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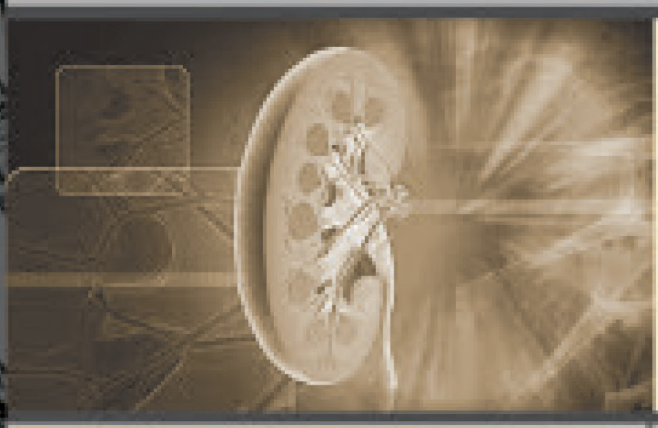

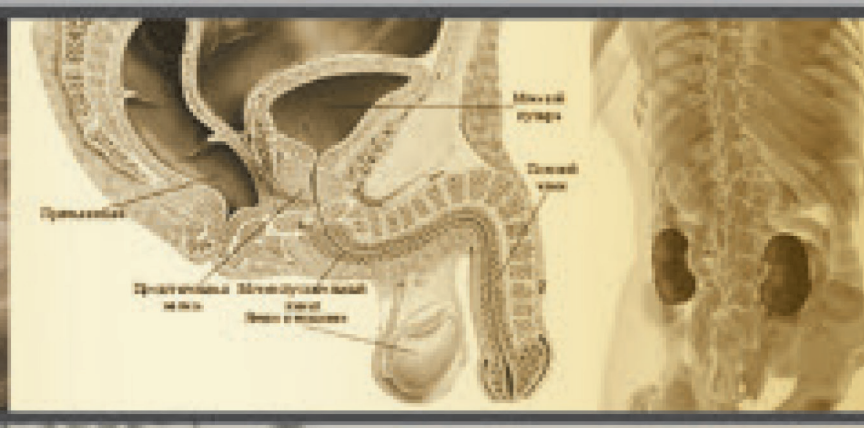

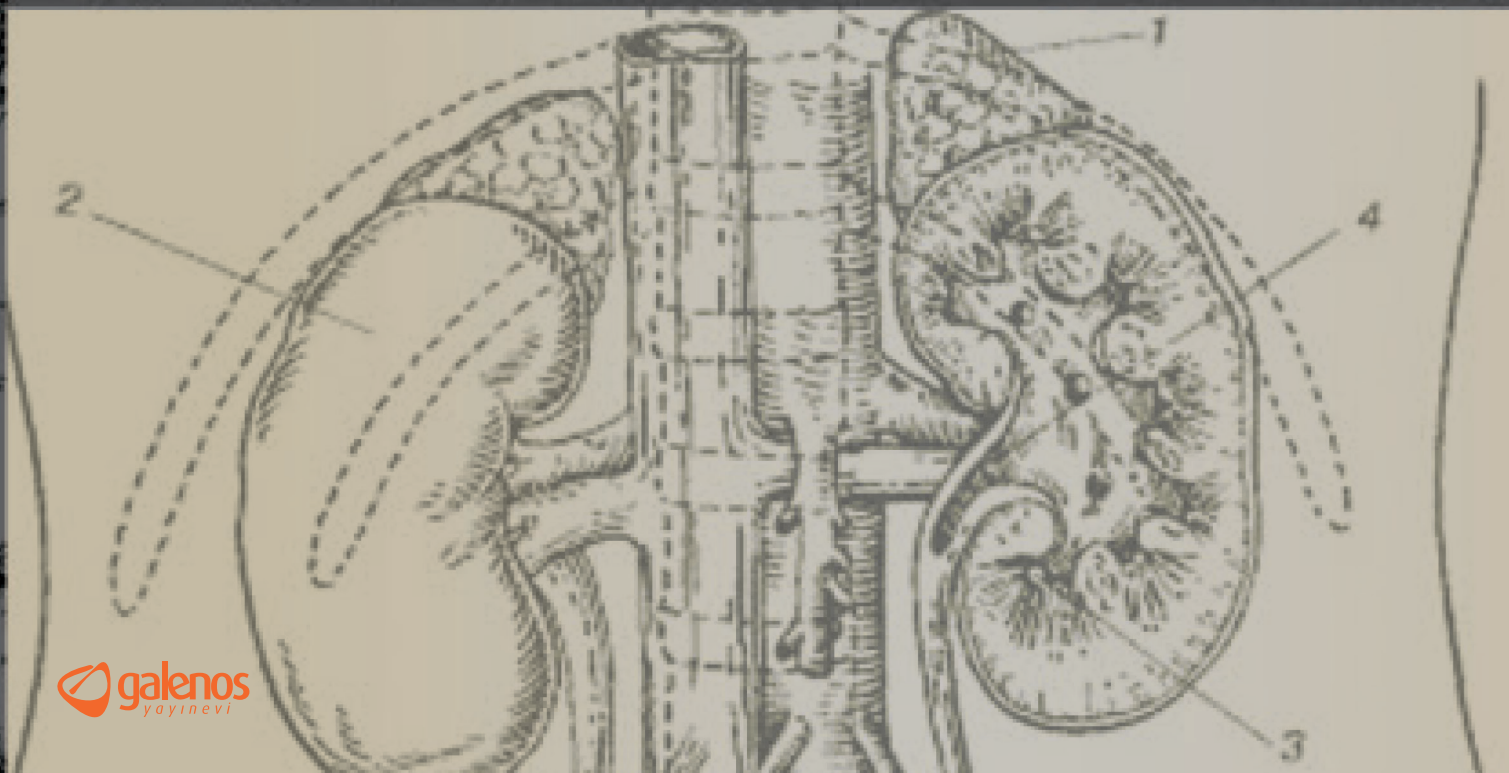

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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr

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REVIEW
Andrology

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The Effects of Boron on Sperm Qualities and Testicular Histopathology in Animal Studies: A Systematic Review

Amin Sani[1], Anis Sani[2], Soroush Sharifimoghadam[3], Mahdi Bahari[2], Masoumeh Emamvirdi[4], Amir Emamvirdi[4], Farhad Tondro Anamag[5], Hanieh Salehi-Pourmehr[5,6], Sakineh Hajebrahimi[5,2], Mustafa Numan Bucak[7]

[1]*Islamic Azad University Faculty of Veterinary Medicine, Tabriz Medical Sciences, Tabriz, Iran*
[2]*Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran*
[3]*Department of Urology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[4]*Selçuk University Faculty of Medicine, Konya, Türkiye*
[5]*Research Center for Evidence-based Medicine, Iranian EBM Centre: A JBI Centre of Excellence, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[6]*Tabriz University of Medical Sciences, Medical Philosophy and History Research Center, Tabriz, Iran*
[7]*Selçuk University Faculty of Veterinary Medicine, Konya, Türkiye*

Abstract

This study systematically reviewed how boron exposure affects animal model sperm parameters and testicular structure. The Embase, Scopus, PubMed, ProQuest, and Web of Science databases were searched up to January 2023. The studies that examined boron's efficacy and safety regarding semen parameters and testicular histopathology in different animal species were included. Studies involving specific derivatives or *in vitro* or human studies were excluded. Two reviewers selected the studies and extracted the data independently. The quality of eligible studies was assessed using the Animal Research: Reporting of *In Vivo* Experiments Essential 10 checklist. The outcomes were summarized and presented in tables. Sixteen studies were included from 1,602 retrieved articles. While some studies demonstrated that boron, at doses of 17.5, 35, and 70 mg/kg for 8 weeks, improved the quality of spermatogenesis in terms of rate of sperm movement, sperm concentration, and total volume of sperm, other studies showed dose-dependent boron toxicity to the reproductive system. While some studies suggest potential benefits of boron supplementation on spermatogenesis, others indicate harmful effects. The conflicting results emphasize the need for further research to establish clear guidelines on the appropriate dosage, duration, and safety of boron in improving sperm quality.

Keywords: Boron, sperm parameters, testicular histopathology, reproductive toxicity, systematic review

Introduction

Boric acid, containing boron, is an inorganic acid often used as a water pH regulator, stabilizer, neutralizer, and buffer in the glass industry, food preparation, beauty industry, agriculture, and pharmaceutical production (1,2). Obviously, with the development of the industry, the importance of this acid and its amount in our environment has increased due to its widespread use. In recent years, the physiological role of boron has attracted the attention of researchers worldwide, especially in the field of the reproductive system (3). Studies on the effects of boron on animals began in the 1990s. According to the European Union report, boron is placed in group 1B of the Globally Harmonized System classification, specifically in the category R60-61. Group R60 weakens the reproductive system, while group R61 is harmful to the fetus (4).

Although the definite role of boron in the physiology of animals is not completely clear, the effects of its supplementation in the diet on bone growth and in the central nervous, endocrine, and reproductive systems have been reported (5,6). Boron increases the level of interleukin-6 and regulates serine protease enzyme activity. It also improves the immune and the antioxidant capacity and calcium metabolism (6). In animals,

Correspondence: Hanieh Salehi-Pourmehr MD, Research Center for Evidence-based Medicine, Iranian EBM Centre: A JBI Centre of Excellence, Faculty of Medicine, Tabriz University of Medical Sciences; Tabriz University of Medical Sciences, Medical Philosophy and History Research Center, Tabriz, Iran
E-mail: salehiha@tbzmed.ac.ir **ORCID-ID:** orcid.org/0000-0001-9030-2106
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most of the studies on the effects of boron focus on mice and rats. The findings of these studies are interesting because they have produced contradictory results regarding Boron's activity. The study showed that high concentrations of boron have positive effects on lipid peroxidation reduction and antioxidant metabolism in mice (7). In rabbits, boron improves antioxidant capacity, sperm quality, and testosterone concentration (8). However, high concentrations of boron have negative effects on the reproductive system of animals. Boric acid causes testicular atrophy in rats and dogs at specific doses and concentrations (9). Another study found that a diet with 1,000 ppm boron, reduced the number of spermatocytes, spermatids, and mature spermatozoa in mice after 30 days (10). Additionally, high dietary boron concentrations have detrimental effects on the reproductive system of male rats, and at a certain dose, these concentrations can lead to acute toxicity and death. In animal tissue studies, toxic concentrations of boron damage the process of spermatogenesis, resulting in testicular atrophy in 10-14 days (11).

According to studies on the effect of boron on the reproductive system of animals, it is believed that boron acts as a double-edged sword that can have beneficial or harmful effects on this system, depending on the dose. Therefore, in this study, we aimed to systematically review the effect of boron on sperm parameters and testicular histopathology in animal models.

Methods

This systematic review followed the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) Statement and the Cochrane Collaboration Handbook. Due to resource limitations and institutional policies at the time, registration was not feasible; furthermore, the narrowly defined scope of this review was considered sufficient to justify the absence of registration.

Data Sources and Search Strategy

The Embase, Scopus, PubMed, ProQuest, and Web of Science databases were thoroughly searched in January 2023. Finding both published and unpublished studies was the goal of the search approach. A three-step search process was used in this study. Following a preliminary, constrained search of MEDLINE, the title and abstract's text words were examined. In January 2023, a second search across all included databases was conducted using all indicated keywords and index phrases: ((((“reproduction”[MeSH Terms]) OR (“reproduction”[Title/Abstract])) OR (“reproductive”[Title/Abstract])) OR (((“infertility”[MeSH Terms]) OR (infertil*[Title/Abstract])) OR (Sperm [Title/Abstract]))) AND ((“boron”[MeSH Terms]) OR (boron [Title/Abstract])).

The last step was to look for further studies in the reference lists of all the indicated papers and articles. This review covered studies that were released on any date and in any language.

Inclusion and Exclusion Criteria

The original studies that examined boron's efficacy and safety of semen parameters and testicular histopathology in different animal species were included. Studies involving specific derivatives or *in vitro*/human studies were excluded. Also, Abstracts, reviews, letters, and theses were excluded.

Study Selection and Data Extraction

The retrieved articles from multiple information sources were organized using PRISMA flowcharts. Two reviewers independently screened all titles and abstracts of the retrieved articles. Additionally, full texts of relevant studies were independently assessed for eligibility, with reasons for exclusion documented for the full texts that were excluded. Data extraction was performed separately by two researchers, and any discrepancies were discussed and resolved. The following data was extracted from the included studies: Author Name, Publishing Year, Country, Study Design, Animal, Sample Size, Age, Diet, Boron Derivative and Dosage, Intervention Duration, Testis Weight, Testicular Morphometry, Pathology Report, Sperm Count/Concentration, Sperm Abnormality, Sperm Motility, and Ejaculate Volume.

Risk of Bias Assessment

Using the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) Essential 10 checklist, two independent reviewers evaluated the methodological quality of the selected articles. The reviewers' probable differences were settled through conversation or by a third reviewer.

