients were significantly higher in the older group with nocturia (respectively; p= 0.04, p= 0.036).

Conclusion: Type 2 DM and multiple medication use are risk factors for nocturia in older women with UI. Evaluation and management of these risk factors may contribute to better clinical outcomes.

Keywords: aged, nocturia, risk factors, urinary incontinence, women

The study was approved by Ethical Committee of İstanbul Medipol University (Approval No: 1051, Date: 26 November, 2021).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Nocturia is defined as one or more awakenings during the night to urinate by the International Continence Society (ICS) (1). Although defined as a symptom rather than a disease, 2 or more urinations per night is considered clinically significant due to the negative effect of nocturia on well-being and health-related quality of life (2). The prevalence of nocturia increases with aging and almost 50 percent of adults ages 50 to 79 have nocturia (3). Also, 60-80% of nocturia cases occur in older adult population (4). A recent study from the National Health and Nutrition Examination Survey showed that 45% of women and 51.5% of men aged 60 and older wake up at least twice each night to urinate (5). While symptoms rarely occur between the ages of 50 and 59, between the ages of 70 and 79, symptoms occur at least twice a night (6).

There are three known mechanisms for the occurrence of nocturia. These are decreased bladder volume, increased urinary output at night, and sleep-related disorders (7). The other related conditions are urgency, benign prostatic hyperplasia and/or bladder outlet obstruction, urinary tract infections, and low bladder capacity (8, 9). Nocturnal polyuria, peripheral edema (without heart failure), congestive heart failure, poor control of diabetes mellitus (DM), excessive fluid intake throughout the day or large fluid intake prior to bedtime, and intake of diuretic substances are caused nocturia with increased urine output at night (10). Sleep apnea, difficulty in sleep maintaining, restless legs syndrome or periodic limb movements are sleep disorders known to cause nocturia (11, 12).

Nocturia, which is more common in older people, is a known risk factor for falls, fractures, and depression (9,13). Nocturia may cause sleep disturbances. It is also related with dependence, obesity, DM, and heart disease (8, 14). Besides, nocturia is an independent risk factor for mortality (15).

Urinary incontinence (UI) is a geriatric syndrome whose frequency increases with aging and is more common in women (16). Since UI is a risk factor for nocturia, the presence of additional risk factors may increase the prevalence of nocturia. Knowing the factors affecting nocturia in women with UI is important in order to prevent the development of possible complications by managing nocturia correctly. Therefore, we aimed to assesment of the factors affecting nocturia in young and older women with UI.

MATERIAL AND METHODS

Study Population

A cross-sectional study has been proposed. The local ethics committee approval was obtained for the study (1051, 26.10.2021). Between November 2021 and March 2022, women who applied to the urology outpatient clinics with the complaint of UI and had stress, urge, and mixed UI as a result of the anamnesis and physical examination evaluation were included in the single-center study. The reason for including only patients with UI in the study is to homogenize the patient groups in terms of this risk factor. The patients included in the study were those who had not had an incontinence operation before and were not taking medical treatment for UI at the time of admission. All of these patients underwent complete urinalysis and urine culture, and as a result of these tests, patients with urinary tract infections were excluded from the study. Two groups have been created as under 60 years old and 60 years old and over patients. Patients who had cognitive dysfunction (severe dementia, persistent cognitive dysfunction due to a past cerebrovascular event, delirium) and could not reply to our questions and the International Consultation on Incontinence Questionnaire- Short Form (ICIQ-SF) were excluded from the study. All patients gave informed consent (written and verbal).

Data Collection

Demographic data, comorbidities, medication history, number of vaginal deliveries, anthropometric measurements [height (cm), weight (kg), waist circumference (cm), body mass index (BMI) (kg/m2)] of the patients were recorded. The ICIQ-SF was administered to all patients to appraise the effect of UI on quality of life (17). Patients who woke up with the need to urinate at 2 or more nights were considered to have nocturia.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences (v21.0, IBM, Chicago, IL, US)) has been used for data

analysis. The statistical power of the study was determined with the G*Power software (version 3.1). For analyzing the association between the age groups with patients' demographic-clinical data has been used by Mann-Whitney U and chi-square tests. Also, the relationship between nocturia and patients' demographic and clinical data was conducted by the Mann-Whitney U and chi-square tests in both age groups. A p-value less than 0.05 has been accepted considered statistically significant.

RESULTS

Ninety-two patients with UI complaints constituted the study population. Two groups were created according to age, under 60 years old (n=47) and 60 years old and over (n=45). When the patient groups aged <60 years and ≥60 years were compared, it was found that the BMI and waist circumference of the patients aged ≥60 years were significantly higher than those of the young (respectively; p=0.034 p= <0.001) (Table 1). Again, the mean number of medications used by the older group was higher more than the younger group, significantly, (p= <0.001). Diuretic and anticholinergic use was higher in the older group than in the younger group (respectively; p= <0.001 p=0.006). The number of comorbidities was higher in patients aged >60 years (p=0.002). The number of patients with type 2 DM was also higher in the older group (p=0.025). The number of vaginal deliveries was 4±2 (mean±S.D) in the ≥60 age group and 2±1.50 (mean±S.D) in the <60 age group, and this difference was statistically significant (p= <0.001) (Table 1). Nocturia was present in 63% of all patients, 55.30% of patients aged <60 years and 71.10% of patients aged ≥60 years, but this difference was not statistically significant (Table 1).

In the comparison between patients with (n= 26) and without nocturia (n= 21) in order to evaluate the factors affecting nocturia in the patient group under 60 years of age, no significant difference was found in terms of demographic and clinical data (Table 2).

There were 32 patients with nocturia and 23 patients without nocturia in the 60 years and older group. The mean number of medications used by patients with nocturia was significantly higher than that of patients without nocturia in the older group (p= 0.04). Also, the number of patients with Type 2 DM in the older group with nocturia (n= 15, 49.20%) was significantly higher than the number of patients with Type 2 DM in those without nocturia (n= 2, 15.40%) (p= 0.036) (Table 3).

Table 1. Demographic and clinical data of the participants.

	<60 age (n=47)	≥ 60 age (n=45)	Total (n=92)	p value
Age (mean±S.D)	48.7±8.5	70.2±7	59.2±13.3	**<0.001**
Height (m) (mean±S.D)	1.6±0.3	1.4±0.1	1.5±0.1	**0.005**
Weight (kg) (mean±S.D)	75.1±12.7	77.2±13.8	76.1±13.2	0.574
Waist circumference (cm) (mean±S.D)	96.6±11.2	106.9±13.2	101.6±13.2	**<0.001**
BMI (kg/m^2) (mean±S.D)	29.9±5.2	32±5.1	31±5.2	**0.034**
Number of medications (median, 25-75)	1.6 (1.2-2.2)	4 (3-5)	2.8 (2.2-3.4)	**<0.001**
Number of diuretic use (n, %)	4 (8.5 %)	18 (40 %)	22 (23.9 %)	**<0.001**
Number of anticholinergic (n, %)	1 (2.1 %)	9 (20 %)	10 (10.9 %)	**0.006**
Number of comorbidities (median, 25-75)	1.5 (1.1-1.9)	2.4 (2-2.9)	1.95 (1.6-2.3)	**0.002**
Type 2 DM (n, %)	8 (17 %)	17 (37.8 %)	25 (27.2 %)	**0.025**
Chronic Kidney Disease (n, %)	0 (0 %)	1 (2.2 %)	1 (1.1 %)	0.304
Number of vaginal delivery (mean±S.D)	2±1.5	4±2	3±2	**<0.001**
ICIQSF (mean±S.D)	14.7±3.6	13.2±4.1	13.9±3.9	0.055
Nocturia (n, %)	26 (55.3 %)	32 (71.1 %)	58 (63 %)	0.117

p value is significant is under 0.05; **BMI: body mass index; **DM**: diabetes mellitus;*
***ICIQ-SF**: The International Consultation on Incontinence Questionnaire-Short Form; **S.D**: Standard Deviation.*

Table 2. Comparison of patients aged <60 years with and without nocturia in terms of demographic and clinical data.

	Nocturia (n=26)	None nocturia (n=21)	p value
Age (mean±S.D)	47.9±8.9	49.6±8.3	0.421
Height (m) (mean±S.D)	1.5±0.1	1.6±0.1	0.797
Weight (kg) (mean±S.D)	75.6±14.2	74.4±11	0.830
Waist circumference (cm) (mean±S.D)	96.4±12.4	96.9±9.7	0.570
BMI (kg/m^2) (mean±S.D)	30.1±6	29.7±4.1	0.949
Number of medications (median, 25-75)	1.7 (1-2.2)	2 (1.4-2.6)	0.974
Number of diuretic use (n, %)	2 (7.7 %)	2 (9.5 %)	0.823
Number of anticholinergic (n, %)	0 (0 %)	1 (3.8 %)	0.364
Number of comorbidities (median, 25-75)	1.4 (0.8-2.1)	1.6 (0.9-2.3)	0.666
Type 2 DM (n, %)	4 (15.4 %)	4 (19 %)	0.740
Chronic Kidney Disease (n, %)	0 (0 %)	0 (0 %)	
Number of vaginal delivery (mean±S.D)	2±1.6	2±1.4	0.982
ICIQSF (mean±S.D)	14.7±3.8	14.7±3.5	0.897

p value is significant is under 0.05; **BMI: body mass index; **DM**: diabetes mellitus;*

***ICIQ-SF:** The International Consultation on Incontinence Questionnaire-Short Form; **S.D**: Standard Deviation.*

Table 3. Comparison of patients aged ≥ 60 years with and without nocturia in terms of demographic and clinical data.