Data Synthesis

The primary outcomes in this study were the change of sperm parameters and testis histopathology in animals with boron exposure. As these outcomes were diverse or heterogeneous (from different animal species), combining the data and conducting a meta-analysis was not possible. The results are summarized and presented in tables.

Results

Study Selection

The electronic search, manual search, and reference check yielded a total of 1,602 citations. After removing duplicate citations, we were left with 919 studies for screening. Based on the titles and abstracts provided, 35 papers were selected,

while 19 articles were disqualified during the full-text selection process. Ultimately, 16 studies were included. For more detailed information on the selection procedure, please refer to Figure 1 in the PRISMA flowchart.

Study Characteristics

In this research, 16 studies were reviewed from 1976 to 2022. These studies were conducted in the United States, Japan, Chile, Egypt, Türkiye and India. The investigated animals were rats, mice, rabbits, African clawed frogs, goats, and Osemi Rams.

Results of Individual Studies

As mentioned, the results of the studies were notably different from each other. In the study of Elkomy et al. (12), Ibrahim et al. (11), Krishnan et al. (13), and Abdel-Wahab et al. (14), boron improved the quality of spermatogenesis. In the Elkomy et al. (12) study, after the administration of boron at the doses of 17.5, 35, and 70 mg/kg for 8 weeks, it was seen that the rate of sperm movement, sperm concentration, and total volume of sperm increased compared to the control group (11). Similarly, the study by Ibrahim et al. (11), which gave a 70 mg/kg boron-containing diet to Osmei rams for 4 months, showed an improvement in total sperm volume and sperm concentration (12). Krishnan et al. (13) also administered 40 ppm of this acid in the form of sodium tetraborate to goats for 60 days and concluded that there was a significant increase in sperm motility compared to the control group. Another interesting result was obtained by Abdel-Wahab et al. (14) in 2022 by administering 70 mg/kg of boric acid to goats for 24 weeks; they observed that goats receiving boron exhibited improvements in the structure of testis tubules, and the activity of Sertoli cells increased. Conversely, other studies have shown that boron toxicity affects the reproductive system. Ayranci et al. (15) administered 1000 mg/kg/day of boric acid to Sprague-Dawley rats for 7 days, and observed an increase in edema in the testicular interstitial tissue and an increase in apoptotic cells. El-Dakdoky et al. (16) also gave 125, 250, or 500 mg/kg of boron to Wistar rats for 60 days, which led to the destruction of spermatogonia, spermatocytes, and spermatozoa with a dose of 250 mg/kg and severe destruction of germ cells with a dose of 500 mg/kg. Lee et al. (10) administered boron to Sprague-Dawley rats with doses of 500-1000-2000 ppm for 90 days. They observed that with a dose of 500 ppm, boron did not cause any complications. However, with a dose of 1000 ppm, germ cell destruction began, and the diameter of seminiferous tubules was reduced. Eventually, testicular atrophy occurred. Tables 1 and 2 represent the characteristics of the included studies.

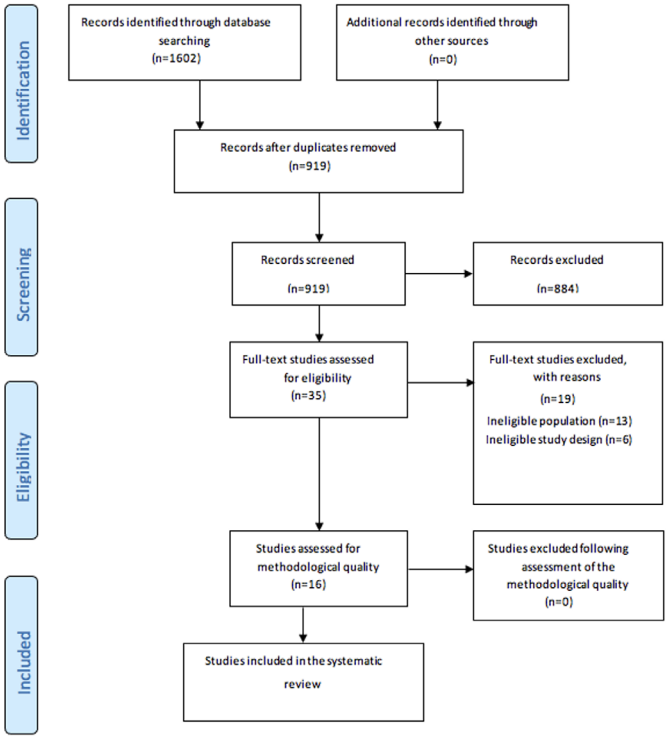

Figure 1. Study PRISMA flow diagram

PRISMA: Preferred reporting items for systematic reviews and meta-analyses

Methodological Quality

The risk of bias assessment of included studies is summarized in Table 3. All studies were of good general quality based on the ARRIVE Essential 10 appraisal checklist.

Discussion

Our systematic review showed contrasting findings. While some studies demonstrated that boron improved the quality of spermatogenesis in terms of sperm movement, sperm concentration, and total volume of sperm at the doses of 17.5, 35, and 70 mg/kg, or improvement in the structure of testis tubules and the activity of Sertoli cells, other studies have shown that boron toxicity to the reproductive system is dose-dependent. For example, 1000 mg/kg/day of boric acid increased edema in the testicular interstitial tissue and apoptosis in cells of rats, and it led to the destruction of spermatogonia, spermatocytes, and spermatozoa or germ cells, a reduction of the Seminiferous tubules diameter, and eventually testicular atrophy. Boron is a mineral found in various food sources that has recently received attention for its effect on male fertility (17). Treatment with boric acid in rats, mice, and dogs has been found to reduce fertility and sperm production. However, in some studies, beneficial effects on these processes have been observed, which seem to be dose-dependent. Toxic effects were observed at higher doses, and the substance is beneficial at lower doses. This systematic review examines the studies on boron and its effects on the reproductive system of animals, along with their contradictory results.

Table 1. Baseline characteristics of studies

No	Author (year)	Country	Study design	Animal	Population size		Age	Diet	Boron			Treatment duration
					Boron	Control			Derivative	Dosage	Dosage in control	
1	Dixon et al. (24) (1976)	USA	Serial mating study	Sprague-Dawley rats	30	-			Borax (11.3% boron)	Three groups: 0.3, 1.0, or 6.0 mg/L of drinking water	-	90 days
2	Lee et al. (10) (1978)	USA	Randomized controlled trial	Sprague-Dawley rats	54	18			Borax	500, 1000, and 2000 ppm	0	60 days
3	Treinen and Chapin (19) (1991)	USA	Randomized controlled trial	Fischer 344 (CDF (F344)/ CrlBr) rats	36	30	120 day	Powdered NIH-07 feed	Boric acid	9000 ppm	0	4 weeks
4	Ku et al. (25) (1993)	USA	Randomized controlled trial	Fischer 344 (CDF (F344) rats	216	54	60 to 70 days	Powdered NIH-07	Boric acid	3000, 4500, 6000, or 9000 ppm	B levels <20 ppm	9 weeks
5	Chapin and Ku (1994) (26)	USA	Reproductive assessment by continuous breeding study	CD-1 mice	6	4	11 weeks		Boric acid	1000, 4500, and 9000 ppm		28 days
6	Nomiyama et al. (27) (1996)	Japan	Randomized controlled trial	Wister rat	24	12	13 weeks	Pellet and distilled water ad libitum	Diborane via inhalation	Two groups: 0.1 or 1.0 ppm for 6 hr/day, 5 days/ week	0	8 weeks
7	Bustos-Obregon et al. (28) (2007)	Chile	Randomized controlled trial	Mice (Mus musculus, CF-1 strain)	10	10	85 days	Commercial pellet and water ad libitum		12 mg of boron/L in drinking water	0.6 mg boron/L in drinking water	42 days
8	Espinoza-Navarro et al. (29) (2007)	Chile	Randomized controlled trial	Mice (CF-1 strain)	32	16		Standard conditions of living	Boric acid	Two groups: 2.0 to 6.0 mg boron/L in drinking water and 12.0 mg boron/L in drinking water	0.54 mg boron/L in drinking water	60 days
9	Bustos-Obregón and Olivares (30) (2012)	Chile	Randomized controlled trial	mice (Mus domesticus, CF-1 strain)	10	10	85 days	Standard animal room conditions		12 mg boron/L in drinking water	0.6 mg boron/L in drinking water	42 days
10	El-Dakdoky and Abd El-Wahab (16) (2013)	Egypt	Randomized controlled trial	Wister rat	24	8	12 weeks	Standard laboratory pellets and water ad libitum	Boric acid	Three groups: 125-250-500 mg boric acid/kg body weight/day	0	60 days
11	Elkomy et al. (12) (2015)	Egypt	Randomized controlled trial	V. line rabbits	15	5	10 months	Pellet diet ad libitum	Boric acid	Three groups: 17.5, 35, 70 mg boron /kg	0	8 weeks
12	Fort et al. (31) (2016)	USA	Randomized controlled trial	African clawed frog xenopus laevis	48	12	3 years	Salmon starter - dry pellets ad libitum	Boric acid	Four groups: 5 - 7.5 -10 - 15 mg boron/L equivalent to 28.5, 42.8, 57.0, and 85.5 mg boric acid/L	0	30 days

Table 1. Continued

No	Author (year)	Country	Study design	Animal	Population size		Age	Diet	Boron			Treatment duration
					Boron	Control			Derivative	Dosage	Dosage in control	
13	Ibrahim et al. (11) (2019)	Egypt	Randomized controlled trial	Osemi rats	6	6	4 months	Basal ration ad libitum	Boric acid	400 mg boric acid/kg diet=70 mg boron/kg diet	0	4 months
14	Krishnan et al. (13) (2019)	India	Randomized controlled trial	Goat	7 negative control, 7 selenium supplement as positive control	7		55% roughage and 45% concentrate	Sodium tetra borate	40 ppm in diet	0	60 days
15	Ayranci et al. (15) (2021)	Türkiye	Randomized controlled trial	Sprague-Dawley type albino rats	30	12	12 weeks		Boric acid	1000 mg/kg/day added to the drinking water	0	7 days
16	Abdel-Wahab et al. (14) (2022)	Egypt	Randomized controlled trial	Goat	6	6	4 months	Normal basal composition, roughage and berseem ad libitum	Boric acid	400 mg boric acid/kg diet=70 mg boron/kg diet	0	24 weeks

According to histological studies, the first toxic effect of boric acid on spermatogenesis occurs in germ cells, after which Sertoli cells are destroyed, and the testicle atrophies (18). The researchers also claimed that these toxic effects begin on the seventh day of administration. Treinen and Chapin (19) showed that this boron toxicity is caused by a decrease in blood testosterone levels. Another mechanism that has been proposed for boron toxicity is its cytotoxic effects on sperm DNA, which increases the DNA's fragility. Boron also increases oxidative stress in high doses (11). On the other hand, scientists claim that boron in low doses has beneficial effects on the reproductive system. Ibrahim et al. (11) showed that by administering a low dose of boron, the serum level of testosterone increases, and for this reason, the administration of this substance to rams improved the quality of sperm production, including their volume and movement. In the same way, Elkomy et al. (12) stated that he sought boron administration to increase testosterone, which increased the total number of sperm, their concentration, and their normal shape. Another mechanism that Özdemir et al. (20) has stated for these positive changes in the reproductive system is the antioxidant property of boron. Yildiz et al. (21) also claimed that the administration of this substance at a dose of 200 mg/kg in the drinking water of rams inhibits the production of free radicals. Other researchers believe that the beneficial effects of boron are due to strengthening the activity of serine protease inhibitor proteins (22). This protein is responsible for protecting spermatogenesis by inhibiting microbial activity. Boron also increases the immune system by increasing the activity of gamma interferon, which improves the process of spermatogenesis (23).

The reviewed studies presented diverse and contrasting results regarding the effects of boron on spermatogenesis. Some studies reported positive outcomes, indicating improvements in semen analysis parameters. For instance, Elkomy et al. (12) administered boron at different doses to rats and observed increased sperm movement, concentration, and total volume of sperm compared to the control group. Similarly, Ibrahim et al. (11) found that a diet containing boron improved total sperm volume and concentration in Osemi rams. Krishnan et al. (13) study on goats also revealed a significant increase in sperm motility after boron administration.

Several studies indicated detrimental effects of boron on the reproductive system. Ayranci et al. (15) observed increased testicular interstitial tissue edema and apoptotic cell proliferation in rats exposed to high doses of boric acid. El-Dakdoky and Abd El-Wahab (16) study on Wistar rats showed destruction of various germ cells with increasing doses of boron. Lee et al. (10) research demonstrated that higher doses of boron led to germ cell destruction, reduced seminiferous tubule diameter, and testicular atrophy in rats.

The conflicting results observed in the reviewed studies suggest that the effect of boron on spermatogenesis is complex and may depend on factors such as dosage, duration of exposure, and animal species. These variations could explain the discrepancies between the studies. Additionally, it is important to consider the

Table 2. Summary of the results

No.	Author (year)	Sample type	Testis weight	Testicular morphometry	Sperm count/ conc.	Sperm abnormality	Sperm motility	Ejaculate volume	Pathology report
1	Dixon et al. (24) (1976)	Testicular tissue	(g) 0.3 boron: 1.64±0.67, 1 boron:1.66±0.49, 6 boron: 1.71±0.10						Without significant reproductive toxicity.
2	Lee et al. (10) (1978)	Testicular tissue	(g) control: 1.81±0.06, 500 ppm boron: 1.76±0.19, 1000 ppm boron: 0.68±0.16*, 2000 ppm boron: 0.63±0.01*						At 500 ppm, there were no significant adverse effects observed. In contrast, male rats receiving 1000 and 2000 ppm of boron displayed a significant loss of germinal elements, decrease in seminiferous tubular diameter, and accumulation of testicular boron. The testicular atrophy was greatest at the highest dose, and depletion of germ cells was complete after 60 days of exposure.
3	Treinen and Chapin (19) (1991)	Testicular tissue							First testicular lesion noted was an inhibition of spermiation, which appeared on day 7. Widespread exfoliation of apparently viable germ cells and pachytene cell death in stages VII and XIV appeared as exposure continued. After 28 days of dosing, extreme epithelial disorganization and [effect] were observed, indicating the need for further investigation. germ cell loss were evident.
4	Ku et al. (25) (1993)	Testicular tissue							Inhibited spermiation was most reliably reflected by detailed testicular histology, with the more severe cases decreasing epididymal sperm count to levels that could affect fertility.
5	Chapin and Ku (1994) (26)	Testicular tissue	(mg) Control: 140±3, 1000 ppm: 140±4, 4500 ppm: 69±5*, 9000 ppm: 20±1*		Concentration control: 518.6±35.8, 1000 ppm: 532.4±40.9, 4500 ppm: 146.9±26.6 *, 9000 ppm: 2.8±1.7 *		% control: 78.1±3.0, 1000 ppm: 69.0±4.5*, 4500 ppm: 53.3±8.2*, 9000 ppm: 42.9		The first lesion appeared in some animals at day 7, and consisted of an inhibition of sperm release. This progressed in severity, and was soon (day 21) accompanied by a disorganization of the epithelium and the release of immature germ cells. By day 28, there were some atrophic tubules that contained only residual spermatogonia and the somatic Sertoli cells.

Table 2. Continued

No.	Author (year)	Sample type	Testis weight	Testicular morphometry	Sperm count/ conc.	Sperm abnormality	Sperm motility	Ejaculate volume	Pathology report
6	Nomiyama and Abd El-Wahab (27) (1996)	Testicular tissue			Count (106) in head of epididymis: control: 69.1±18.8, 0.1 ppm: 76.5±21.3, 1 ppm: 76.5±9.2 count in body/tail of epididymis: control: 262.5±55.2, 0.1 ppm: 244.1±32.5, 1 ppm: 267.7±35.5	Head abnormality (103) abnormal type: control: 12.8±4.2, 0.1 ppm: 14.3±5.1, 1 ppm: 10.2±6.2 immature type: control: 11.3±4.0, 0.1 ppm: 12.8±4.7, 1 ppm: 9.1±5.9			There were no differences between the testes of control and exposed rats.
7	Bustos-Obregón et al. (28) (2007)	Testicular tissue		(µm) Tubular diameter*: control: 208.9±5.76, boron: 233.3±9.91 epithelial height*: control: 50.4±0.88, boron: 58.3±3.01 tubular lumen*: control: 60.5±1.41, boron: 72.6±4.10					The boron-exposed group exhibits a 27% of histological changes, with a 2% of tubular atrophy, a 7% of tubular obstruction and an 18% of epithelial vacuolization. In the control group, damage was less than 1%.
8	Espinoza-Navarro et al. (29) (2007)	Testicular tissue	(g) control: 0.8±0.834, 2.0-6.0 mg boron: 1.1±0.106*, 12.0 mg boron: 1.3±0.075*						In boron groups the basal epithelium of seminal tubules of the testicles were altered, with an increase in the lumen and an absence of spermatozoids and great presence of vacuolization in the germinative epithelium.
9	Bustos-Obregón and Olivares (30) (2012)	Testicular tissue		(µm) Tubular diameter*: control: 189±2.25, boron: 155±3.47 luminal diameter*: control: 60.2±1.16, boron: 78.1±1.24 epithelial height*: control: 61.0±1.12, boron: 50.7±0.89 tunica albuginea thickness*: control: 107.6±28.4, boron: 29.70±9.1 interstitial area* (% area): control: 14.4±1.00, boron: 29.2±6.57					Boron produces vacuolization, tubular epithelial desquamation and tamponade.

Table 2. Continued

No.	Author (year)	Sample type	Testis weight	Testicular morphometry	Sperm count/ conc.	Sperm abnormality	Sperm motility	Ejaculate volume	Pathology report
10	El-Dakdoky et al. (16) (2013)	Testicular tissue	Right testis (g): control: 1.57±0.03, 125 mg boric acid/ kg/day: 1.49±0.04, 250 mg: 1.38±0.10*, 500 mg: 0.46±0.02*	Seminiferous tubules diameter (µm): control: 234.6±2.48, 125 mg B: 231.7±4.65, 250 mg B: 219.2±2.61*, 500 mg B: 143.0±1.14* germinal cell thickness (µm): control: 70.10±1.11, 125 mg B: 67.34±1.85, 250 mg B: 60.18±0.75*, 500 mg B: 21.00±0.60*	Count (106): control: 36.47±3.94, 125 mg B: 33.70±2.69, 250 mg B: 16.8±1.73*, 500 mg B: 0.03±0.02*	(%) control: 3.10±0.2, 125 mg B: 4.10±0.51, 250 mg B: 12.36±1.58*			Moderate testicular degeneration in B-250 group, the numbers of spermatogonia, spermatocytes and spermatozoa were diminished, vacuolation and degenerative cells in the basal region of the tubules were observed. In B-500 group, almost all germ cells disappeared from the atrophied STs and the testicular vessels appeared severely congested.
11	Elkomy et al. (12) (2015)	Semen analysis			Concentration (10^6): control: 228.56±4.18, 10 ppm: 259.00±2.95*, 200 ppm: 258.50±2.88*, 400 ppm: 265.38±2.83* count (10^6): control: 118.18±13.82, 10 ppm: 171.95±15.39*, 200 ppm: 161.03±13.37*, 400 ppm: 165.50±12.14*	(%) control: 10.34±1.00, 10 ppm: 4.08±0.46 *, 200 ppm: 4.85±0.53 *, 400 ppm: 3.98±0.35*	(%) control: 60.00±4.23, 10 ppm: 81.88±1.64, 200 ppm: 87.19±1.44*, 400 ppm: 91.88±1.01*	(mL) control: 0.51±0.06, 10 ppm: 0.66±0.06, 200 ppm: 0.62±0.05, 400 ppm: 0.62±0.03	
12	Fort et al. (31) (2016)	Testicular tissue			Count (10^6): control: 2.2±0.03, 5 mg boron/L: 2.1±0.02, 7.5 mg boron/L: 2.1±0.03, 10.0 mg boron/L: 2.0±0.0, 15.0 mg boron/L: 1.8±0.1*	(%) control: 0.02±0.001, 5.0 mg boron/L: 0.02±0.001, 7.5 mg boron/L: 0.02±0.001, 10.0 mg boron/L: 0.03±0.003, 15.0 mg boron/L: 0.04±0.005*			The general appearance and location of the testes was normal and histological evaluation of the testes was not deemed necessary.
13	Ibrahim et al. (11) (2019)	Semen analysis			Sperm concentration/mm^3: control: 1.35±0.06, boron: 3.35±0.07*	Primary (%): control: 2.00±0.37, boron: 1.67±0.33 secondary (%): control: 15.6±0.84, boron: 7.83±1.11*		(mL): control: 0.57±0.07, boron: 1.12±0.33*	
14	Krishnan et al. (13) (2019)	Testicular tissue, Semen analysis	(g): control: 169.00 ±14.6, boron: 185.3±11.80				Significantly higher total sperm motility (%) and total progressive motility (%) as compared to control		

Table 2. Continued

No.	Author (year)	Sample type	Testis weight	Testicular morphometry	Sperm count/ conc.	Sperm abnormality	Sperm motility	Ejaculate volume	Pathology report
15	Ayranci et al. (15) (2021)	Testicular tissue	(g): control: 3.033±0.362, boron: 2.426±0.623*						Edema in the interstitial area in the testis tissue, increase in Leydig cells, basal membrane thickening in the seminiferous tubules, more apoptotic cells.
16	Abdel-Wahab et al. (14) (2022)	Testicular tissue		Diameter of seminiferous tubules: large tubules: control: 672.24±5.44, boron: 750.05±5.21*, small tubules: control: 510.04±3.66, boron: 548.06±3.55* height of spermatogenic cells: control: 154±1.21, boron: 180.22±1.19*					Boron supplementation succeeded remarkably in improving the testicular architecture and appeared with normal morphology and included seminiferous tubules lined by normal spermatogenic cells and Sertoli cells. The lumen of the tubules was noticed to include huge amount of spermatid and sperms. Also, the interstitial tissues were found to contain blood capillaries and interstitial cells.

*: p-value<0.05
Red: Negative effect
Green: Positive effect
White: No difference

different methods and protocols used in each study, which may have contributed to the divergent outcomes. It should be noted that the studies conducted on animals may not directly translate to human results. Animal models can provide insights into potential effects, but further research is necessary to determine the impact of boron on human spermogram parameters.

The main limitations of this review were the diverse protocols and methods used in the included studies. As the outcomes of the included studies were diverse or heterogeneous, combining the data and conducting a meta-analysis was not possible. In these instances, the systematic review focuses on qualitatively summarizing the findings, identifying patterns, and discussing the implications of the diverse outcomes. Although a meta-analysis may not be feasible, a comprehensive systematic review can still provide valuable insights into the research field by highlighting gaps in knowledge, suggesting future research directions, and facilitating evidence-based decision-making. Although in the current study, most of the included studies showed a negative effect, the findings supported the conclusion that treatment with boron caused testicular toxicity, which was characterized by a dose-dependent reduction in epididymal sperm counts at higher doses and decreased spermiation at lower doses. Investigations on boron's impact on the reproductive system have revealed that at large dosages, it can be cytotoxic. A minor link was found between blood boron levels and the average number of DNA strand breaks in spermatozoa in a zone of boric acid/borate production in Bandırma, Türkiye. Another study found that while boron compounds are not genotoxic even at the highest concentrations, they do produce oxidative stress when used in increasing amounts. Another limitation was that a great number of the studies in this subject were conducted before 2000, and it was not appropriate to exclude them. Therefore, given the potential changes in experimental standards and protocols (i.e. testicular immunohistochemistry and fluorescent immunohistochemistry staining along with most of the high-power field microscopes), these changes may have affected our conclusion.

Table 3. Critical appraisal results of eligible studies

No	Study	Q1A	Q1B	Q2A	Q2B	Q3A	Q3B	Q4	Q5	Q6	Q7A	Q7B	Q8A	Q8B	Q8C	Q9A	Q9B	Q10A	Q10B
1	Dixon et al. (24) (1976)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
2	Lee et al. (10) (1978)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
3	Treinen and Chapin (19) (1991)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
4	Ku et al. (25) (1993)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
5	Chapin and Ku (1994) (26)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
6	Nomiyama et al. (27) (1996)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
7	Bustos-Obregón et al. (28) (2007)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
8	Espinoza-Navarro et al. (29) (2007)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
9	Bustos-Obregón and Olivares (30) (2012)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
10	El-Dakdoky and Abd El-Wahab (16) (2013)	Y	Y	Y	N	N	Y	N	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	NA
11	Elkomy et al. (12) (2015)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
12	Fort et al. (31) (2016)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
13	Ibrahim et al. (11) (2019)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
14	Krishnan et al. (13) (2019)	Y	Y	Y	N	Y	Y	N	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
15	Ayranci et al. (15) (2021)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA
16	Abdel-Wahab et al. (14) (2022)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	Y	Y	N	Y	NA

Y: Yes, N: No, U: Unclear, NA: Not applicable; the ARRIVE Essential 10: Compliance Questionnaire: Q1A: Are all experimental and control groups clearly identified?; Q1B: Is the experimental unit (e.g. an animal, litter or cage of animals) clearly identified?; Q2A: Is the exact number of experimental units in each group at the start of the study provided (e.g. in the format 'n=')?; Q2B: Is the method by which the sample size was chosen explained?; Q3A: Are the criteria used for including and excluding animals, experimental units, or data points provided?; Q3B: Are any exclusions of animals, experimental units, or data points reported, or is there a statement indicating that there were no exclusions?; Q4: Is the method by which experimental units were allocated to control and treatment groups described?; Q5: Is it clear whether researchers were aware of, or blinded to, the group allocation at any stage of the experiment or data analysis?; Q6: For all experimental outcomes presented, are details provided of exactly what parameter was measured?; Q7A: Is the statistical approach used to analyse each outcome detailed?; Q7B: Is there a description of any methods used to assess whether data met statistical assumptions? Q8A: Are all species of animal used specified?; Q8B: Is the sex of the animals specified?; Q8C: Is at least one of age, weight or developmental stage of the animals specified?; Q9A: Are both the timing and frequency with which procedures took place specified?; Q9B: Are details of acclimatisation periods to experimental locations provided?; Q10A: Are descriptive statistics for each experimental group provided, with a measure of variability (e.g. mean and standard deviation, or median and range)?; Q10B: Is the effect size and confidence interval provided?