	Nocturia (n= 32)	None nocturia (n= 23)	p value
Age (mean±S.D)	71.4±7.1	67.2±5.9	0.052
Height (m) (mean±S.D)	1.55±0.04	1.56±0.04	0.870
Weight (kg) (mean±S.D)	78±14.6	75±11.6	0.625
Waist circumference (cm) (mean±S.D)	108.3±14	103.2±10.7	0.287
BMI (kg/m^2) (mean±S.D)	32.5±5.3	31±4.6	0.249
Number of medications (median, 25-75)	4.5 (3.5-5.6)	3 (1-5.5)	**0.04**
Number of diuretic use (n, %)	12 (37.5 %)	6 (46.2 %)	0.591
Number of anticholinergic (n, %)	8 (25 %)	1 (7.7 %)	0.188
Number of comorbidities (median, 25-75)	2.7 (2.2-3.1)	1.9 (1-2.9)	0.092
Type 2 DM (n, %)	15 (49.2 %)	2 (15.4 %)	**0.036**
Chronic Kidney Disease (n, %)	0 (0 %)	1 (7.7 %)	0.113
Number of vaginal delivery (mean±S.D)	4.1±2.1	3.6±2.1	0.420
ICIQSF (mean±S.D)	13.8±3.5	11.6±5.2	0.195

p value is significant is under 0.05; BMI: body mass index; **DM: diabetes mellitus;*

***ICIQ-SF**: The International Consultation on Incontinence Questionnaire-Short Form; **S.D**: Standard Deviation.*

DISCUSSION

Approximately half of patients with daytime urinary urgency are also known to have clinically significant nocturia (8). Therefore, to prevent further increased risk of nocturia, which is already high in patients with UI, we evaluated other factors influencing the occurrence of nocturia in women with UI. In our study, in which we assessed the factors affecting nocturia in young and older women patients with UI, we found that Type 2 DM and the high number of medications are risk factors for nocturia in older patients with UI.

There are many known risk factors for nocturia (18). Aging is one of the most important risk factors for nocturia. Studies in the literature support that the incidence of nocturia increases with age (19). In our study, the incidence of nocturia was higher in the older group than in the younger group. However, this difference was not statistically significant. This may be related with the low number of patients in the groups. Recognition and management of nocturia-associated factors are important, especially in older adults, as nocturia causes geriatric syndromes such as falls, hip fractures, immobility and weakness, lower sleep quality, increased fatigue, and depression. (18, 20- 22).

Caffeine, alcohol, anticholinergics, cholinesterase inhibitors, beta-blockers, diuretics, and with diuretic effects such as lithium are medications known to affect patients' nocturia (8). The reason for this may be that some medications with a high anticholinergic drug burden, such as antidepressants, and antipsychotics cause detrusor overactivation. Another reason may be drug interactions and adverse drug reactions, which increase as the number of medications taken increases. No relationship has been found between diuretic and anticholinergic use and nocturia in both age groups, while the high number of medications used in older patients was found to be associated with nocturia, in this study. In a recent study in the literature investigating the association between nocturia and comprehensive geriatric assessment parameters in older men, a positive correlation was found between the number of medications used and the frequency of nocturia (23). Also, in a study conducted in older women, a significant relationship was found between polypharmacy and nocturia, regardless of the type of medication used similar to our study (24). Both polypharmacy and UI are risk factors for nocturia. The combination of the two conditions may increase the risk of nocturia. In our study, it was found that the number of medications used in older women with UI was a risk factor for nocturia, but this association was not found in the younger group. Since the significantly lower number of medications used in the younger group check against the older group, increased medication interactions in older adults, and adverse medication reactions that occur as the number of medications increases may be related to this situation.

With the increase in aging, changes in lifestyle, increasing obesity rates, the incidence of Type 2 DM is also increasing. DM is one of the independent risk factors for UI in women. A study conducted in Turkey found that the prevalence of UI increased significantly in diabetic women (24). DM is also a known risk factor for nocturia (8). Diabetic neuropathy, osmotic diuresis due to glucosuria, and polydipsia due to dry mouth are the pathophysiologies thought to cause this condition (25). In a study investigating the risk factors for nocturia in both genders, DM was associated with nocturia in women but was not associated in men (26). Besides, in a study comparing young and old female patients, similar to our study, it was found that nocturia was more common in older women with diabetes than in younger women with diabetes (27). The fact that DM is a risk factor for both UI and nocturia suggests that the risk of developing nocturia may be increased in women with UI who have Type 2 DM. In our study, Type 2 DM was found to be a risk factor for nocturia in older women with UI. The reason that this result was not found in the young group may be due to the significantly lower incidence of Type 2 DM in young patients compared to the older group.

It is known that the prevalence of nocturia is high in chronic kidney disease (CKD) patients and its severity is related to the stage of the disease (28). However, this relationship could not be found because the number of patients with CKD was very small in our study.

The strength of our study is that, according to our

knowledge, it is the first study to assess the risk factors affecting nocturia in young and older women with UI. Our study has some limitations. The first limitation is the absence of a control group without UI. The second limitation is the small number of patients in the groups. Our study needs to be supported by studies with a higher patient numbers, including the control group without UI.

CONCLUSION

The basic approach in incontinence patients with nocturia is based on the underlying cause. In our study, Type 2 DM and the number of medications used are risk factors for nocturia in the older group. More effective clinical results may be obtained with a multidisciplinary approach by questioning the presence of Type 2 DM and multiple medication use in this patient group in more detail, or by examining the presence of nocturia in patients with these risk factors.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by Ethical Committee of İstanbul Medipol University (Approval Number: 1051, 26.10.2021) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; MS, RBS, Data acquisition; MS, RBS, Data analysis and interpretation; MS, RBS, Drafting the manuscript; MS, RBS, Critical revision of the manuscript for scientific and factual content; MS, RBS, Statistical analysis; MS, RBS, Supervision; MS, RBS.

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Case Report / Olgu Sunumu

Spontaneous severe retroperitoneal hemorrhage with concomitant renal pelvis rupture during the course of COVID-19 infection: a case report

COVID-19 enfeksiyonu geçiren hastada böbrek pelvis rüpürünün eşlik ettiği spontan ciddi retroperitoneal kanama: olgu sunumu

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Özet

Spontan renal pelvis rüptürü nadir rastlanılan ürolojik olay olup idrarın extravazasyonuna neden olan bir durumdur. Sıklıkla üriner sistemde gelişen obstrüksiyonlara sekonder olarak pelvis içi basıncın artması sonucu gelişir. Spontan retroperitoneal hematom da yine benzer şekilde travma veya altta yatan bir patoloji olmaksızın ortaya çıkan retroperitoneal kanamalardır. Bu çalışmada 63 yaşında antikoagulan tedavisi alan Covid-19 tanılı bir bayan hastada, retroperitonda spontan olarak oluşan hematom ve hematomun basısına sekonder olarak gelişen spontan renal pelvis rüptürü olgusunu sunuyoruz. Bu olgu ışığında Covid-19 infeksiyonuna bağlı yaygın endotel hücre hasarının, spontan ciddi retroperitenal kanamaya ve eşlik eden renal pelvis rüptürüne neden olabileceğini vurgulamak istiyoruz. Nadir görülen durumlar olan spontan renal pelvis rüptürü ve spontan retroperitoneal kanamanın aynı anda aynı hastada görüldüğü literatürde ilk kez bildirilmektedir.

Anahtar Kelimeler: antikoagulan tedavi, COVID-19, renal pelvis rüptürü, retroperitoneal hematom, üriner obstrüksiyon

Abstract

Spontaneous rupture of the renal pelvis is a rarely encountered urological event that causes extravasation of urine. It often occurs as a result of increased intrapelvic pressure secondary to obstructions developed in the urinary system. Similarly spontaneous retroperitoneal hematoma is retroperitoneal hemorrhage that occurs without trauma or an underlying pathology. In this study, we present a case of spontaneous rupture of the renal pelvis that developed secondary to compression of the hematoma that occurred spontaneously in the retroperitoneum in a 63-year-old female patient who received anticoagulant therapy with the diagnosis of Covid-19 infection. In the light of this case, we would like to emphasize that widespread endothelial cell damage associated with Covid-19 infection may cause spontaneous severe retroperitenal bleeding and accompanying renal pelvis rupture. In which both the rarely encountered spontaneous rupture of the renal pelvis and spontaneous retroperitoneal bleeding are seen simultaneously in the same patient, is reporting for the first time in the literature.

Keywords: anticoagulant treatment, COVID-19, renal pelvis rupture, retroperitoneal hematoma, urinary obstruction

INTRODUCTION

Spontaneous or atraumatic renal pelvis rupture is an extremely rare condition. It usually develops after a pathological condition that leads to obstruction in the urinary system (1). It has been reported that the renal pelvis, which is very poorly supported by the parenchyma of the kidney, cannot withstand the increasing pressure after the emerging obstruction and ruptures (2). Urine extravasation occurs following development of rupture, and complaints such as flank pain, abdominal pain, nausea and vomiting become manifest as in the case with urinary stone disease (3). Similarly, spontaneous retroperitoneal hematoma is also a rare event and it is a retroperitoneal bleeding that occurs without trauma, urinary stone disease, or an underlying pathology. In this study, we report a case of spontaneous rupture of the renal pelvis that occurred secondary to compression of the hematoma developed in the retroperitoneum in a female patient diagnosed with Covid-19 infection who received anticoagulant therapy. As far as we know, this case, in which both the rarely encountered spontaneous rupture of the renal pelvis and spontaneous retroperitoneal bleeding are seen simultaneously in the same patient, is reported for the first time in the literature.

CASE REPORT

A 63-year-old female patient applied to our emergency department with complaints of weakness, high fever, cough and shortness of breath. It was learned that the patient, who had no history of systemic disease, had a positive Covid-19 test performed in another center 3 days ago. Chest Computed Tomography (CT) of the patient revealed findings compatible with acute viral pneumonia. Then the treatment of the patient was initiated with ceftriaxone [(2 x 1 gram (g) / intravenous (iv)], hydroxychloroquine [(2 x 200 milligram (mg)], ascorbic acid (2 x 3 g iv) and enoxaparin sodium [(2 x 6000 international units (IU) / 0,6 milliliter (ml)]. Four days after her hospitalization, the patient developed colicky pain felt on the left flank and lower abdominal quadrants. Urology consultation was requested because the patient with an urethral catheter had no urine output for the last 3 hours and swelling in the suprapubic region was detected, considering that the patient developed urinary retention. On physical examination, costovertebral angle tenderness on the left side and a mass localized slightly to the left in the suprapubic area were palpated. Ultrasonography revealed the presence of an empty bladder and a large cystic appearance adjacent to the left lateral posterior wall of the bladder. Mild hydroureteronephrosis was found on the left side of the patient's CT, which was taken without contrast agent administration (Figure 1A). No contrast agent leakage was detected in the perirenal or periureteral area in the CT taken immediately after the patient was administered iv contrast agent (Figure 1B). The absence of contrast medium leakage may be due to CT taken immediately after administration of the contrast agent. However no fluid collection was observed in the perirenal area in the same film. In order to monitor the ureters, CT scan was performed again 15 minutes after contrast agent administration. Significant extravasation of contrast material and fluid collection were detected in the perirenal and periureteral area (Figure 1C). On the lower abdomen tomography, a cystic mass consistent with a hematoma of approximately 13 cm, originating from the abdominal anterolateral wall muscles, extending to the left posterolateral side of the bladder and pushing the bladder towards right anterolateral direction was detected (Figure 2). Urinary extravasation and the bladder pushed by the hematoma were clearly detected in three-dimensional CT (Figure 3A). The patient underwent emergency operation due to a decrease in her hematocrit values and deterioration in her hemodynamic parameters despite blood transfusion. The hematoma was evacuated by controlling the bleeding focus localized on the lateral aspect of the rectus muscle. The patient was treated conservatively for renal pelvis rupture. In the control tomography taken on the 3rd postoperative day of the patient, who was followed up with a catheter, the fluid around the renal pelvis and ureter was absorbed. Extravasation of contrast agent was not detected and the bladder was found to return to its normal position (Figure 3B). The patient was discharged after completion of her Covid-19 treatment. Radiological investigations did not reveal the presence of a urinary stone. The patient had no history of urinary stone disease and renal mass.