Conclusion

The systematic review highlights the contrasting findings regarding the effect of boron on spermogram parameters. The study's findings will help researchers better understand the limitations of boron toxicity. While some studies suggest potential benefits of boron supplementation on spermatogenesis, others indicate harmful effects. The conflicting results emphasize the need for further research to establish clear guidelines on the appropriate dosage, duration, and safety of boron supplementation in improving sperm quality and fertility. Understanding the underlying mechanisms of boron's effects on spermatogenesis is crucial for addressing male infertility and developing targeted interventions in the future.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.S., An.S., S.S., M.B., M.E., A.E., F.T.A., H.S-P., S.H., M.N.B., Concept: H.S-P., M.N.B., Design: H.S-P., S.H., Data Collection or Processing: A.S., An.S., S.S., F.T.A., H.S-P., S.H., Analysis or Interpretation: An.S., S.S., F.T.A., A.E., Literature Search: A.S., M.B., M.E., Writing: A.S., An.S., M.B., M.E., M.N.B., A.E.

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ORIGINAL RESEARCH
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Investigation of the Psychometric Properties of the Turkish Version of the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

Fatma Vural[1], Sevgi Çolak[2]

[1]Dokuz Eylül University Faculty of Nursing, Department of Surgical Nursing, İzmir, Türkiye
[2]Dokuz Eylül University Health Sciences Institute, Department of Surgical Nursing, İzmir, Türkiye

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

Expanded Prostate Cancer index for Clinical Practice (EPIC-CP) is a validated tool for assessing the quality of life in prostate cancer patients, but its Turkish version has not been studied. This study validates the Turkish version of EPIC-CP, demonstrating its high reliability and validity. The findings suggest that the Turkish EPIC-CP is a suitable tool for evaluating the quality of life in Turkish prostate cancer patients and can be used effectively in clinical and research settings.

Abstract

Objective: This study was conducted to examine the psychometric properties of the Turkish version of the Expanded Prostate Cancer index for Clinical Practice (EPIC-CP).

Materials and Methods: The sample of this study consisted of 80 patients diagnosed with prostate cancer who applied to urology and oncology outpatient clinics. Data were collected between February 2021 and July 2021. The content validity of the scale was evaluated by consulting 11 experts from the field of surgical nursing. The Content Validity index, Explanatory and Confirmatory Factor Analysis were used for validity, while Pearson Correlation Analysis and Cronbach Alpha Coefficient were used for reliability.

Results: Overall prostate cancer quality of life score (minimum 0-maximum 60). The score was calculated as 26.26±9.6. For the validity of the scale, it was determined that the Content Validity index was 1.0 for each item of the scale, the factors used in the Explanatory Factor Analysis explained 74.403% of the total variance, the factor loads of the items were over 0.40 in the Confirmatory Factor Analysis, and all correlation relationships were significant. The total Cronbach's α value, which shows the reliability and internal consistency of the scale, was determined to be 0.83.

Conclusion: As a result of the statistical evaluations, the Turkish validity and reliability of the EPIC-CP was found to be high. Considering these results, this developed scale can be used successfully for research to be conducted in Türkiye.

Keywords: Prostate cancer, quality of life, reliability, validity

Introduction

Prostate cancer is the second most common type of cancer among men worldwide, after lung cancer, and its incidence is increasing (1). According to GLOBACAN 2020 data: 1,414,259 men were diagnosed with prostate cancer and 375,304 men died from prostate cancer. 3.8% of all deaths from cancer in men are due to prostate cancer (2).

Today, due to the increase in population, the more frequent screening of serum prostate-specific antigen (PSA) values in men, the expansion of prostate biopsy indications, and advances in surgical techniques, more patients are diagnosed with prostate cancer. With the increase in early detection of prostate cancer and advances in treatment, the survival rates of patients are also increasing (2,3).

Correspondence: Fatma Vural Prof., Dokuz Eylül University Faculty of Nursing, Department of Surgical Nursing, İzmir, Türkiye
E-mail: fatmavural72@gmail.com **ORCID-ID:** orcid.org/0000-0001-6459-2584
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Although prostate cancer is asymptomatic at an early stage, patients may experience urinary retention, nocturia, hematuria, stool thinning due to rectal compression, painful defecation, weakness, anorexia, and weight loss in the later stages as the cancer progresses. According to the clinical stage of the disease, hormonal therapy, radiotherapy, chemotherapy, cryotherapy, or radical prostatectomy are among the treatment options (4,5).

Depending on the prostate cancer treatment method and complications, patients are faced with many conditions that will negatively affect their quality of life, such as urinary incontinence, changes in bowel habits, and sexual dysfunction. Each of these situations has negative effects on the perception of quality of life (6). Health-related quality of life is an important parameter in cancer management that enables clinicians to evaluate how treatment side effects affect patients. Validated and reliable measurement tools should be used to assess quality of life (6,7).

The University of California-Los Angeles Prostate Cancer index (UCLA-PCI) was developed by Litwin et al. (8) to assess the quality of life of patients with prostate cancer worldwide. The Expanded Prostate Cancer index Composite (EPIC), consisting of 50 items, EPIC-26, consisting of 26 items, were developed by Wei et al. (9), inspired by UCLA-PCI. Because these forms of EPIC are difficult to use, as the number of items is high and the application is impractical, the "Expanded Prostate Cancer index Composite for Clinical Practice (EPIC-CP)" consisting of 10 questions and 16 items was created. EPIC-CP is used in many studies evaluating the quality of life of patients with prostate cancer around the world (10).

Recently, a study to examine the Turkish psychometric properties of EPIC-CP, which is used by clinicians and researchers in the evaluation of the quality of life of patients with prostate cancer, has not been conducted. For this reason, this study, which examines the Turkish psychometric properties of EPIC-CP, will be useful in evaluating the quality of life of patients with prostate cancer and in planning care and interventions to improve it.

Materials and Methods

This research was conducted as a methodological study to examine the psychometric properties of the Turkish version of EPIC-CP. The sample of the study consisted of 80 patients who applied to the urology and oncology outpatient clinic of a university hospital between February and July 2021, and were diagnosed with prostate cancer. In the literature, it is recommended to calculate the sample size by taking at least 5 times the number of items in the measurement tool (11). EPIC-CP consists of 10 questions and 16 items. Therefore, 80 patients were included in the study, five times the total number of items.

Data were collected using the face-to-face interview method. Inclusion criteria: All patients diagnosed with prostate cancer, who are under treatment or under follow-up, who speak and understand Turkish, and who voluntarily agree to participate in the study. Exclusion criteria: patients with relapsed prostate cancer and patients with psychiatric problems using antipsychotic, antidepressant, and anxiolytic drugs.

Ethical Aspect of Research

Permission was obtained by e-mail from lead author Peter Chang, who developed the EPIC-CP scale. Ethics committee approval was obtained from the Non-Interventional Clinical Research Ethics Committee of a Dokuz Eylül University Hospital (date: 10.04.2019 and decision no: 2019/09-05). Then, permission was obtained from the institution where the study was conducted.

Data Collection Tools

Data were collected using the Patient Descriptive Characteristics Form and EPIC-CP prepared by the researchers. Patient Descriptive Characteristics Form: consists of 10 questions in total, in which socio-demographic characteristics of patients such as age, marital status, education level, and income level, and clinical characteristics such as the patient's PSA value, Gleason Score, tumor extent, and treatment methods are assessed. Information about the PSA value, Gleason score, and tumor spread of the patients was obtained from the medical records.

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

This index, developed by Chang et al. (10), aims to evaluate the effect of treatment on the quality of life of prostate cancer patients in a short period of time. EPIC-CP is inspired by the first form of the index, EPIC, and the second, abbreviated form, EPIC-26. EPIC-CP is a Likert-type measurement tool consisting of 16 items, structured into 10 questions, with clinical ease of use. The index consists of five sub-dimensions that determine the quality of life of patients with prostate cancer. These: urinary incontinence, urinary irritation/retention, bowel functions, sexuality, and hormonal symptoms. The value given to each question is between zero and four points. Each sub-dimension ranges from zero to 12 points. Higher scores indicate worse symptom severity and worse quality of life. With EPIC-CP, both [the sub-dimensions affecting the quality of life of the prostate cancer patient can be evaluated (minimum 0-maximum 12)], as well as the general evaluation of the quality of life (minimum 0-maximum 60), can be conducted. The first item in the index is an independent general urinary disorder item with no scoring (10).

Statistical Analysis

In the analysis of the data using the IBM SPSS Statistics 21.0 program, number, percentage, and mean were used for descriptive statistics. The Content Validity index and Explanatory Factor Analysis were calculated for validity, while the Pearson Correlation Analysis and Cronbach's Alpha Coefficient were calculated for reliability. The AMOS program was used in the Confirmatory Factor Analysis, for validity. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. P<0.05 was considered significant.

Results

Demographic and Clinical Characteristics

The mean age of the patients participating in the study was 72.96±8.44. Sixty-five percent were married, 52% were primary-secondary school graduates, 41% had income equal to expenditure, 49% had a Gleason score of 8 to 10, and 61% had metastatic spread of the tumor. The mean PSA value of the patients was found to be 28.39±4.31 ng/mL. The overall prostate cancer quality of life score was 26.26±9.6. When the sub-dimensions were examined, it was determined that the patients had the highest sexual symptom scores (8.62±2.39), which were significantly associated with a reduction quality of life (Table 1).

Table 1. Socio-demographic and clinical characteristics of patient (n=80)

Characteristics	n	%
Marital status		
Single	15	18.8
Married	65	81.3
Education level		
Illiterate	5	6.3
Primary-secondary school	52	65
High school	13	16.3
University	10	12.5
Income level		
Income less than expense	23	28.8
Income equals expense	41	51.3
Income is more than expense	16	20
Gleason score		
Gleason score ≤6	7	8.8
Gleason score 7	24	30
Gleason score 8-10	49	61.3
Spread of tumor		
Organ-limited	9	11.3
Local spread	10	12.5
Metastatic	61	76.3

n: Number of samples

Validity Analysis

Language Validity

For the EPIC-CP, which was translated into Turkish, opinions were obtained from 11 experts. To test the comprehensibility of the items in the language-valid scale, the scale was applied to a small group with the characteristics of the sample group. In this study, considering the number of scale items and the sample size, the instrument was applied to 8 prostate cancer patients with characteristics similar to those in the study. After the application, the comprehensibility of the questions was tested. Since no negative or positive feedback was received, the study continued. Patients participating in the pilot study were excluded from the sample.

Content Validity

Expert opinions were evaluated according to the Scope Validity index Davis technique. The experts were given the original form of EPIC-CP and the Turkish form together and were asked to assess and make a selection regarding the suitability of the scale items (A: item is appropriate, B: item should be reviewed, C: item should be seriously reviewed, D: item is not suitable). KGI is calculated as follows: The number of experts who assigned A and B to each item of the scale is divided by the total number of experts. If the KGI is greater than 0.80, the substance is considered sufficient in terms of scope validity (12). In this study, KGI was calculated as 1.0 for each item of the scale. According to expert opinions, the draft form of the scale was rearranged finalized.

Construct Validity

In the factor analysis, the Kaiser-Meyer-Olkin (KMO) test was applied to test whether the sample size was suitable for factor analysis. As a result of the analysis, the KMO value was 0.821. In addition, when the results of the Bartlett's Sphericity test were examined, it was seen that the obtained chi square value was acceptable [$\chi^2(78)=517.372$; $p<0.05$].

Descriptive and Confirmatory Factor Analysis

To reveal the factor pattern of the scale, principal components analysis was chosen as the factorization method and varimax was selected as the rotation method. In the explanatory factor analysis conducted to reveal the factor pattern of the scale, 3 items were removed from the scale due to low factor load (EPICCP7, EPICCP8, and EPICCP9) and the remaining 13 items were collected in 4 sub-dimensions. These factors explain 74.403% of the total variance (Table 2).

Confirmatory Factor Analysis was conducted to determine whether the items and their sub-dimensions explained the original structure of the scale. In the analysis, the factor loads of the substances were above 0.40 and all correlations were significant (Figure 1).

Reliability Analysis

Internal Consistency (Cronbach Alpha Coefficient)

When the reliability of the scale and sub-dimensions of the Turkish version of EPIC-CP was evaluated separately, the reliability coefficients were found to be 0.841 for the first dimension, 0.834 for the second dimension, 0.833 for the third dimension, 0.781 for the fourth dimension, and 0.874 for the overall scale, indicating a good degree of reliability. The fact that Cronbach's Alpha values are greater than 0.60 shows that the scales used are reliable (13). This meant that the scale used in the study was determined to have a good degree of reliability.

Item Analysis and Total Score Correlation

The relationship between the scores from the scale items, and the total score of the scale, is explained by item analysis and total score correlation. When the correlations between the variables are examined, the factor loadings of the substances are over 0.40 and all correlation relationships are significant (Table 3).

According to confirmatory factor analysis, the analysis determined that the 13 items and 4 sub-dimensions that make up the scale were related to the scale structure. The values accepted for the fit index calculations are shown in Table 4.

Discussion

The KGI of the EPIC-CP scale was calculated as 1.0 for each item. In the literature, it is emphasized that these rates should be above 0.80 (12). The results of this study showed that experts reached a consensus on the content of the scale.

The adequacy of the data and sample size for factor analysis was evaluated using the Bartlett's test of sphericity and the

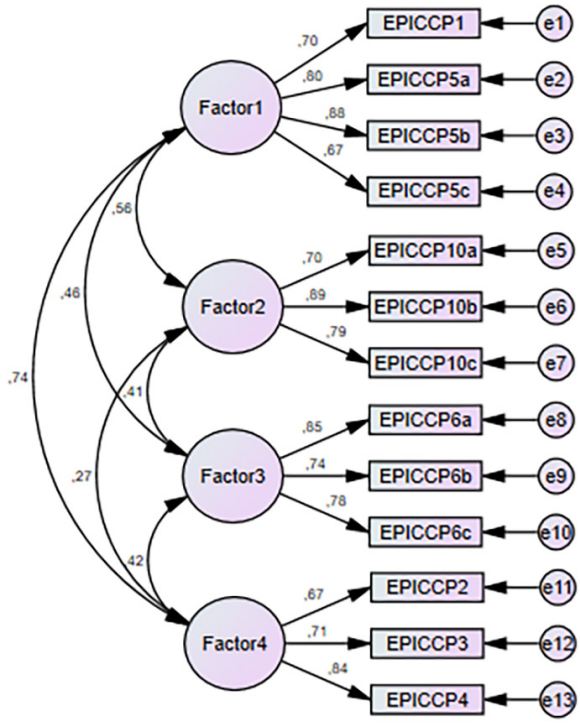

Figure 1. Model for first level multi-factor confirmatory factor analysis of the scale

Table 2. Explanatory factor analysis results of the scale

	Factors				
Items	**F1: Urine irritation/ retention**	**F2: Hormonal symptoms**	**F3: Bowel functions**	**F4: Urinary incontinence**	**Total item correlation**
EPICCP1	0.799				0.656
EPICCP5a	0.794				0.730
EPICCP5b	0.746				0.751
EPICCP5c	0.706				0.600
EPICCP10a		0.880			0.635
EPICCP10b		0.815			0.769
EPICCP10c		0.796			0.685
EPICCP6a			0.881		0.722
EPICCP6b			0.837		0.687
EPICCP6c			0.784		0.679
EPICCP2				0.838	0.610
EPICCP3				0.758	0.641
EPICCP4				0.681	0.640
Reliability	0.841	0.834	0.833	0.781	0.874
Variance explained (%)	22.026	18.339	18.140	15.899	74.403
KMO =0.824; χ^2(78) =517.372; Bartlett Sphericality test (p)=0.000, KMO: Kaiser-Meyer-Olkin test, p<0.05					

Table 3. Results regarding the measurement model of the scale					
Factors	**Expressions**	**Factor loadings**	**Standard error**	**t-values**	**p**
F1: Urinary irritation/retention	EPICCP1	0.700	-	-	-
	EPICCP5a	0.796	0.141	6.456	***
	EPICCP5b	0.881	0.141	6.986	***
	EPICCP5c	0.670	0.128	5.501	***
F2: Hormonal symptoms	EPICCP10a	0.702	-	-	-
	EPICCP10b	0.892	0.205	6.584	***
	EPICCP10c	0.791	0.174	6.300	***
F3: Intestinal functions	EPICCP6a	0.852	-	-	-
	EPICCP6b	0.743	0.115	6.601	***
	EPICCP6c	0.778	0.135	6.855	***
F4: Urinary incontinence	EPICCP2	0.666	-	-	-
	EPICCP3	0.713	0.260	5.238	***
	EPICCP4	0.837	0.308	5.697	***

***: p<0.05

Table 4. Scale structural model integrity of fit values		
	Structural model values	**Recommended values**
CMIN/DF	1.415	≤5
RMSEA	0.073	≤0.08
GFI	0.864	≥0.80
CFI	0.948	≥0.80
TLI	0.932	≥0.80
IFI	0.950	≥0.80
RFI	0.801	≥0.80
SRMR	0.074	≤0.10

KMO test. The Bartlett sphericity test value is expected to be statistically significant and the KMO value is expected to be higher than 0.60 (14). In this study, Exploratory Factor Analysis, KMO, and Bartlett's tests, met the necessary conditions, and the number of samples and data was suitable for factor analysis.

In the explanatory factor analysis performed to reveal the factor pattern of the scale, 3 items were removed from the scale (EPICCP7, EPICCP8, and EPICCP9) due to their low factor loading, and the remaining 13 items, were collected in 4 sub-dimensions. These factors explain 74.403% of the total variance. It is considered sufficient if the variance explained in multi-factor designs is above 50% (11).

EFA factor loads ranged from 0.68 to 0.88. The fact that the factor loadings measured from each sub-dimension are more than 0.30 indicates a strong factor structure (14). The results of this analysis showed that the factor loads in the EFA were at the desired level. In the original scale, the results could not be compared because EFA was not performed (10).

According to the CFA analysis, the fit indices were RMSEA ≤0.08, and GFI, CFI, IFI, RFI, NFI, NNFI were ≥0.80. These values indicate that there is a significant relationship between the scale and its sub-dimensions. According to the CFA results, the data were found to be compatible with the model, and the sub-dimensions were related to the scale. In the CFA analysis, the factor loads of the items varied between 0.67 and 0.89. The factor loads are above 0.40 and all correlation relationships are significant. In the original form of the scale, the results could not be compared because CFA was not performed (10).

Cronbach's alpha coefficient measures the average correlation between items in the scale. This value is expected to be close to 1 (15,16). In this study, the Cronbach's alpha coefficient for both the total scale and its sub-dimensions was greater than 0.70. This finding shows that the scale and its sub-dimensions are reliable. The items were sufficient to measure the relevant subject and the scale had good reliability. The Cronbach's alpha coefficient of the scale and sub-dimensions was found to be 0.64-0.84 in the original scale (10). Lourenço et al. (17), in 2020, found the Cronbach's alpha coefficient to be 0.35-0.82 for the sub-dimensions of the scale. The reliability coefficient results from this study were found to be consistent with those of the original scale.

To show that each item can measure at the expected level, an item-total score analysis was conducted to explain the relationship between the score of each item and the total score of the scale. This value is expected to be >0.40 (15). The total score correlation of the Turkish version of the scale was 0.67 to 0.89. These results show that the sub-dimensions of the scale are correlated with the total score and each item is reliable. The item total score analysis in the original scale was found to be ranging from 0.31-0.83 (10). However, since the section on sexual problems, which reduced the item total score, was included in its original format in the analysis, the item-total score correlation was higher in this study.

As a result, the Turkish version of EPIC-CP consists of four sub-dimensions and 13 items. Each sub-dimension is scored as 0-12 points. The total score of the scale is the sum of all sub-dimensions, totaling 48.

Study Limitations

Some patients in the study had undergone open radical prostatectomy, and patients who had other surgical treatment options (laparoscopic or robotic radical prostatectomy) were not included in the sample. This situation may affect the generalizability of the scale. In addition, while the scale originally had five sub-dimensions, it was reduced to four in the Turkish version, with the sexuality sub-dimension being removed from the scale. The absence of a sexuality sub-dimension in the Turkish version creates a limitation.

Conclusion

The Turkish validity and reliability of EPIC-CP are high. It is thought that its use in Turkish society will be useful in evaluating the quality of life of patients with prostate cancer and in planning care and interventions to improve it.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Non-Interventional Clinical Research Ethics Committee of a Dokuz Eylül University Hospital (date: 10.04.2019 and decision no: 2019/09-05).

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

Footnotes

Authorship Contributions

Concept: F.V., S.Ç., Design: F.V., S.Ç., Data Collection or Processing: S.Ç., Analysis or Interpretation: F.V., S.Ç., Literature Search: F.V., S.Ç., Writing: F.V., S.Ç.

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

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ORIGINAL RESEARCH
Pediatric Urology

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The Comparison of Postoperative Quality of Life of Children and Adolescents who Underwent Minimally Invasive and Major Surgery for Vesicoureteral Reflux Disease: A Retrospective Cohort Study

Berk Hazır[1], Müjdat Ayva[1], Merve Kaşıkçı[2], Halime Tuna Çak[3], Serdar Tekgül[1], Hasan Serkan Doğan[1]

[1]Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Türkiye
[2]Hacettepe University Faculty of Medicine, Department of Biostatistics, Ankara, Türkiye
[3]Hacettepe University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Ankara, Türkiye

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

Since their physical and psychological impacts are considered severe, major surgeries in pediatric urology often receive less attention compared to minor procedures. However, studies investigating long-term quality of life with evenly distributed patient groups based on diagnosis are still lacking. We believe that urologists should take into account not only the surgical procedures, complications, and follow-up challenges but also the psychological consequences associated with these interventions.

Abstract

Objective: We aimed to compare endoscopic subureteric injection with conventional open ureteral reimplantation in vesicoureteral reflux disease (VUR) in terms of long-term postoperative quality of life (QoL) to find potential factors that would predict the psychological outcome.

Materials and Methods: This retrospective cohort was based on data from February 2016-December 2019 on 115 children and adolescents (4-18 years old) who underwent elective surgery due to VUR disease and were hospitalized thereafter. Patients were divided into two groups according to the surgery they underwent, "endoscopic subureteral hyaluronic acid/dextranomer copolymer injection" (n=65), and "open ureteroneocystostomy" (n=50). With their mothers, the patients filled out the Pediatric QoL Questionnaire (PedsQL) remotely 2 to 6 years post-surgery (median 49 months), and the postoperative QoL was compared among the patients with regard to the QoL. Those with congenital or concomitant diseases were excluded.

Results: In VUR, patients undergoing either type of surgery had similar scores in all domains in PedsQL. In other words, postoperative QoL levels did not differ between endoscopic treatment and conventional open ureteral reimplantation. Furthermore, linear regression analysis identified maternal higher education level as the only significant predictor of higher postoperative QoL (estimate: 10.89; 95% confidence interval: 1.54-20.23; p=0.023). Conversely, factors such as surgery type, length of hospital stay, previous surgical experience, and patients' age at the time of the survey were not associated with postoperative long-term QoL.

Conclusion: The less invasive surgical modalities of VUR in the pediatric age group do not provide a significant advantage over open surgeries regarding the long-term postoperative QoL.

Keywords: Endourology, general urology, pediatric urology

Correspondence: Berk Hazır MD, Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Türkiye
E-mail: berkhazir@gmail.com **ORCID-ID:** orcid.org/0000-0002-8907-8781
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Introduction

The World Health Organization states that being healthy requires a combination of physical, mental, and social well-being beyond the absence of disease or infirmity (1). Quality of life (QoL) is, therefore, a fundamental part of pediatric practice. Many diseases can hinder children from engaging in physical and social activities. Thus, their QoL is frequently reduced because of diseases (2). Moreover, QoL is affected significantly by surgeries. In a cohort of 915 children who underwent many different types of inpatient surgery, such as general surgery, urology, and orthopedics etc., QoL scores declined significantly in 23% of children after one month (3).

The relationship between surgery and the development of a child's QoL and sense of well-being has been explored in pediatric urology. A recent study from our group investigated 151 children and adolescents undergoing different elective urological surgeries, and compared major versus minor surgeries, as well as open versus endourological surgeries (4). In that study, we found high parental preoperative psychiatric symptoms, number of previous surgeries, and female sex were associated with lower postoperative QoL. Schönbucher et al. (5) specifically evaluated the impact of hypospadias surgery in children and adolescents, finding that the severity of the disease was closely linked to lower QoL scores.

Investigating the effect of primary surgeries specific to a disease on QoL may be valuable for deciding surgical strategies. In vesicoureteral reflux disease (VUR), even though open ureteroneocystostomy (UNC) has higher success rates than endoscopic treatment, endoscopic procedures may be preferred to open techniques in reasonable indications, such as due to parental preference, having lower grades of reflux, and mild clinical course (6). We have avoided laparoscopic and robotic-assisted interventions for reflux as their superiority is still questioned and these techniques have not gained wide popularity among pediatric urologists (7). Thus, these techniques have not been preferred in our clinic.