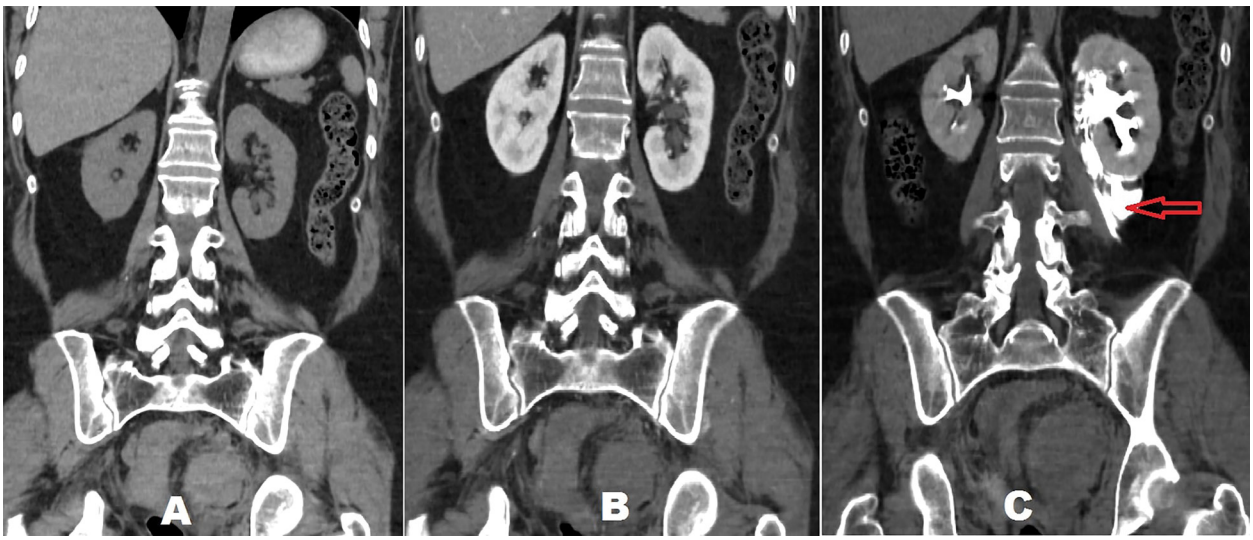


Figure 1.A: Computed Tomography (CT) image taken before administrationn of the opaque material: Any fluid collection is not seen in the perirenal area
B: CT image obtained after administration of contrast material. Still, any fluid collection and extravasation of contrast material is not seen.
C: CT image taken 2 hours after administration of contrast material: Intense contrast material extravasation is seen (red arrow).

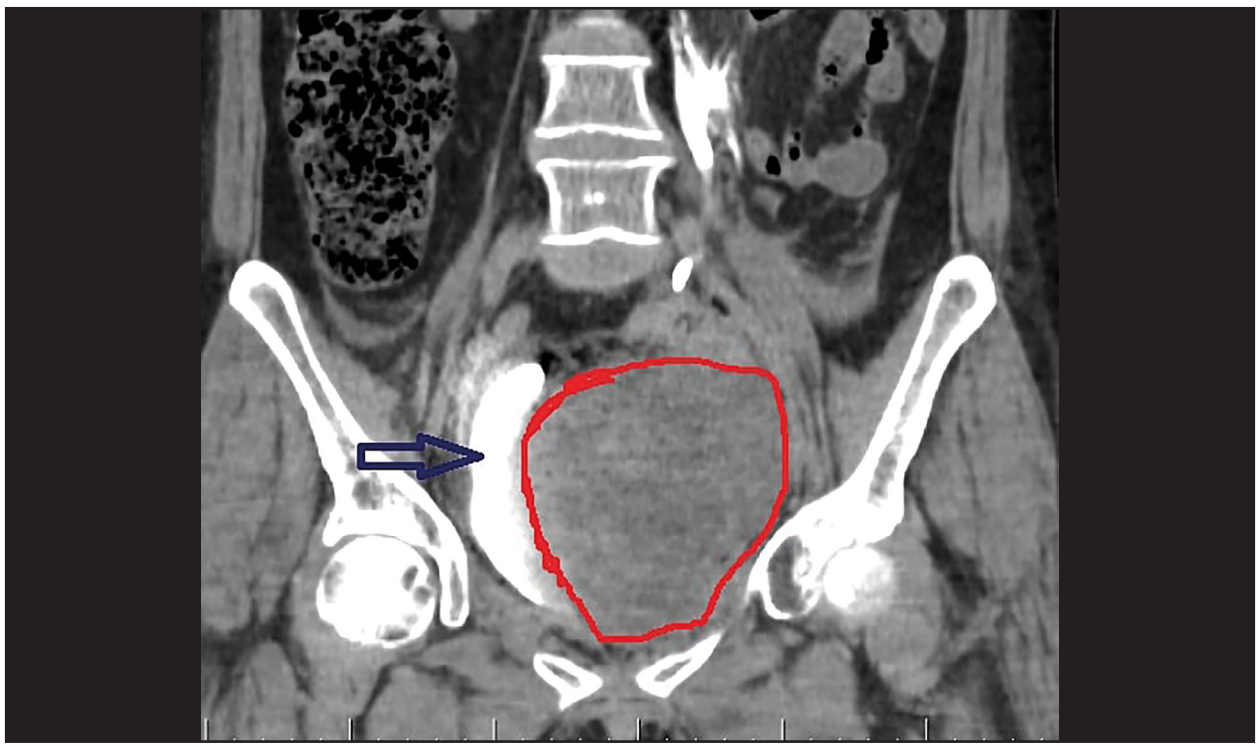


Figure 2: Computed Tomography image of retroperitoneal hematoma (area surrounded by red lines) pushing the bladder (blue arrow) to the right

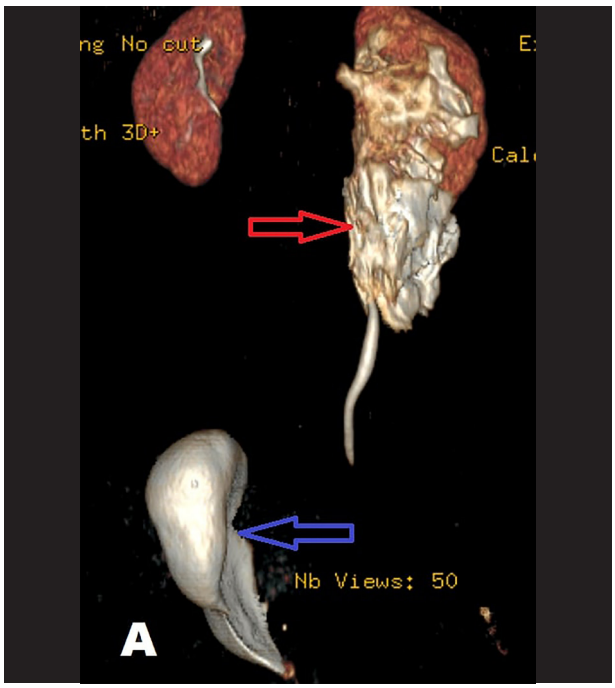
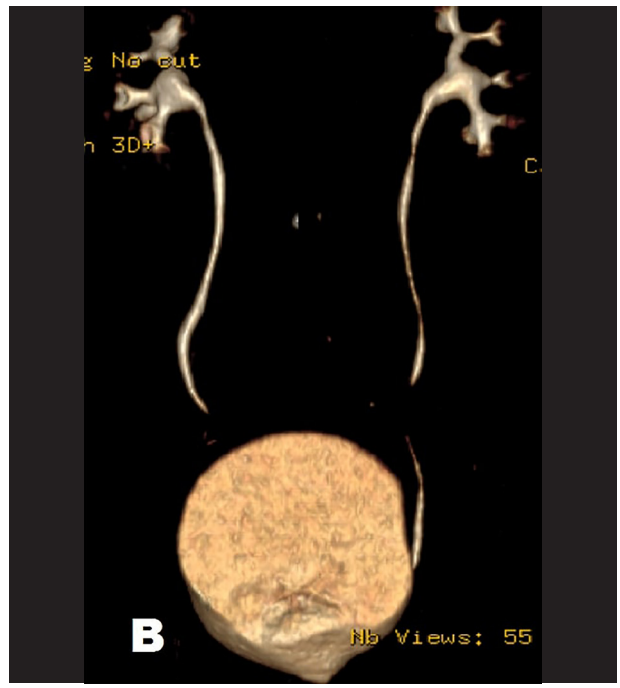


Figure 3.A: Urine extravasation (red arrow) due to left renal pelvis rupture is seen. The bladder is pushed to the right (blue arrow) due to compression of the hematoma.



B: Computed Tomography image taken on the 3rd postoperative day after the evacuation of the hematoma: Urine extravasation is not observed and the bladder is in its normal position.

DISCUSSION

Spontaneous rupture of the renal pelvis with urine extravasation is a rare condition and usually occurs in cases of urinary obstruction due to the presence of stones and tumors. Also, extrinsic factors such as pregnancy, hematoma or tumors of adjacent organs may play a role in the development of renal pelvis rupture by causing obstruction.