We aimed to explore the differences in VUR surgeries with regards to the postoperative QoL outcome through a cohort that included both minimally invasive and major surgery groups, and to find which factors would predict the outcome.

We hypothesized that more extensive surgery in VUR would affect QoL and psychological well-being adversely in pediatric patients.

Materials and Methods

Patient Selection

All patients and parents gave informed consent before the study's initiation. We included all pediatric patients (under the age of 18) who underwent an elective VUR between February 2016 and December 2019, and spent at least one night in the surgical in-patient ward. Most of the patients were referred to our institution from other cities, as it serves as a tertiary center for pediatric urology. They were hospitalized one day before surgery for anesthesia preparation. Each surgical procedure was performed under general anesthesia.

Children with neurogenic bladder and those over five years old, with apparent bladder-bowel dysfunction, as determined by the Dysfunctional Voiding Scoring System, were excluded from the study.

Twenty patients were excluded from the study due to factors potentially affecting the QoL and psychological well-being. These factors include having moderate or severe intellectual disabilities preventing essential cooperation (n=3), psychiatric disorders, such as attention deficit hyperactivity disorder, tic disorders, and developmental coordination disorder, diagnosed or currently being treated (n=4), and multiple congenital anomalies (n=10). Additionally, patients whose parents have a level of language or education that would hinder cooperation with the surveyor were excluded (n=3).

The perioperative data of the study population and accompanying medical information were obtained from the hospital's electronic data system as well as the patients' written documents in the hospital archive. This retrospective cohort study had approval from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO20/697, date: 25.08.2020).

Outcome Measures

1. Pediatric Quality of Life Questionnaire (PedsQL) 4.0: This questionnaire assesses the health-related QoL levels in children/adolescents aged 2-18 years in three domains: physical, psychosocial, and overall health-related QoL. This form is tailored for each group: 2-4, 5-7, 8-12, and 13-18 years. We used parent-reported and child/adolescent self-reported forms for subjects between 4 and 18 years to evaluate health-related QoL levels. Higher scores demonstrate a higher QoL (8-11). In the literature, this questionnaire's reliability, validity, sensitivity, and responsiveness to meaningful change in health-related QoL in healthy children, and children with acute and chronic health conditions have been proven (12). This is a validated questionnaire that has been adapted for use in the Turkish language (10,11).

2. The Strengths and Difficulties Questionnaire (SDQ): This behavior screening survey was developed to evaluate positive social behaviors and emotional and behavioral problems in children/adolescents aged between 2 and 17 years (13). Twenty-five items are categorized into 5 scales: Emotional symptoms (5 items); conduct problems (5 items); hyperactivity/inattention (5

items); peer relationship problems (5 items); prosocial behavior (5 items). In this study, the questionnaire was filled out by parents. This questionnaire was evaluated by medical professionals and found to be valid and reliable in the Turkish language (14). Higher scores indicate worse behavioral conditions.

An elective VUR surgery was carried out on 173 children and adolescents. After implementing the determined exclusion criteria, 153 patients were eligible for the study. Of these, thirty-eight patients (24.8%) could not be reached following the operation. PedsQL and SDQ were applied to the rest of the patients (n=115), and their mothers postoperatively.

All patients were admitted to the hospital one day before their surgeries, and there were no severe or long-term complications observed post-surgery. The patients were discharged after a complete recovery and made regular visits to clinic for routine follow-ups. The rest of the patients and their mothers were later contacted by phone and asked to complete the questionnaires to determine their long-term psychological well-being. The participants responded to the relevant questionnaire according to their age group.

The patients were divided into two surgical groups for analysis:

a. Endoscopic subureteral injection (ESI) with Hyaluronic Acid/Dextranomer copolymer (65 patients)

b. Open (ureteroneocystostomy) (50 patients).

The impact on the long-term psychological well-being of these surgeries was compared.

Statistical Analysis

The Stats (15) and the onewaytests (16) R packages were used to perform statistical analysis. Descriptive statistics of the participants were given as quantity and percentages; group characteristics were given as mean ± standard deviation or medians and minimum-maximum values according to whether they were normally distributed or not. The patient data were divided into two surgery groups: ESI and UNC. These groups are compared, regarding postoperative sociodemographic and psychological features. To identify between-group differences, nominal variables were compared using the Pearson chi-square test. After the Shapiro-Wilk test was implemented, normally distributed continuous variables were compared with an independent samples t-test, and the Mann-Whitney U test was performed for non-normally distributed data. Following univariate analyses, multiple linear regression models were developed to investigate the combined effects of surgery types and clinically important variables on postoperative long-term QoL scores. P<0.05 was defined as the level of statistical significance.

Results

One hundred and fifteen patients who underwent elective VUR surgery in the study were successfully evaluated with the questionnaires. The median time between the surgery and the psychosocial evaluation, which included the patients and their parents, was 47 months (26-73 months). Table 1 details the baseline characteristics of the participants.

Sociodemographic and Perioperative Features

The ESI group included 65 children/adolescents, while the UNC surgery group consisted of 50 participants. All patients in the UNC group underwent the intravesical approach. The number of females was significantly higher in the ESI group (76.9% *vs.* 52%; p=0.005). Excluding the length of postoperative hospital stays (median; ESI *vs.* UNC: 1 day *vs.* 5 days; p<0.001) and the age during the psychosocial evaluation (median; ESI vs. UNC: 9 years *vs.* 7 years; p=0.046), other sociodemographic features were similar between the surgery groups; such as the time gap between the surgery and psychosocial evaluation, age during the surgery, the proportion of subjects who had previous surgery, and maternal age. These findings are presented in Table 2.

QoL and Psychiatric Symptoms

Both parent-reported and child-reported QoL scores in all domains were comparable between the groups. Furthermore, the ESI and the UNC group had no differences regarding SDQ scores in 5 domains. However, the SDQ emotional problems scores are significantly higher in patients who have undergone UNC surgery (median, ESI *vs.* UNC: 0 *vs.* 1; p=0.007). These results are shown in Table 2.

Linear Regression Analysis

Type of surgery, length of hospital stay, previous surgery experience, patient's age at the time of the survey, and mother's education level were determined as factors that could affect the postoperative QoL scores. These factors were examined with linear regression models. It was found that the patient's mother with a higher education level was the only predictor for higher postoperative long-term QoL scores (estimate: 10.89; 95% confidence interval: 1.54-20.23; p=0.023). These results are presented in Table 3.

Discussion

Current findings revealed that the type of surgery performed made no significant difference in postoperative QoL levels for children with VUR. Moreover, the type of surgery could not be used to predict the pediatric patients' postoperative QoL.

Table 1. Descriptive statistics of the participants				
			n	(%)
Mother's health status	Healthy		93	80.9
	Having a disease requiring medication		22	19.1
Mother's education level	Primary school		17	14.8
	Secondary school		24	20.9
	High school		29	25.2
	University		45	39.1
Family structure	Separated family		5	4.3
	Nuclear family		98	85.2
	Extended family		12	10.4
Mode of presentation	Antenatal hydroureteronephrosis		19	16.7
	Febrile urinary tract infection		74	64.9
	Non-febrile urinary tract infection		7	6.1
	Impairment in kidney functions		9	7.9
	Urinary incontinence		2	1.8
	Unsuccessful reflux surgery		3	2.6
Previous surgeries	Yes		31	27.0
	No		84	73.0
Performed surgeries	Endoscopic procedure	Unilateral	25	21.7
		Bilateral	40	34.7
	Open ureteroneocystostomy	Unilateral	22	19.2
		Bilateral	28	24.4

Table 2. Postoperative sociodemographic and psychological features of the patients in different groups					
			ESI (n=65)	UNC (n=50)	p
Between the surgery and psychosocial evaluation (month)			46 (26-73)	51 (26-72)	0.210[a]
Age during the surgery (year)			5.0 (0-13)	3.0 (0-13)	0.117[a]
Age during the psychosocial evaluation (year)			9.0 (2-17)	7.0 (3-16)	0.046[a]
Previous surgeries		Yes	28 (43%)	26 (52%)	0.342[b]
		No	37 (57%)	24 (48%)	
Maternal age (year)			38.56±5.83	37.58±5.58	0.360[c]
Postoperative hospital stays (day)			1.0 (1-7)	5.0 (1-8)	<0.001[a]
Maternal education level	Primary school graduate		9	8	0.763[b]
	Secondary school graduate		13	11	
	High school graduate		19	10	
	University graduate		24	20	
SDQ (emotional symptoms)			0 (0-9)	1.0 (0-7)	0.007[a]
SDQ (conduct problems)			1.0 (0-6)	1.0 (0-7)	0.232[a]
SDQ (hyperactivity/inattention)			3.0 (0-10)	5.0 (0-10)	0.081[a]
SDQ (peer relationship problems)			2.0 (0-9)	2.0 (0-10)	0.512[a]
SDQ (prosocial behaviour)			9.0 (0-10)	8.0 (3-10)	0.250[a]
SDQ (total)			16 (10-30)	17 (9-35)	0.329[a]
PedsQL psychical			75 (0-100)	75 (40-100)	0.843[a]
PedsQL psychosocial			75 (33-100)	77 (27-100)	0.845[a]
PedsQL total score			74.28±14.44	74.61±16.48	0.909[c]
PedsQL psychical-parent reported			59 (25-100)	59 (22-100)	0.927[a]
PedsQL psychosocial-parent reported			72 (33-97)	78 (25-95)	0.117[a]
PedsQL total score-parent reported			67 (47-98)	70 (37-97)	0.305[a]

ESI: Endoscopic subureteral injection, UNC: Ureteroneocystostomy, SDQ: The strengths and difficulties questionnaire, PedsQL: Pediatric quality of life questionnaire
[a]: Mann-Whitney U test, [b]: Pearson chi-square test, [c]: Student's t-test

Table 3. Linear regression analysis of the total score of PedQL					
Predictors	**Patients having vesicoureteral reflux disease**				
	Estimates	**Standard error**	**Confidence interval**	**Statistic**	**p**
(Intercept)	57.77	6.96	43.97-71.57	8.30	<0.001
Surgery type	-0.75	4.94	-10.55-9.065	-0.15	0.880
Secondary school graduate mother	8.81	5.04	-1.19-18.80	1.75	0.084
High school graduate mother	7.83	4.98	-2.04-17.70	1.57	0.119
University graduate mother	10.98	4.71	1.65-20.32	2.33	0.022
Age during the psychosocial evaluation	0.80	0.43	-0.05-1.65	1.87	0.064
Postoperative hospital stays	0.50	1.10	-1.69-2.69	0.45	0.653
Previous surgery	0.63	3.32	-5.95-7.21	0.19	0.851
PedsQL: Pediatric quality of life questionnaire. In this regression model, the variable representing mothers who graduated from primary school was accepted as a reference, and three dummy variables were developed and used					

However, patients who underwent UNC surgery due to VUR tended to have more significant emotional problems than patients who had an ESI. Besides, the schooling degree of the mother can predict the pediatric patients' postoperative QoL level.

As well as the characteristics of the disease and the patient, the parental preference is also important in decision about making management. Ogan et al. (17) reported that parents of VUR patients prefer antibiotic prophylaxis as initial treatment. As the years on follow-up pass, parents would choose definitive correction, and although ESI is less effective than UNC, they prefer ESI with the idea of being less invasive. Moreover, a latter study showed that antibiotic prophylaxis was preferred as the initial therapy for VUR, in time, given persistent VUR, preferences shifted toward surgery. After a period of time, the preference for open surgery increased, which was perceived as a more durable and permanent solution, and the preference for endoscopic surgery decreased (18). These findings underscore the importance of providing accurate and unbiased data to involve parents in building a management plan. Comparing ESI to UNC, there is no difference in the long-term psychological outcomes. Minimally invasive procedures do not always mean minimal psychological effects, especially in the pediatric age group. Therefore, treatment plans can be developed without considering psychological outcomes, as they seem equivalent.