Extravasation of urine is defined as the escape of the urine from at any level of the urinary collecting system extending from calyces to the urethra. This condition is defined spontaneously if it has occurred due to etiologic factors other than trauma, iatrogenic manipulation, previous surgeries or the presence of degenerative kidney disease (4). It has been reported that rupture is often seen in fornices with thinner wall and in cases where the intrapelvic pressure rises above 25 -75 mmHg (4). In a systematic review of 108 cases, Gershman et al., indicated that stone-related obstruction (74.1%) was the most common cause of spontaneous renal pelvis rupture (5). Compressions caused by abdominal/pelvic masses or pregnancy, retroperitoneal fibrosis, congenital abnormalities, iatrogenic or post-radiation strictures are among the other causes. In the same study, in 8.3% of the cases, any etiologic factor for rupture could not be demonstrated.

It has been reported that the increased pressure within the pelvicalyceal system may cause rupture of the renal pelvis, leading to urinary extravasation (6). Contrast agents are reported to be strong osmotic diuretics and accelerate rupture in acute obstructive conditions (7). In another study, a positive association between the incidence of peripelvic extravasation of contrast agent and intravenous dose of contrast agent has been demonstrated in patients presenting with acute renal colic (8). In another study, Chien et al. reported a case of bilateral spontaneous renal rupture after administration of opaque agent to a patient with increased residual urine due to benign prostatic hyperplasia (9). Our case may also be important in terms of showing the relationship between contrast material and urine extravasation. In our case, urinary extravasation was not observed in the early period following the administration of contrast material, while obvious

urinary extravasation was observed in the late period. This is an important finding as it shows that administration of contrast agent facilitates the development of spontaneous renal rupture in the obstructed urinary tract.

Spontaneous retroperitoneal hematoma is also a rare condition, defined as retroperitoneal bleeding that occurs without an underlying pathology, trauma, surgery, or invasive intervention (10). The retroperitoneal space is located just behind the peritoneum and it is divided into three zones as: the central-medial zone (Zone I), the perirenal zone (Zone II) and the pelvic zone (Zone III) which includes the bladder (11). Rupture of parenchymal lesions such as angiomyolipomas, cysts, and renal carcinomas or aneurysms of the retroperitoneal vessels can lead to spontaneous retroperitoneal bleeding. It has been reported that a high degree of clinical suspicion is required to make a diagnosis (11). It is a clinical picture progressing with high mortality and morbidity rates, and it has been reported to be frequently associated with anticoagulant use (12). In the literature, a mortal case of massive retroperitoneal hemorrhage due to enoxaparin use has been reported (13). In a previous study, it was reported that endothelial damage is an important clinical finding in severe Covid-19 patients (14). Therefore, it has been stated that the risk of thrombosis or bleeding in critically ill patients with Covid-19 is higher than in healthy people (15). The patient we described was also receiving enoxaparin treatment for Covid-19 infection. Respiratory distress and increased pressure due to coughing may be the cause of bleeding in this patient receiving anticoagulant therapy.

The main principle for the treatment of spontaneous rupture of the renal pelvis is to eliminate the underlying problem, if possible. As in our case, by evacuating the hematoma, relieving pressure on the ureter and reducing renal pressure can provide spontaneous recovery. However, in cases where obstruction cannot be eliminated immediately, such as tumor invasion, a double J ureteral stent should be inserted, and if not possible, a percutaneous nephrostomy tube should be inserted to provide decompression of the kidneys. Use of anticoagulants is prevalent in most patients with spontaneous retroperitoneal hematoma, and a reversal of the coagulopathy is required to prevent further bleeding (11). If needed, blood transfusion should be performed. Sometimes, if the bleeding focus can be localized, embolization may be required. More rarely, the patient's hemodynamic parameters may be impaired and surgical intervention may be required, as in our case.

CONCLUSION

In our study, we report a case of spontaneous rupture of the renal pelvis that occurred in patient with Covid-19 infection who were receiving anticoagulants. The reason for the rupture was the hematoma that developed due to spontaneous retropertioneal bleeding causing obstruction by compressing the ureter. Widespread endothelial cell damage associated with Covid-19 infection might be the underlying mechanism for the spontaneous retroperitenal bleeding. Therefore, in patients with Covid-19 infection spontaneous renal rupture and spontaneous severe retroperitoneal bleeding should be considered as a possible urological emergency.

Conflict of Interest

All authors declared that there is no conflict of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

Conception and design; OA, ME, ND, KÇ, Data acquisition; OA, ME, Data analysis and interpretation; OA, ME, ND, KÇ, Drafting the manuscript; OA, ME, ND, Critical revision of the manuscript for scientific and factual content; OA, ME, ND, KÇ, Supervision; OA, KÇ.

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Case Report / Olgu Sunumu

Sphenoid wing metastasis of prostate cancer: a rare case

Prostat kanserinin sfenoid kemik metastazı: nadir bir olgu

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Özet

Prostat kanserinin sfenoid kanat metastazı son derece nadir bir durum olup özellikle ilk başvuru anında beklenen bir bulgu değildir. Kafa tabanı kemiklerine olan metastazların gösterilmesi güç bir durumdur. Bu durum bazen nörolojik ve görme ile ilgili problemlere sebep olabildiği için klinisyen tarafından kolaylıkla atlanabilir. Prostat karsinomunun nörolojk veya görme ile ilgili semptomlara eşlik ettiği durumlarda intrakranial metastaz olabileceği hatırlanarak gerekli görüntülemeler yapılmalıdır. İntrakranial metastaza bağlı semptomu olan hastalara palyatif radyoterapi uygulanabilmesine rağmen hastalığın prognozu çoğunlukla kötüdür. Biz bu yazımızda sfenoid kanat metastazı tespit edilen 75 yaşındaki prostat kanserli olguyu literatürü de gözden geçirerek tartıştık.

Anahtar Kelimeler: prostat kanseri, sfenoid kemik, metastaz

Abstract

A sphenoid metastasis of prostate cancer is an extremely rare entity and it is not an expected finding especially in the first presentation. It is difficult to demonstrate the metastasis on skull base. Sometimes, it may cause neurological and vision problems, and can be easily omitted by clinician. When prostate carcinoma is accompanied by neurological and vision problems, one should keep in mind that these may be related to intracranial metastasis, and should perform necessary imaging studies. Patients with symptoms related to intracranial metastasis can take receive palliative radiotherapy but prognosis is generally poor. In this report, we discussed a 75 years-old patient with prostate cancer and sphenoid metastasis under the light of current literature.

Keywords: prostate cancer, sphenoid bone, metastasis

INTRODUCTION

Although the prostate cancer was reported to have been metastases most frequently to the bones, it is well known that the sphenoid metastasis is extremely rare. Lindsberg et al. had previously reported a case of bilateral sphenoid wing metastasis (1). Although metastasis to the skull base can be seen as the first finding of prostate cancer, it usually manifests itself late in the course of the disease (2). The syndromes described as regards the metastatic site include the orbital, parasellar, middle-fossa, jugular foramen, and occipital coldly syndrome. Computed tomography (CT) and bone scintigraphy are helpful to demonstrate bone erosion. However, Magnetic Resonance Imaging (MRI) is more useful examination method for diagnosis. Radiotherapy is the standard treatment method. However, hormone-sensitive or chemosensitive patients can benefit from hormone therapy or chemotherapy. Lesions can be surgically removed in selected patients (3). In this article we discussed a 75 years old patient with sphenoid wing metastasis of prostate cancer.

CASE REPORT

A 75 years old male patient applied to our outpatient clinic with the complaint of voiding difficulty lasting for three months duration. In his anamnesis internal urethrotomy operation had been performed due to urethral stricture six months ago. In addition, the Prostate Spesific Antigen (PSA) value was found to be 20 ng/ml and 12 core prostate biopsies were reported as benign. Physical examination was normal except for swelling and strabismus in the left eye. The prostate gland was palpated as endured and diffuse hard on digital rectal examination. PSA value were found to be as 98 ng/ml. Thereupon, 12 core prostate biopsy was performed again under transrectal ultrasound (TRUS) guidance. The result of histopathological examination was reported as prostatic adenocarcinoma Gleason 4+4. In the whole body bone scintigraphy, an image compatible with metastasis was seen in the ala major region of the sphenoid bone and at the base of the left orbit. A cranial, orbit and paranasal region CT revealed a mass lesion involving ala majora of the left sphenoid bone (Figure 1). Thereupon, antiandrogen (bicalutamide 50 mg) and bisphosphonate treatments have started and the patient underwent bilateral orchiectomy procedure with simultaneously transurethral resection of prostate (TUR-P) procedure to relieve the lower urinary tract symptoms. During cystoscopy, it was observed that the left ureteral orifice was occupied by tumoral prostate tissue. Histopathological evaluation of TUR-P material was reported as acinar type prostate adenocarcinoma Gleason 4+5 (Figure 2). The PSA value of the patient, measured after three months, was found to be 9.2 ng/ml. At the third month, control CT was performed to reevaluate the status of the lesion in the sphenoid bone. Comparison of the control cranial tomography with the first images revealed that there was no significant change in the lesion. The patient was consulted radiation oncology and radiotherapy was considered for metastasis in the sphenoid wing. However, the patient died 4 months after the initial diagnosis due to intervening pulmonary infections and poor general condition. The patient and his relatives signed an informed consent agreement.

DISCUSSION

Prostate cancer metastases most commonly affect bone tissue. In addition, visceral organs such as the lung, liver and adrenal gland, as well as tertiary lymph nodes in the mediastinal and supraclavicular regions may be involved. (4). The intracranial metastasis of prostate carcinoma is a relatively rare entity. In antemortem studies the rate of intracranial metastasis due to a prostate carcinoma has been reported to be 0.1-0.2% (5). In large autopsy series a 1.3% to 2% rate of intracranial metastasis due to prostate adenocarcinoma has been reported (6).