As in other fields, assessing QoL and psychological well-being is a prominent topic in pediatric urology (4,19-21). QoL is a marker that allows the monitoring of the level of recovery in the postoperative period (19). A recent prospective study from our institution involving 151 pediatric urology patients who underwent either major or minor urological surgeries found the predictive factors for early postoperative QoL (4). However, this study's data were heterogeneous in terms of surgical diversity. Specific surgeries were evaluated with respect to their effect on postoperative QoL in pediatric urology patients (19,21). This study uniquely compares minor and major surgeries in pediatric urology. Until now, clinicians have generally perceived the long-term negative impact of major surgeries on QoL as greater than that of minor surgeries. This perception is primarily based on the severity of major surgical procedures and the way these surgeries are communicated to patients and their families. However, our results were not in accordance with the interpretation above. The results can be explained by the following: Firstly, all surgeries impair patients' physical integrity regardless of their severity. Even though the endoscopic treatment of VUR is minimally invasive, it may not prevent a deterioration in QoL. Secondly, children who undergo major surgeries suffer from more postoperative pain than those who undergo minor surgeries (22). However, since the median time between the surgery and psychosocial evaluation was relatively long in this study, postoperative pain, recovery-related anxiety, and activity restrictions in patients who underwent UNC surgery had already diminished, leading to an overall improvement in their QoL. In addition to that, in the postoperative period, pediatric patients in the UNC group required regular wound dressing and care, which may negatively impact QoL. However, wound healing and care in the study population were completed before the initiation of this study. Another point to note is that all patients who underwent UNC surgery were discharged with Double J stents. They displayed ureteral stent associated symptoms including pain and urinary side effects until its removal which was carried out under anesthesia 4-6 weeks after the surgery. It likely impaired postoperative QoL; however, its effect would have significantly lessened by the time of the study. Lastly, many parents might have chosen reimplantation, which had a higher success rate, even though the immediate post-operative morbidity may have been higher. It is likely that the patients who underwent open

reimplantation might have had fewer post-operative tests, such as voiding cystourethrography (VCUG), because of high success; those who underwent endoscopic treatment may have had more post-operative tests (like multiple VCUGs) repeated, so this may have reduced the QOL difference between the two groups. However, the morbidity associated with open surgery must not be overlooked, and families should be counseled accordingly.

High SDQ emotional subscale scores demonstrate the risk of suffering from concurrent clinical anxiety and depression (23). In this study, high emotional scores were confirmed in patients who underwent UNC surgery. Patients' history may contribute to these findings since patients who had major surgery frequently experienced more severe symptoms (24). Additionally, having an incision following UNC surgery and the need for observation with a urethral catheter for patients in the surgical in-patient ward may explain the findings.

Mothers are almost always the primary caregivers of their children following discharge from the hospital, and they should be able to thoroughly understand the instructions given to them by physicians in the postoperative period. To illustrate, possible surgical and medical complications must be instantly recognized at home once symptoms develop. Parental attention allows pediatric patients to seek medical consultation before the complications become severe or permanent. Wound care, pain management, and effective administration of medicine prescribed by medical doctors are the other instructions they should follow carefully. An adequate educational level of patients' caregivers is essential to understanding the instructions thoroughly. It may prevent a decrease in QoL scores and maintain psychological well-being in the postoperative period. Therefore, we speculate that the effect of maternal education level is more apparent than was previously considered. Mothers of patients who underwent open surgery might better identify the problems and be more conscious of how to overcome them in the management of the postoperative process. The strong association between maternal education level and postoperative QoL in VUR disease might be attributable to several factors.

The main strength of our study is that the sample of participants is evenly distributed in both surgery groups. QoL and emotional scores were compared among the surgeries, and a unique predictor for higher long-term postoperative QoL in VUR was found.

Study Limitations

This study also has some limitations. This study took place in a tertiary referral hospital where a selected group of patients was treated. The age range of the patients was quite broad. Furthermore, some patients and their parents were not able to be reached in order to participate in the study, which may have resulted in selection bias. Even though both PedsQL and SDQ are very well validated and widely used measures for QoL and psychiatric symptom assessment, they still carry the limitations of subjectivity with self-reported Likert-type scales. Moreover, the variables used in the regression model were defined as clinically meaningful, even though they were not significant in univariate analysis. The majority of children and their families may have forgotten postoperative discomfort, such as incision pain; bladder spasms in the open surgery group; the effects of urethral catheterization; and the inconvenience of prolonged hospitalization due to the time gap between the procedure and the completion of the survey. Lastly, due to the nature of the retrospective cohort, children with an underlying/pre-existing psychiatric disease could not be evaluated or excluded through clinical interview.

Conclusion

Whether being treated for VUR with an endoscopic or open surgery may result in similar long-term postoperative QoL remains a subject of investigation. Pediatric urologists should take into consideration that minimally invasive surgeries, notwithstanding their minority, may have a similar effect on long-term postoperative QoL to that of major surgeries.

Ethics

Ethics Committee Approval: This retrospective cohort study had approval from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO20/697, date: 25.08.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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A Bibliometric Analysis of Stem Cell Research in Infertility: Insights and Trends

Ozan Alper Alkoç[1], Çağrı Gümüşkaptan[2], Faruk Altınbaşak[3]

[1]Hitit University Faculty of Medicine, Department of Anatomy, Çorum, Türkiye
[2]Hitit University Faculty of Medicine, Department of Medical Biology, Çorum, Türkiye
[3]Hitit University Faculty of Medicine, Department of Histology and Embryology, Çorum, Türkiye

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

Infertility affects millions worldwide, and stem cell therapies have emerged as a promising alternative to traditional treatments. Despite increasing research, there has been a limited number of comprehensive bibliometric analyses regarding global trends, key contributors, and influential studies. This study analyzes 1,710 articles (1982-2024) using bibliometric mapping, identifying key authors, institutions, and research trends. The findings highlight the dominance of the United States and China in publications, the rising focus on spermatogonial stem cells, and the need for global collaboration to enhance research diversity and impact.

Abstract

Objective: This study aims to examine, using bibliometric mapping methods in the Web of Science database, the development of research articles related to infertility, which has become a significant global issue, and an innovative treatment method, stem cells, between 1982 and 2024.

Materials and Methods: Initially, 1,710 articles were retrieved using the keywords "stem cell" and "infertility". The data were analyzed using the Biblioshiny web interface in Bibliometrix, an open-source R package. The analyses were conducted under several categories: Basic data information, annual scientific production, country and institutional analysis, co-authorship and influential authors, most-cited articles, Bradford's law analysis, and Sankey diagrams.

Results: According to the findings, the United States ranks first among the countries with the most publications, while the Chinese Academy of Sciences stands out as the leading institution researching stem cell applications in infertility treatment. The journals publishing the most on the topic were identified as *Human Reproduction* and *Biology of Reproduction*. Keyword analyses revealed that recent research trends focus on spermatogonial stem cells, reproductive biology, and germline cells.

Conclusion: This study demonstrated the potential of stem cell therapies in infertility treatment and the dynamics of the scientific literature in this field. Consequently, the increasing number and diversity of studies on stem cells and infertility indicate that scientists in the field are highlighting and exploring this topic more extensively.

Keywords: Bibliometric analysis, biblioshiny, infertility, stem cell, Web of Science

Introduction

Infertility is a major health issue affecting millions of couples worldwide, limiting or preventing biological conception. The World Health Organization defines infertility as the failure to achieve pregnancy after one year or more of regular, unprotected intercourse (1,2). Globally, 10-15% of couples experience infertility, which imposes psychological, social, and economic burdens (3,4). Infertility may result from genetic, hormonal, or environmental factors, as well as age-related reproductive decline, structural anomalies, and infections (5). Alongside conventional methods and assisted reproductive technologies, innovative strategies like stem cell therapies are gaining attention (6). Induced pluripotent

Correspondence: Faruk Altınbaşak MD, Hitit University Faculty of Medicine, Department of Histology and Embryology, Çorum, Türkiye
E-mail: farukaltinbasak7@gmail.com **ORCID-ID:** orcid.org/0000-0002-6816-1367
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stem cells, with their self-renewal and differentiation potential, offer therapeutic promise in restoring fertility (7).

Stem cells are undifferentiated cells present in embryonic, fetal, and adult stages, capable of self-renewal, long-term proliferation, clonality, and differentiation based on the body's needs (8,9). Their versatile differentiation potential, ability to promote angiogenesis, immunomodulatory effects, and paracrine signaling make them promising candidates for infertility treatment (10). Therefore, stem cell research offers new therapeutic possibilities and hope for reproductive restoration, with growing evidence supporting the efficacy and safety of stem cells. In recent years, interest in stem cell therapies has surged, as reflected by the increasing number of publications. However, bibliometric analyses on this specific topic remain scarce. These analyses are valuable for assessing research trends, impact, and knowledge flow in a given field (11,12). The Web of Science (WoS) Core Collection is among the most widely used citation databases for these analyses, offering data on publication trends, authors, journals, institutions, countries, languages, and funding (13,14). Additionally, the Bibliometrix R package enables in-depth visual and quantitative analysis of collaboration networks, themes, and influential literature (15,16).

In this context, evaluating the role of stem cell therapies in infertility is essential to understand the scientific development in this field. This study aims to explore the evolution and impact of research on stem cell-based infertility treatment between 1982 and 2023, using bibliometric tools to reveal trends and key contributions.

Materials and Methods

This bibliometric study was based on data retrieved from the WoS Core Collection, a widely recognized citation database in academic research. The search was conducted on August 15, 2024, using the query TS = ("stem cell" AND "infertility"), targeting titles, abstracts, author keywords, and keywords plus. The search was limited to original research articles published in English between 1982 and 2024. Non-article documents (e.g., reviews, editorials, conference abstracts) were excluded, and data were downloaded in plain text format compatible with bibliometric tools.

The WoS Core Collection was chosen for its high-quality indexing, rich metadata, and compatibility with Bibliometrix and Biblioshiny used in this study. Although databases like Scopus and PubMed offer valuable data, WoS ensures consistency, reproducibility, and data integrity. Analyses included:

- **Descriptive metrics** (publication trends, citation averages)
- **Citation and productivity mapping** (top authors, articles, core journals via Bradford's Law)
- **Network analyses** (co-authorship, institutional and country collaborations)
- **Keyword co-occurrence and trend analysis** (bubble plots, Sankey diagrams)
- **Geographical and citation network visualizations** (global output maps, cluster-based citation networks)

Since the study used publicly available data from published literature, no ethical approval was required.

Results

Bibliometric Overview of the Study Period

The period covered by our study ranges from 1982 to 2024. The analyzed dataset comprises 1,710 articles from 580 distinct scientific sources (excluding books and reviews). The annual growth rate of academic publications in our field is 11.37%. The average time elapsed since the publication of the examined articles is 7.21 years, with 30.59 citations per document on average. Additionally, the total number of references obtained from the data is 57,394 (Table 1).

In our study, when analyzing the developmental trend of publications over the years, it is observed that the publication

Table 1. Details of publications between 1982 and 2024 using the keywords "infertility" and "stem cells"

Description	Main information about data	Results
Timespan		1982:2024
Sources (journals)		580
Documents		1710
Annual growth rate (%)		11.37
Document average age		7.21
Average citations per document		30.59
References		57394
	Document contents	
Keywords plus (Id)		4010
Author's keywords (De)		3172
	Authors	
Authors		8849
Authors of single-authored documents		52
	Authors collaboration	
Single-authored documents		55
Co-authors per document		7.39
International co-authorships (%)		23.33
	Document types	
Article		1710

rate, which began in 1982, remained relatively limited until the 1990s. However, in the following years, research in this field gained momentum. The number of publications reached an exceptionally high level in the 2000s and peaked at 174 in 2022 (Figure 1).

Average Citations by Year

Figure 2 shows the average citation counts of articles between 1982 and 2023. Citations generally followed a fluctuating trend, with a significant increase in 1997, surpassing 15. A decline was observed in the 2000s, followed by stabilization. An increase was observed in 2019, but a decrease was observed in 2023. The peak in the late 1990s mainly indicates that studies published during this period were heavily cited.

Sankey-based Visualization of Citation and Keyword Networks

Upon examining the Sankey diagram related to our study, it is clear that in the first column, which lists the analyzed studies cited by authors in the literature, Kanatsu-Shinohara, 2003 ranks first, followed by other studies. In the middle column, the names of researchers actively contributing to this field are displayed, positioning them at the center of the scientific network. At the top of this column is the researcher "Orwig KE". The third column shows which key topics or keywords are associated with the cited studies, with "spermatogonial stem cells (SSCs)" ranking first (Figure 3).

Journal-based Analysis of the Literature

Our literature searches show that the journal *Human Reproduction* (63) has the highest number of publications using stem cell and infertility keywords. This journal is followed by *Biology of Reproduction* (54) and *Fertility and Sterility* (48). The other journals listed are shown in Figure 4.