Patients with intracranial metastasis of prostate cancer generally present with neurologic symptoms and this situation can be overlooked by many clinicians. The sphenoid bone metastasis of prostate cancer is an extremely rare occurrence (1). It may be difficult to identify metastatic lesions to the ethmoid, sphenoid, and sometimes frontal, temporal, and occipital bones with current imaging methods. Even in autopsies it might be hard to demonstrate these lesions (7). It should be kept in mind that intraocular metastasis can develop due to prostate carcinoma in patients with

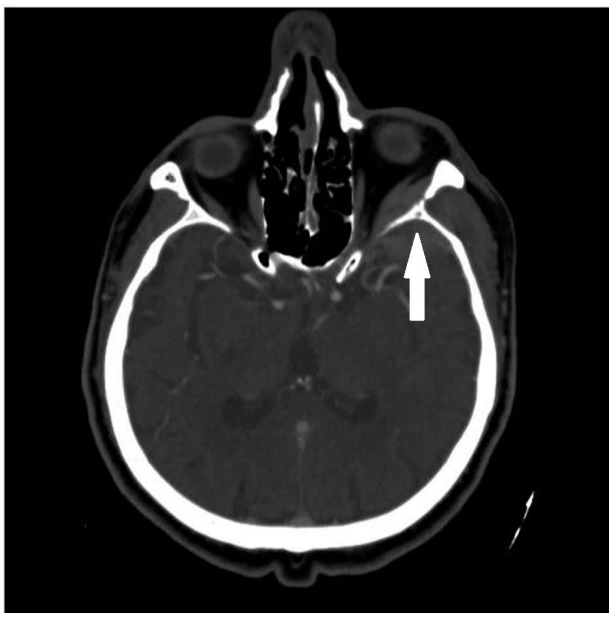

Figure 1: Brain CT; Sphenoid wing metastasis of prostate carcinoma (white arrow)

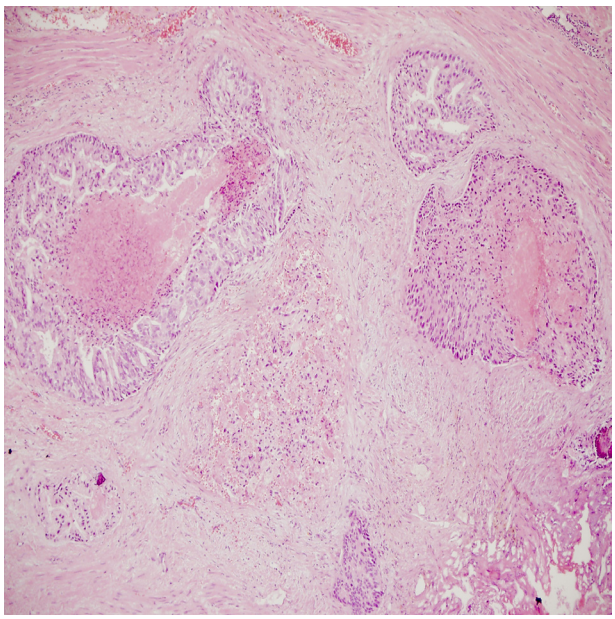

Figure 2: Adenocarcinoma areas in which Gleason score is 4+5 in TUR-prostatectomy material.

eye problems. Orbital and ocular metastases associated with prostate cancer have also been reported (8, 9).

Clinical staging of prostate cancer is done with the AJCC (American Joint Committee on Cancer) TNM (tumor-node-metastasis) system. Digital rectal examination, PSA measurement, and TRUS-guided prostate biopsy can be used in the diagnosis, localization, and staging of prostate cancer. Multiparametric MRI makes an important contribution in this staging. (10). Methods such as CT, MRI or lymph node sampling can be used to evaluate lymph node involvement. MRI has no significant superiority over CT in demonstrating lymph node involvement (11). Imaging methods such as thoracoabdominal CT, MRI and Tc-99m methylene diphosphonate (MDP) can be used for metastasis evaluation. MRI is more sensitive than CT and bone scintigraphy in detecting small bone metastases (12). Ga-68 PSMA PET/CT is an imaging method that has found more use in recent years. It is used in the evaluation and treatment planning of patients with biochemical recurrence after primary curative treatments, and in the detection of metastatic disease in the initial staging of high-risk prostate cancer (13, 14). It can also be used in patient selection before PSMA-based theranostic (therapeutic+diagnostic) applications (15).

CT can be used to show lytic bone lesions in the diagnosis of skull base metastasis. However, MR imaging is more superior in the diagnosis of accompanying dural invasion and brain metastasis. Radionuclide bone scan has a relatively weaker sensitivity in the diagnosis of lytic bone lesions. Remodeling of the one is needed for this technique to be useful. Although bone scintigraphy is negative, MR imaging can give positive results (16).

The skull base metastasis of the prostate cancer can be via direct invasion, lymphatic spread and/or vascular embolization. Prostate cancer is a tumor sensitive to radiotherapy, chemotherapy, and hormone therapy. In the treatment of the metastasis to the skull base of the primary prostate cancer, conventional fractional radiation therapy is the standard treatment as well as radio surgery and stereotactic radiation technique. Moreover, chemotherapy can be used in cases where unsuccessful maximal androgen blocking hormone therapy in prostate carcinoma with bone metastasis. In skull base tumors, surgical treatment is limited with selected cases. It should be kept in mind that long term use of bisphosphonate for palliative treatment in patients with painful bone metastasis can cause mandibular bone necrosis (16).

The prognosis of patients with skull base metastasis is not good and average life expectancy is less than 1 year. The survival rates in patients with cranial nerve paralysis have been reported to be less than 5 months (17). Our patient died 4 months after the first diagnosis, which is consistent with the literature. Clinicians should be vigilant to recognize skull base metastasis of prostate carcinoma. An intracranial metastasis should be suspected and the necessary imaging studies performed especially when neurologic signs and sights problems are accompanied by prostate cancer.

Conflict of Interest

All authors declared that there is no conflict of interest.

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Author Contributions

Conception and design; FA, Data acquisition; FA, Data analysis and interpretation; FA, Drafting the manuscript; FA, Critical revision of the manuscript for scientific and factual content; FA, Statistical Analysis; FA, Supervision; FA.

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Review / Derleme

Is it time to stage prostate cancer using molecular imaging?

Prostat kanserinde moleküler görüntüleme ile evrelemenin vakti geldi mi?

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Özet

Prostat kanseri erkeklerde en sık saptanan kanserlerden birisidir. Tanı koyulduktan sonra tedavi planlaması ve prognozun öngörülebilmesi amacı ile görüntüleme yöntemleri eşliğinde evreleme yapılması gereklidir. Son yıllarda yaşanan teknolojik ilerlemeler ışığında yeni görüntüleme yöntemleri klinik kullanıma girmiştir. Bu amaçla Prostat spesifik membran antijeni (PSMA) pozitron emisyon tomografisi (PET) görüntüleme yöntemi ön plana çıkmıştır. Anatomik ve fonksiyonel görüntüleme sağlaması nedeni ile tümoral (T), nodal (N) ve metastatik (M) açıdan evrelemede birçok avantaja sahiptir. Bu derlemede prostat kanseri evrelemesinde PSMA-PET yönteminin güncel durumu ele alınmıştır.

Anahtar Kelimeler: prostat kanseri, evreleme, pozitron emisyon tomografi

Abstract

Prostate cancer is one of the most common cancers in men. After the diagnosis is made, staging should be undertaken with imaging methods in order to plan the treatment and predict the prognosis. Parallel to technological developments in recent years, new imaging methods have entered into clinical use. Among these methods, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has come to the fore since it provides anatomical and functional imaging and has many advantages in tumor (T), nodal (N) and metastatic (M) staging. This review discusses the current status of the PSMA-PET method in prostate cancer staging.

Keywords: prostate cancer, staging, positron emission tomography

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers in men. It is strongly suspected in the detection of abnormal digital rectal examination (DRE) findings and/or increased prostate specific antigen (PSA) levels. The exact diagnosis of PCa is made after the histopathological examination of the tissue obtained by a needle biopsy of the prostate (1). The most common prostate malignancy is prostatic adenocarcinoma.

After the diagnosis of PCa, it is necessary to use clinical data and imaging methods to determine the risk level and stage the disease. Clinical data used to determine the risk level include DRE findings, serum PSA level, and Gleason score obtained during biopsy. Using these data, patients can be classified as low-, medium- and high-risk groups (D'Amico risk classification) (2,3) (Table 1). It is necessary to stage the disease using imaging methods in order to plan the treatment to be applied after diagnosis, perform follow-up after treatment, and predict prognosis. With the technological advances in recent years, new imaging methods have been introduced into clinical use, and it is considered that they will find more place in staging in the near future (4). Multi-parametric magnetic resonance imaging (mpMRI) and positron emission tomography (PET) stand out among new imaging methods that have been adopted in clinical use in recent years.

Recently, PET imaging has become the most investigated method since it provides both anatomical and functional evaluation (5). Prostate-specific membrane antigen (PSMA) is a 750-amino acid transmembrane glycoprotein with folate hydrolase activity expressed by the prostatic epithelium known as N-acetyl-L-aspartyl-L-glutamate peptidase 2 or glutamate-carboxypeptidase. PSMA is a multifunctional enzyme-acting protein capable of activating signaling cascades related to cell nutrition, survival, proliferation, and migration, and the increased expression of this protein in PCa and different malignancies serves as an important theranostic target (6). The theranostic approach is the name given to the combination of a therapeutic agent and a diagnostic method used to define the effect of this agent. It is formed by combining the words therapy and diagnostics/diagnosis. In PET imaging, PSMA is labelled with Gallium-68 (Ga-68) or Fluorine-18 (F-18) radioisotopes to reach the target tissue. Compared to F-18, Ga-68 has many advantages, such as lower positron energy emission and longer half-life, which improves image quality. Therefore, Ga-68 has come to the fore in PET imaging, becoming the most researched method in terms of PCa in recent years. Ga-68 is a Ge-68/Ga-68 generator product with a half-life of 67.63 minutes and a positron emission of 89%. Ga-68-labeled PSMA inhibitor radiosynthesis was first demonstrated by Banerjee et al. at Johns Hopkins University on a preclinical model (7). Later, Eder et al. developed Ga-68 PSMA-11 and showed that this agent specifically entered the cell and maintained its high levels in human prostate cancer cells (8). Since then, other compounds with similar bio-distribution and imaging features, including Ga-68 PSMA-617 and Ga-68 PSMA I&T have also been developed (9). Ga-68 PSMA compounds are all abbreviated as Ga-68 PSMA in international guidelines due to their similarities. In the initial staging of PCa, although there are only limited scientific data, Ga-68 PSMA PET/CT is generally recommended as a new-generation imaging method, since it can provide additional information and potentially contribute to the prediction of possible changes in disease management if conventional imaging is negative or there are suspicious findings (10-12). The latest European Urology Association PCa guidelines state that Ga-68 PSMA PET/CT offers more precise staging than conventional CT and whole body bone scintigraphy in the initial staging of high-risk PCa; however, it is also emphasized that there are not yet sufficient results to prove this. Nevertheless, it is considered that molecular imaging methods will play a larger role in the near future. In this review, the growing role of PET imaging in tumoral (T), nodal (N) and metastatic (M) staging of the disease is summarized.

Role of PSMA-PET/CT in tumor staging

As is known, T staging is generally based on DRE findings. Depending on the practitioner's experience, this subjective method determines the patient's T stage by evaluating parameters such as whether the tumor is palpable, involvement of the lobes, and signs of inva-

Table 1: D'Amico risk classification

Definition			
Low risk	**Medium risk**	**High risk**	
PSA < 10 and GS < 7 (ISUP 1) and cT1-2a	PSA 10-20 or GS 7 (ISUP 2/3) or cT2b	PSA > 20 or GS > 7 (ISUP 4/5) or cT2c	Any PSA value Any GS cT3-4 or cN+
Localized			**Local advanced**

***GS**: Gleason score, **ISUP**: International Society of Urological Pathology, **PSA**: Prostate-specific antigen*

sion (13,14).The contribution of conventional imaging methods to T staging is limited. In parallel with the technological advances in recent years, these limitations have been significantly overcome with mpMRI. The addition of at least two of three methods (diffusion-weighted and contrast-enhanced imaging, and/or apparent diffusion coefficient mapping) to conventional T1 or especially T2-weighted imaging has significantly contributed to the detection of clinically important PCa cases. Although mpMRI has a high negative predictive value, it is clear that there are lesions that cannot be visualized by MRI (15). In a recent prospective study by Lopci E et al., the diagnostic value of Ga-68 PSMA-PET/CT was investigated on 97 patients with suspected PCa, who had negative or positive findings of mpMRI but negative prostate biopsy results. A targeted fusion prostate biopsy was carried out in 64 patients who had PET-positive areas, and clinically significant PCa was detected in 36% (n = 23) of these patients. The authors concluded that Ga-68 PSMA-PET/CT would be sufficient to detect clinically significant PCa in cases where PCa suspicion continues despite a negative initial biopsy (16). In another study in which 21 high-risk PCa cases were evaluated for primary staging, conventional imaging methods and PSMA-PET imaging were compared in terms of their diagnostic accuracy. It was reported that PSMA-PET had a higher diagnostic accuracy than MRI, CT and bone scintigraphy. Although PSMA-PET was not superior to mpMRI in detecting prostatic lesions, it had higher performance in detecting lymph node involvement compared to MRI (95.2% vs 80%). It was also reported to have higher sensitivity than conventional CT in detecting extrapelvic lymph node and bone metastases (100% vs. 75% and 100% vs. 62.5%, respectively) (17). With the development in PET MRI methods and their adaptation to biopsy procedures, they are expected to have higher sensitivity and specificity in detecting PCa in the near future. In addition, studies conducted to evaluate extraprostatic extension before surgery and predict the preference of nerve-sparing surgery and possible biochemical recurrence have reported that PSMA-PET could be a useful imaging method in the assessment of these factors (18).

Role of PSMA-PET/CT in nodal staging

Enlarged lymph nodes dissection provides the most accurate nodal staging. Conventional imaging methods offer only limited information concerning lymph node involvement in preoperative clinical staging. According to calculations performed using the current nomograms of Briganti, Partin and Memorial Sloan Kettering Institute, bilateral enlarged lymph nodes dissection is recommended for patients with a >5% value (19,20). There are many studies concerning the use of the PSMA-PET method for nodal staging. In a study by Maurer et al. including 130 cases in the medium- and high-risk groups, the efficacy of PSMA-PET in detecting nodal involvement before radical surgery was evaluated compared to conventional methods. In that study, it was reported that conventional imaging methods were not sufficient in demonstrating lymph node involvement before radical prostatectomy, while PSMA-PET had higher sensitivity but moderate specificity and reduced the possibility of lower staging of the disease (21). In a meta-analysis conducted by Kim et al., the sensitivity and specificity of PSMA-PET in detecting nodal involvement in medium- and high-risk patients were reported as 71% and 95%, respectively.

Although the authors noted that a more accurate result was achieved in patients with PSMA-PET positivity, they also emphasized that lymph node involvement could not be definitively excluded in those with negative results (22). In another retrospective study evaluating high-risk PCa cases in terms of lymph node involvement, Badaus et al. found the sensitivity and specificity of PSMA-PET to be 33.3% and 100%, respectively. The authors underlined the importance of size in the evaluation of nodal involvement and found the mean size to be 4.3 mm for false-negative metastases and 13.8 mm for node-positive cases (23). In another recent meta-analysis assessing current imaging methods used for lymph node staging, the sensitivity and specificity of diffusion-weighted imaging-MRI in detecting nodal involvement smaller than 1 cm were found to be 41% and 94%, respectively. It was also suggested that PSMA-PET had a higher sensitivity and would soon have a wider area of use in this patient group (24). In another study evaluating the use of Ga-68 PSMA-PET/CT in initial lymph node staging in 51 newly diagnosed high-risk PCa cases, the histopathological correlation analysis revealed that the sensitivity, specificity and accuracy values were 67%, 88%, and 81%, respectively for PSMA-PET and 20%, 99%, and 72%, respectively for conventional imaging (MRI and CT) in a subgroup of patients in which ≥15 lymph nodes were excised (n = 37). The authors stated that Ga-68 PSMA PET/CT was superior to conventional imaging in detecting nodal metastasis, but lymph node dissection remained the gold standard for nodal staging (25). According to these literature data, PSMA-PET/CT seems to have the potential to replace conventional abdominal-pelvic CT in the nodal staging of PCa.

Role of PSMA-PET/CT in M staging

PCa mostly metastasizes to the bone, which is most commonly detected using whole-body bone scintigraphy (26). However, there is an increasing number of studies reporting that PSMA-PET is more efficient in the determination of regional and extra-pelvic metastases compared to conventional imaging methods. (27) In a study involving 129 patients, Schmidt-Hegeman et al. reported that PSMA-PET was superior to CT in detecting distant metastases, and it also assisted in making a decision for adjuvant or salvage radiotherapy when PSA was >0.5 after prostatectomy (28). In recent years, with the widespread use of PSMA-PET, there has been a transition from localized disease and subsequent definitive treatments to systemic treatments. Bone metastases of PCa are mostly blastic-sclerotic; however, they can also be of mixed character, such as lytic-destructive and lytic-blastic. While bone metastases do not yet show reactive-blastic activity in bone tissue, active tumor cells can be detected in the early bone marrow period based onGa-68 PSMA in the presence of molecularly low PSA levels (29, 30). Hofman et al. examined the initial staging of high-risk PCa using Ga-68 PSMA-PET before definitive treatments, such as surgery and radiotherapy. In a multicenter prospective randomized phase III study (proPSMA study) including 302 patients, the authors found that Ga-68 PSMA-PET was superior to conventional methods in detecting lymph node and distant metastases (accuracy: 92% vs. 65%). They also stated that Ga-68 PSMA-PET could specifically detect nodal-visceral and early bone metastases in low-volume disease with high tumor/background activity (activity uptake observed in areas other than physiological distribution is interpreted as pathological). Thus, it was suggested that Ga-68 PSMA-PET assisted in planning an appropriate treatment and revising patient management if necessary, and it had the advantage of involving less radiation exposure compared to traditional methods (19.2 mSv vs. 8.4 mSv). It was also emphasized that there was a need to update current guidelines in light of this information (31). However, criticizing this study, Moore argued that the high cost of PSMA-PET and its low availability in healthcare centers were the most important barriers to the adoption of this method (32). Molecular imaging plays a role not only in staging but also in the treatment management of metastases by targeting PSMA. Targeting PSMA with Lutetium-177, also known as radioligand therapy, has been reported to be effective in the treatment of metastases in patients who have castration-resistant PCa, which is an extremely important development for this patient group (33,34). These findings show that PSMA-PET/CT has significant potential for a theranostic approach not only in the diagnosis phase but also in the treatment phase.

CONCLUSION

It is reported that PSMA-PET is a promising method that can singularly present the data obtained by the combined use of conventional tomographic imaging and whole body bone scintigraphy during the initial detection of PCa. In many recent studies, PSMA-PET/CT has been shown to be more efficient than conventional imaging methods in detecting the presence of intra-prostatic tumors, evaluating nodal involvement, and detecting distant metastases. Although there are no recommendations for the routine use of PSMA-PET in current guidelines, it would not be a far-fetched prediction to state that in the very near future, PSMA-PET will be increasingly adopted for the diagnosis and treatment of PCa and current guidelines will be updated accordingly, as this method becomes more commonly available and more affordable.

Conflict of Interest

All authors declared that there is no conflict of interest.

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Author Contributions

Conception and design; ÖG, AA, Drafting the manuscript; ÖG, Critical revision of the manuscript for scientific and factual content; FP, AA, Supervision; FP, AA.

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Review / Derleme

Active surveillance of prostate cancer with multiparametric magnetic resonance imaging: Review of the literature

Prostat kanserinin aktif izleminde multiparametrik manyetik rezonans görüntüleme: literatür gözden geçirilmesi

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Özet

Günümüzde aktif izlem, düşük riskli prostat kanserine sahip erkeklerde küratif tedaviye alternatif ve kabul edilebilir bir yönetim olarak popülerlik kazanmıştır. Aktif izlem, hastaya gerekli olmayan müdahalelerden kaçınmayı veya önlemeyi, böylece aşırı tedaviyle ilişkili morbiditeyi azaltmayı amaçlar. Güncel kılavuzlarda aktif izlem yaygın olarak kabul görmesine rağmen hem doktor hem de hasta için ileri evre hastalık ve tekrarlayan biyopsi gereksinimi endişesini ortadan kaldıramamaktadır. Bu durum, aktif izlem protokolünde hastalığın durumu hakkında fikir verebilecek, non-invaziv bir yöntem ihtiyacını ortaya çıkarmaktadır. Görüntüleme yöntemlerindeki son teknolojik gelişmeler, modern anatomik ve fonksiyonel sekansların tanımlanması, prostat kanserinin saptanması, risk değerlendirmesi ve takibinde multiparametrik manyetik rezonans görüntülemenin (mpMRG) artan bir role sahip olmasını sağlamıştır. MpMRG'nin başlıca avantajları, üstün anatomik ve kontrast çözünürlüğüne sahip olması, iyonize radyasyonun olmaması ve multi-planar görüntüleme özelliğinin olmasıdır. Ayrıca mpMRG'de PIRADS sınıflaması, prostat kanserinin raporlanmasındaki standardizasyonu sağlamakta ve radyologlar arasındaki yorumlara olan güvenilirliği artırarak avantaj sağlamaktadır. Çalışmamız prostat kanserinin aktif izleminde güncel bilgiler ışığında mpMRG'nin rolünü değerlendirmeyi ve özetlemeyi amaçlamaktadır.

Anahtar Kelimeler: aktif izlem, prostat kanseri, multiparametrik manyetik rezonans görüntüleme

Abstract

Nowadays, active surveillance has gained popularity as an acceptable management alternative to definitive treatment for men with low-risk prostate cancer. Active surveillance aims to delay or prevent unnecessary interventions – thereby reducing the morbidity associated with overtreatment. Despite widespread acceptance from current guidelines, active surveillance does not eliminate the concern that the advanced disease and repeat biopsy anxiety for both the clinician and the patient. This situation leads to the search for a method that is non-invasive and can give an idea to the clinician about the status of the disease in the active surveillance protocol. Recent technological advancements and the introduction of modern anatomical and functional sequences have led to a growing role for multiparametric magnetic resonance imaging (mpMRI) in the detection, risk assessment, and monitoring of prostate cancer. The main advantages of MRI are its superior anatomic and contrast resolution, lack of ionizing radiation, and multi-planar capabilities. In addition, standardization of reporting findings such as PI-RADS in mpMRI in prostate cancer provides an advantage by increasing inter-reader reliability among radiologists. This study aims to evaluate and summarize the role of magnetic resonance imaging in the active surveillance of prostate cancer.

Keywords: active surveilliance, prostate cancer, multiparametric magnetic resonance imaging

INTRODUCTION

Prostate cancer is the second most common cancer in men (1). A worldwide prevalence study showed that there were 1,414,259 newly diagnosed prostate cancer patients in 2020 (2). The number of patients diagnosed with prostate cancer has been increasing over the years with the development of diagnostic methods. In parallel with this, the number of patients suitable for low-risk prostate cancer and active surveillance (AS) is increasing.

Active surveillance is a method in which the course of the disease is followed instead of definitive treatment in low-risk prostate cancer. It is applied with a follow-up program determined for patients who meet the appropriate conditions. In contrast to the watchful waiting method, it is necessary to know surgery or other definitive treatment methods may be required in the future for the patients followed up with AS. In the watchful waiting method, patients are given symptomatic treatments, not curative treatment (3). There are many different protocols for patient identification suitable for AS (Table 1).

Table 1. Current active surveillance protocols for prostate cancer

Institution	Clinical Stage	Gleason score	Positive cores	Single core positivity	PSA value
JHU	≤T1c	≤6 (3+3)	≤2	≤50%	≤10
ERSPC (PRIAS)	≤T2a	≤6 (3+3)	≤2		≤10
MSKCC	≤T2a	≤6 (3+3)	≤3	≤50%	≤10
UCSF	≤T2a	≤6 (3+3)	≤2		≤10
AUA	≤T2a	≤6 (3+3)	≤3		≤20
NCCN	≤T2a	≤6 (3+3)	≤3		≤10
EAU	≤T2a	≤6 (3+3)			≤10

***JHU:** Johns Hopkins University, **ERSPC:** European Randomized Study of Screening for Prostate Cancer, **PRIAS:** Prostate Cancer Research International Active Surveillance, **MSKCC:** Memorial Sloan Kettering Cancer Center, **UCSF:** University of California, San Francisco, **AUA:** American Urological Association, **NCCN:** National Comprehensive Cancer Network, **PSA:** Prostate specific antigen, **EAU:** European Association of Urology*

It is very important to evaluate the AS patient correctly. Patients included in AS should be well informed and their demands and thoughts should be evaluated at every stage. Understandably, patients find it difficult to accept a conservative method such as AS after the diagnosis of prostate cancer. In the large-scale study of Miller DC et al. involving 24,450 patients, 55% of the patients chose definitive treatment over AS (4).

As with the patient selection for AS, how AS will be applied also differs between protocols? The DECTECTIVE consensus in the European Association of Urology (EAU) guidelines specified the follow-up protocol as digital rectal examination (at least 1 per year), prostate specific antigen (PSA) (1 per 6 months) and repeat biopsies (5). There is no consensus in the literature on the follow-up protocol. In general, patients are followed up with PSA and repeated biopsy follow-ups.

Follow-up with AS can cause anxiety for both the patient and the clinician. Many studies have been conducted on the reliability of AS. The two most extensive of these were carried out by John Hopkins University and Toronto University. Survival rates in these studies were calculated as 99.9% and 94.3%, respectively (6, 7). With these and similar results, AS before radical prostatectomy is considered in low-risk patients diagnosed with prostate cancer. However, it should not be forgotten that 60% of AS patients will need definitive treatment within 10 years (8). This situation is related to both the progression of the disease over time and the missed clinical significance of cancer at the initial pathology.

Our aim in this review of the literature is to present the use of mpMRI in prostate cancer patients undergoing AS with up-to-date information.

Methods

We designed our study by conducting a comprehensive literature review written in English, including Embase and Pubmed database. Studies containing the search terms 'active surveillance', 'mpMRI', and 'prostate cancer' were evaluated. In addition, current valid guidelines for prostate cancer were evaluated. First thirty articles and reviews on the role of mpMRI in active surveillance diagnosis and follow-up were reviewed.

Multiparametric Magnetic Resonance Imaging

For many years, the diagnosis of prostate cancer was made by a biopsy performed blindly from 12 areas of the prostate under the guidance of transrectal ultrasonography (TRUS). MpMRI is an imaging modality that has gained popularity in prostate cancer in recent years. It is frequently used by clinicians in terms of diagnosis, follow-up, and staging of prostate cancer. The term multiparametric describes the addition of diffusion-weighted and dynamic-weighted images to T2 images. Since inflammatory and benign hyperplastic processes are similar to prostate cancer in T2 imaging, a multiparametric system has been adopted for prostate cancer imaging (9). The PI-RADS system for prostate cancer evaluation was defined by the American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR). Lesions are evaluated by scoring increasing according to prostate cancer risk. PI-RADS version 2 was defined in 2015 and PI-RADS version 2.1 was defined in 2019 (10).

MpMRI stands out with its superior anatomical image and high malignancy involvement rates. For localized prostate cancer, it can evaluate all areas of the prostate in detail, not just the peripheral zone. In the study of Schouten G. et al. with 176 patients, patients with a negative prostate biopsy and increased PSA value were examined. Malignant cells were detected in 202 of the 277 lesions marked in mpMRI. One hundred forty-one of these lesions originate from the anterior prostate, which is difficult to reach on standard TRUS biopsy (11). Lawrenceschuk et al. reported that 69% of biopsies taken from suspicious areas in mpMRI in patients with negative TRUS biopsy had tumors in the anterior area. (12). These results show us the importance of having mpMRI-based initial pathology of patients to be AS.

Role of Multiparametric Magnetic Resonance Imaging in The Decision of Active Surveillance

The clinical characteristics of the patient, pathology result, life expectancy, possible side effects of treatment, and patient preference are important when deciding on AS. In patients followed up with AS, an upgrade stage can be observed in subsequent biopsies. The inaccuracy of the first pathology result and the progression of the disease over time can cause this situation. In the study conducted by Alam R. et al., patients in the low-risk patient group were made biopsy again 2 years later. In 35% of patients, the Gleason stage upgraded compared to biopsy pathology (13). As supported by this study, the application of mpMRI biopsy instead of TRUS biopsy gives the clinician confidence in being close to the actual pathology when making the AS decision.

The decision of AS has been made according to the TRUS biopsy result for a long time. The compatibility of the biopsy result with the actual cancer stage of the prostate is important for the accuracy of the AS decision. In a recent study by Xu N. et al., biopsy pathologies and radical prostatectomy pathologies of patients were evaluated. When all patients were evaluated in the study, there was a 22.7% stage upgrade in radical prostate pathologies compared to biopsy pathologies. In a comparison of mpMRI and TRUS, mpMRI biopsy was found to have higher reliability in predicting the final pathology (14). In the other study conducted by Siddiqui et al. with 582 patients, TRUS biopsy and mpMRI biopsy were performed in the same session. A higher Gleason score was calculated on mpMRI biopsy in 32% of patients (15). The results of these studies show that mpMRI biopsy may be safer for the decision of AS.

With the widespread use of mpMRI, studies on the subject have also increased. In the meta-analysis of Goel et al., the similarity of the mpMRI biopsy result to the final pathology was evaluated. In the analysis in which 1215 patients were evaluated, TRUS biopsy and mpMRI biopsy and radical prostatectomy pathology results were examined. It was observed that the pathological

increase was significantly less in the mpMRI group (16). It is important to reduce the number of patients whose initial biopsy pathology is found to be underestimated and for whom AS is decided. In this respect, confidence in mpMRI biopsy is increasing over time.

Evaluation with mpMRI before the first biopsy can also be predictive of progression. In the study conducted by Vargas et al., 388 patients who were under AS were evaluated. In the study, it was found that patients with a lesion in mpMRI before the first biopsy were more likely to progress than other patients (p= 0.001). This study shows us that patients with mpMRI biopsy for AS will be followed more safely in terms of significant prostate cancer (17).

Role of Multiparametric Magnetic Resonance Imaging for Patients Followed with Active Surveillance

In mpMRI evaluation, a PI-RADS score between 1 and 5 is given to each lesion. The PI-RADS score was associated with an increased risk of prostate cancer from 1 to 5. A meta-analysis of 13 studies evaluating patients with suspected or diagnosed prostate cancer examined the sensitivity of mpMRI to clinically significant prostate cancer. Although there was heterogeneity between the results of the studies, the mean positive predictive values of lesions with PI-RADS scores of 3,4, and 5 were 12%, 48%, and 72%, respectively (18). The aim in AS is not to miss clinically significant prostate cancer, so it can be expected that mpMRI will be included more in the algorithm in patients followed up with AS.

The follow-up of patients managed with AS is as important as the criteria for deciding treatment. Digital rectal examination, one of the procedures included in the standard follow-up protocol, is not an objective evaluation. PSA value is a parameter that is affected by many factors and follows a fluctuating course. Intermittent standard TRUS biopsy is an invasive procedure that affects patient comfort, as well as there is a risk of missing clinically significant cancer as previously stated. For these reasons, there are studies on the development of the AS protocol.

Even if mpMRI is not included in protocols for AS, it is included in many research topics. In a study conducted by Felker ER et al., mpMRI images were added to the evaluation in addition to PSA value and examination findings in patients followed up with AS. The addition of serial mpMRI images in addition to the PSA value made a significant difference in predicting pathological progression in the study with a mean follow-up of 28 months. In the logistic regression analysis, AUC 0.87 in the evaluation made with PSA value, increased to AUC 0.91 when mpMRI analysis was added (p= 0.044) (19). This study showed that AS patients to be followed up with mpMRI will get rid of unnecessary biopsies and evaluate prostate areas that are difficult to reach with biopsy.

MpMRI results are also an interesting subject in the follow-up of patients who are diagnosed with prostate cancer with TRUS biopsy and will be followed up with AS. In the study conducted by Schoots IG et al., 1159 patients were evaluated. Cancer upgrade was observed in 27% of patients who underwent mpMRI target biopsy and systemic biopsy. While only the mpMRI target biopsy cancer upgrade missed 10%, when only a systemic biopsy was evaluated, it was seen to miss 7%. An increase of 35% was observed in patients with positive MRI and 12% in patients with negative MRI (20). This shows that the combination of mpMRI and systemic biopsy is important in the follow-up of AS patients. The success of negative mpMRI findings in excluding prostate cancer provides patients and physicians with the power to continue AS with confidence.

The reliability of negative mpMRI results is very important in patients followed up with AS. MpMRI reports a high negative predictive value (82-95%) in the detection of clinically significant prostate cancer in the literature (21). Therefore, a negative mpMRI result will rule out the presence of occult lesions and confirm that the low-risk disease detected on biopsy is indeed low-risk and shed light on patients followed up with AS (22). In the light of these findings, the AUA guideline was also recommended as an expert opinion in the follow-up of mpMRI AS patients (23).

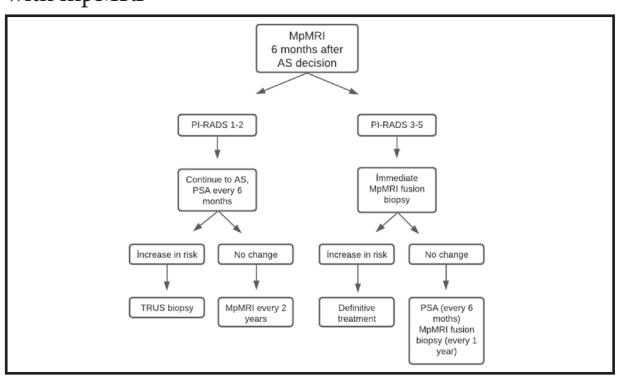
One of the largest studies in the literature on the subject is The Active Surveillance Magnetic Resonance Imaging Study (ASIST). Standard TRUS biopsy and mpMRI biopsy results were evaluated in the follow-up of patients with AS. After two years of follow-up, fewer surveillance failures were observed in the mpMRI arm

(23% and 9.9%) (24). This and similar large-scale studies strengthen the association between AS and mpMRI.

Follow-up of patients with intermittent biopsies is a difficult process to adapt. In addition, prostate biopsy has many complications such as hematuria, rectal bleeding, pain, and sepsis. It has been observed that patients experience adaptation problems over time, even though the process before them is explained when the decision to AS is taken. In a study by Womble R. et al., it was observed that 53.2% of the patients who were AS stopped their prostate biopsy follow-up (25). In another study; Lee EK. et al stated that the patients did not have any problems in compliance with PSA follow-up. However, the rate of discontinuation of intermittent prostate biopsy was reported as 47% in this study (26). The possibility of following AS patients with mpMRI instead of intermittent biopsies will help patients and physicians avoid these problems.

MpMRI can be handled in many ways in the diagnosis and follow-up of AS. Although it is important to avoid unnecessary biopsy in AS patients, the advanced disease should not be missed. MpMRI may also be included in AS protocols in this regard in the future. Even if there is no increase in PSA in active follow-up patients, a new lesion or advanced lesion to be detected in mpMRI may give an early biopsy chance. An active surveillance (AS) algorithm was demonstrated in a review published by Glass AS et al., University of California-Davis Medical Center. Preventing delayed diagnosis with mpMRI will also provide an advantage to clinicians (27). An algorithm that may be appropriate in the light of current data is shown in Figure 1.

Figure 1. Active surveillance algorithm of prostate cancer with mpMRI



CONCLUSION

Today, conservative approaches are gaining importance in prostate cancer as in many diseases. When AS is applied with correct diagnosis and correct follow-up protocols, it prevents patients from facing a major surgery such as radical prostatectomy. However, the discomfort caused by repetitive biopsies and the heterogeneous nature of the PSA value makes physicians think about AS. MpMRI in the diagnosis and follow-up of prostate cancer has led to revolutionary changes. Its place in the diagnosis of prostate cancer is now seen as undisputed. Its place in patients in the AS stage has not been clarified. There are also disadvantages associated with mpMRI. It is not easy to access in every clinic, it is an expensive method, it is related to the radiologist's comments and its interpretation may vary from person to person. In the future, it is possible to follow up patients with AS with mpMRI with high confidence instead of serial biopsies and PSA follow-up. MpMRI can be integrated into the AS follow-up protocol by evaluating the existing literature data. Future prospective studies will also be needed on this topic.

Conflict of Interest

All authors declared that there is no conflict of interest.

Financial Disclosure

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Author Contributions

Conception and design; FY, Data acquisition; UÇ, Data analysis and interpretation; UÇ, FŞ, Drafting the manuscript; FY, UÇ, FŞ, Critical revision of the manuscript for scientific and factual content; FY, FŞ, MB, Statistical analysis; UÇ, Supervision; FY, MB.

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Revisions

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial period is over.

AFTER ACCEPTANCE

Accepted manuscripts are copy-edited for grammar, punctuation, and format. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested. The journal owner and the editorial board are authorized to decide in which volume of the accepted article will be printed. Authors may publish their articles on their personal or corporate websites by linking them to the appropriate cite and library rules.

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DERGİSİ
The New Journal of Urology

PEER REVIEW PROCESS

The Double-Blind Peer Review Process

1. Submission of Paper

The corresponding author submits the paper via Dergipark online system to the journal (http://dergipark.gov.tr/journal/1455/submission/start).

2. Editorial Office Assessment

Editorial Office checks the paper's composition and arrangement against the journal's Author Guidelines to make sure it includes the required sections and stylizations. The quality of the paper is not assessed at this point.

3. Appraisal by the Editor-in-Chief

The Editor-in-Chief assigns submission to Section Editor to see through the editorial process. Section Editor checks that the paper is appropriate for the journal and is sufficiently original and interesting. If not, the paper may be rejected without being reviewed any further.

4. Invitation to Reviewers

The Section Editor sends invitations to individuals he or she believes would be appropriate reviewers. As responses are received, further invitations are issued, if necessary, until the required number of acceptances is obtained – commonly this is 2.

5. Response to Invitations

Potential reviewers consider the invitation as anonymous against their own expertise, conflicts of interest and availability. They then accept or decline. If possible, when declining, they might also suggest alternative reviewers.

6. Review is Conducted

The reviewer sets time aside to read the paper several times. The first read is used to form an initial impression of the work. If major problems are found at this stage, the reviewer may feel comfortable rejecting the paper with-out further work. Otherwise they will read the paper several more times, taking notes so as to build a detailed point-by-point review. The review is then submitted to the journal, with a recommendation to accept or reject it – or else with a request for revision (usually flagged as either major or minor) before it is reconsidered.

7. Journal Evaluates the Reviews

The Section Editor considers all the returned reviews before making an overall decision. If the reviews differ widely, the editor may invite an additional reviewer so as to get an extra opinion before making a decision.

8. The Decision is Communicated

The Section Editor sends a decision email to the author including any relevant reviewer comments as anonymous.

9. Next Steps

If accepted, the paper is sent to language Editor. If the article is rejected or sent back for either major or minor revision, the Section Editor should include constructive comments from the reviewers to help the author improve the article. At this point, reviewers should also be sent an email or letter letting them know the outcome of their review. If the paper was sent back for revision, the reviewers should expect to receive a new version, unless they have opted out of further participation. However, where only minor changes were requested this follow-up re-view might be done by the Section Editor.

- After these;
- Copyedit submission
- Layout
- Corrections
- Publishing the submissions on the web page as early print
- Creating issues
- Organize Table of Contents
- Publishing the issue on the web page and printing hardcopy.

We are applying the same steps on The Double-Blind Peer Review Process when we got the in-house submission.

TAMPROST MR
Tamsulosin HCl

Prostat tedavisinde
Hayata TAM Uyum

Referanslar:
1. Lepor et al, Long-Term Evaluation of Tamsulosin in BPH: Placebo- Controlled, Double-blind extension of Phase III trial. UROLOGY, 51: 901–906, 1998,
2. Tamprost MR Kısa Ürün Bilgisi,
3. Rahardjo et al, International Journal of Urology (2006) 13, 1405–1409,
4. Neurourology and Urodynamics 29:1276–1281 (2010)

DAHA FAZLASINA ULAŞMAK İÇİN OKUTUN

Xatral® XL
alfuzosin 10 mg

BPH tedavisinde

CİNSEL DİSFONKSİYONLARI[1,2,3] X'LEYİN!

İMPOTANS

LİBİDO AZALMASI

ANORMAL EJAKÜLASYON

Referanslar:
1. Xatral XL Kısa Ürün Bilgisi
2. Van Kerrebroeck P. et al. Eur. Urol. 2000; 37: 306-313.
3. Van Moorselaar LUTS and sexual dysfunction: indications for management for BPH European 2003 Urology Supplement 2;13-20

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