Identification of Core Resources with Bradford Distribution

The data were also analyzed using Bradford's law to show journal distribution. In Figure 5, the horizontal axis shows the logarithmic journal ranking, and the vertical axis shows the number of articles. The shaded gray area marks the core sources with the highest publication counts. Key journals include

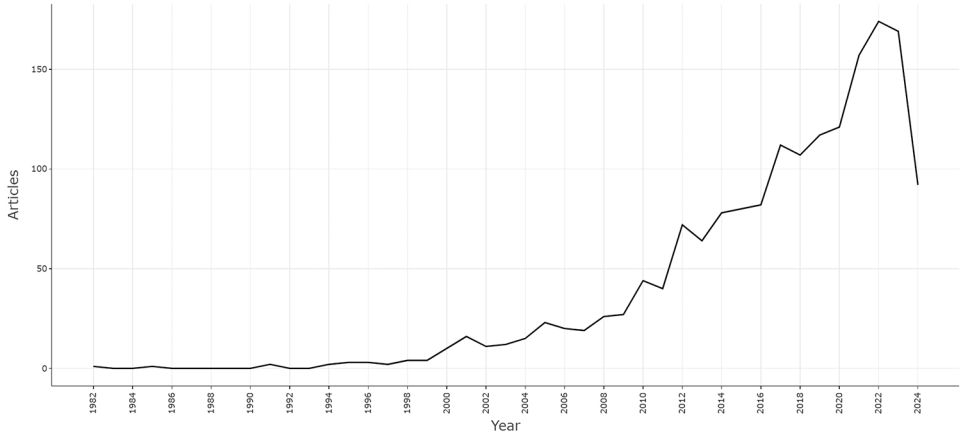

Figure 1. The numerical distribution of publications in the literature between 1982 and 2024

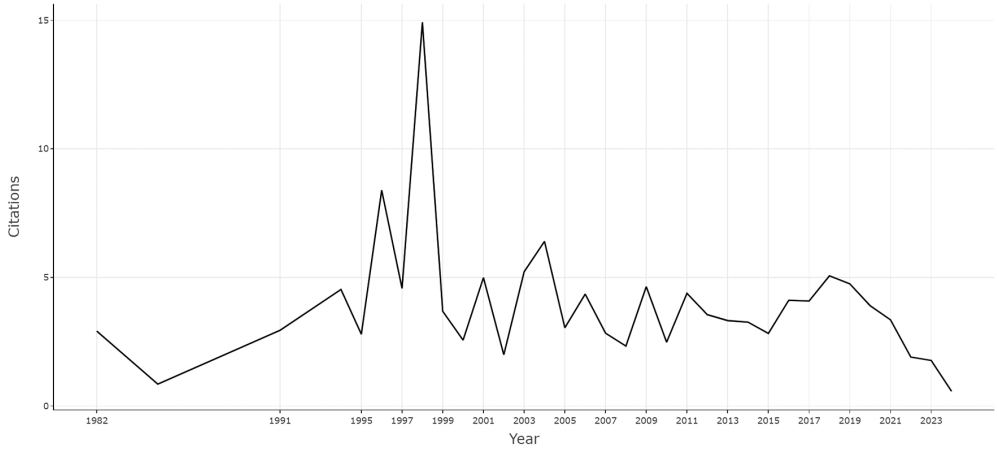

Figure 2. The distribution of the average citation counts of articles published between 1982 and 2024 by year

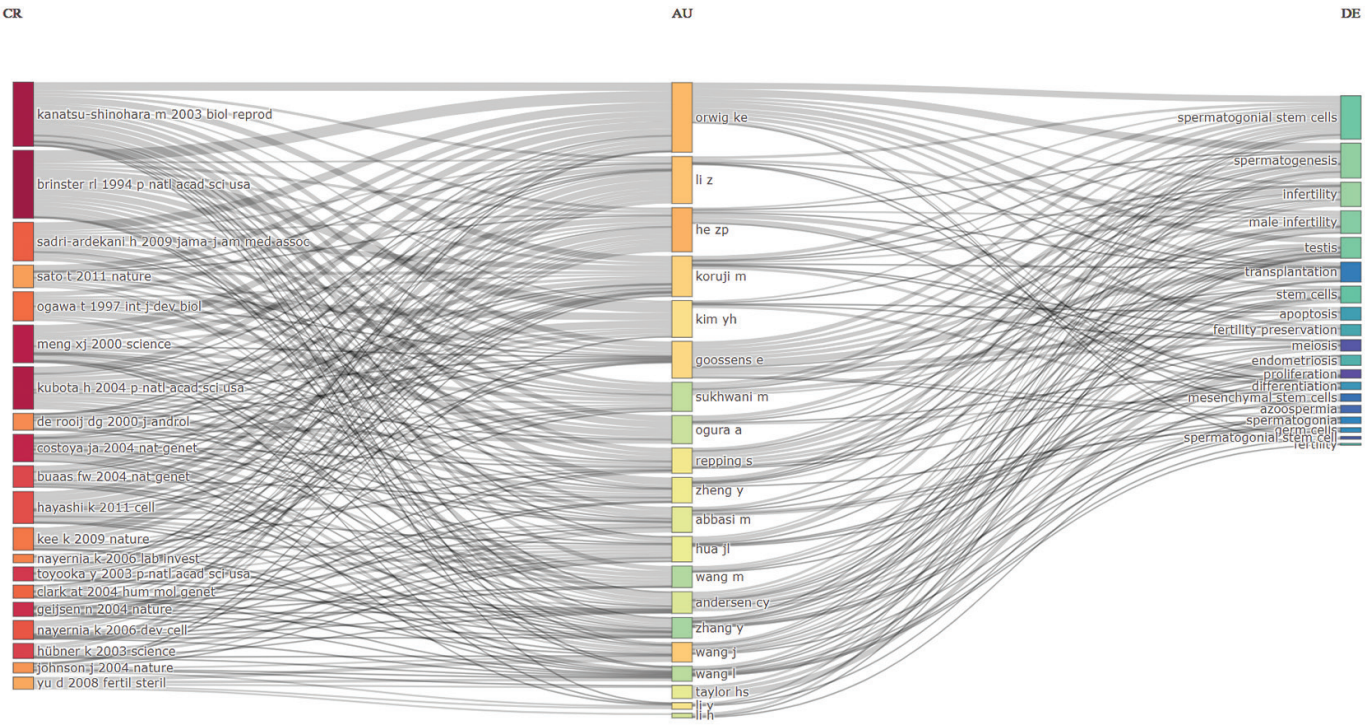

Figure 3. Three-field Sankey diagram (left column → keywords plus, middle column → authors, and right column → keywords of cited works)

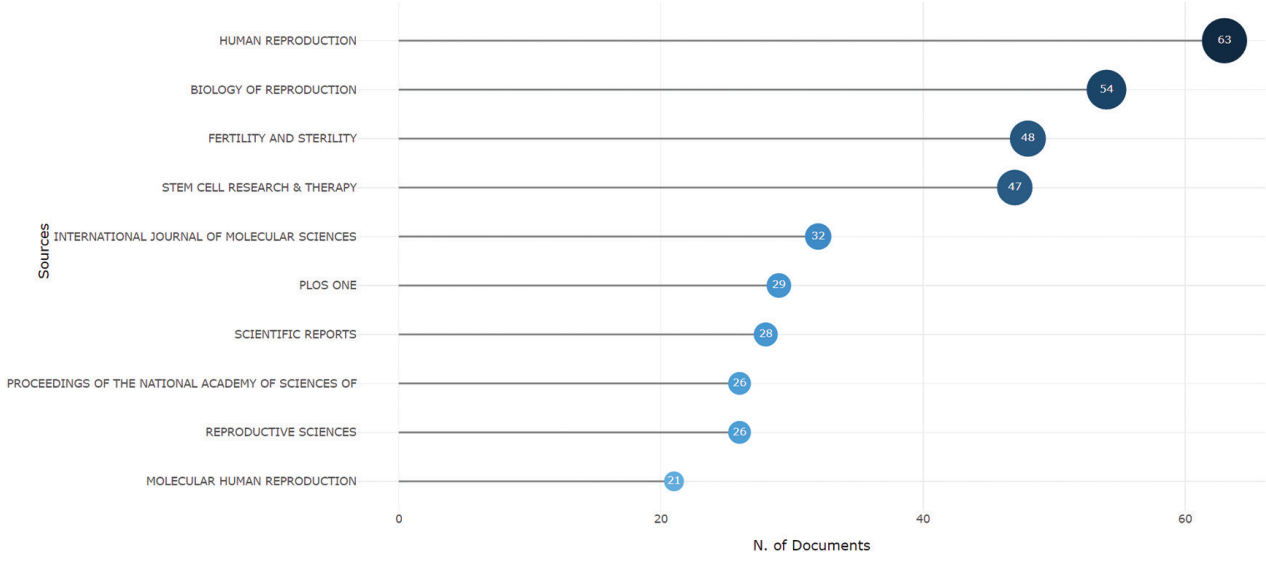

Figure 4. The top 10 journals with the highest number of publications from the literature search using the keywords stem cells and infertility

Human Reproduction, *Biology of Reproduction*, and *Fertility and Sterility*, with others listed in the figure.

Most Productive Authors in the Field

When examining the top 10 active authors with the most publications on stem cells and infertility, our research found that the researcher HE ZP (29) ranks first. They are followed by "Orwig KE" (27) and "LI Z" (22). The other active authors are shown in Figure 6.

Institutional Analysis of Research Productivity

In our study, results were evaluated not only individually for research on stem cells and infertility but also from an institutional perspective. This analysis is vital for understanding the academic activity levels and research productivity of institutions in this field. As shown in Figure 7, the Chinese Academy of Sciences and the University of California System had the highest number of publications, with 118 and 112 papers, respectively. The Tehran

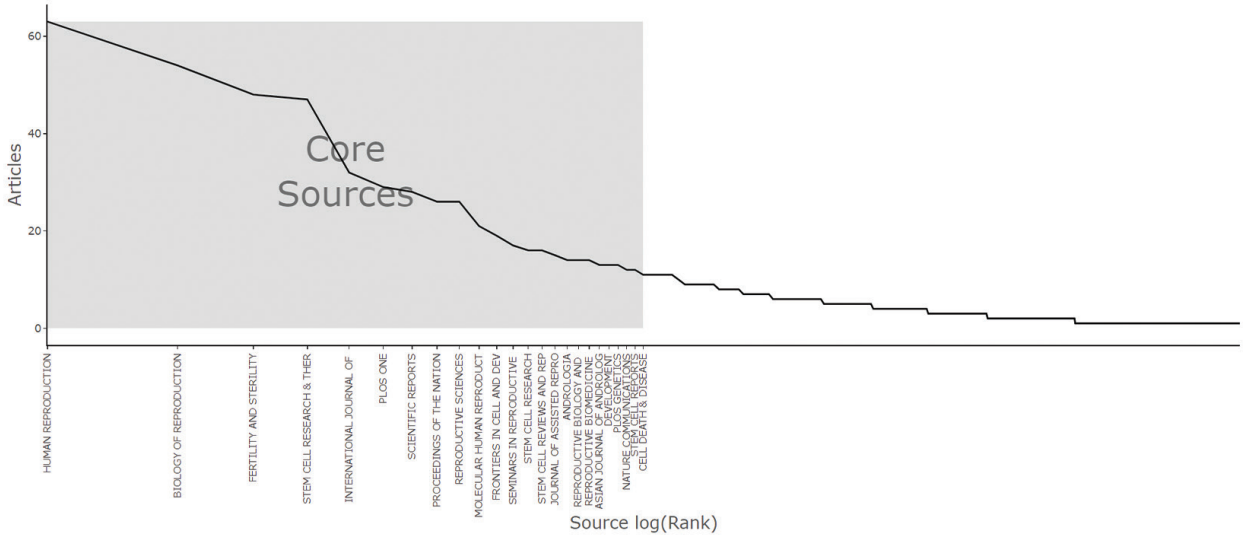

Figure 5. Core journals and article distribution in the literature according to Bradford's law

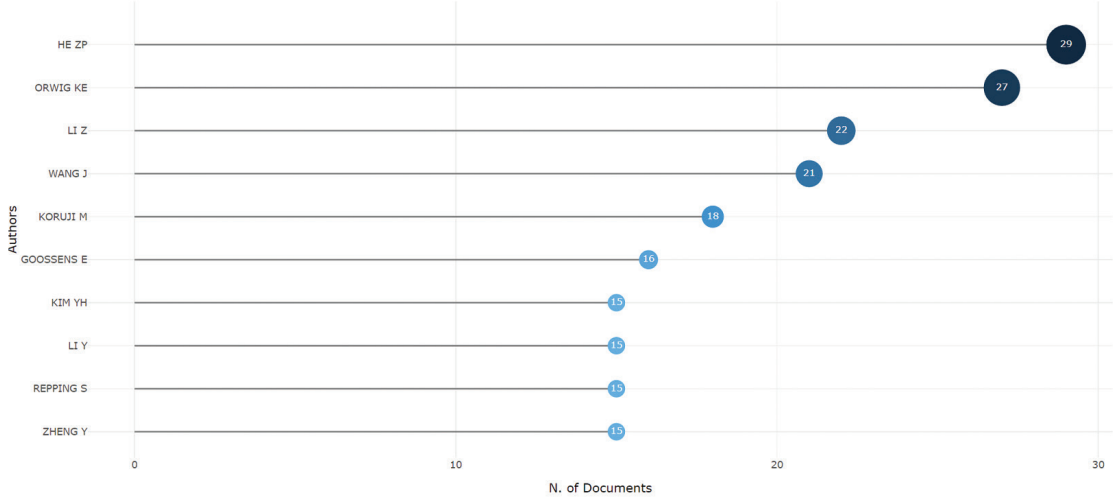

Figure 6. Top 10 authors by publications

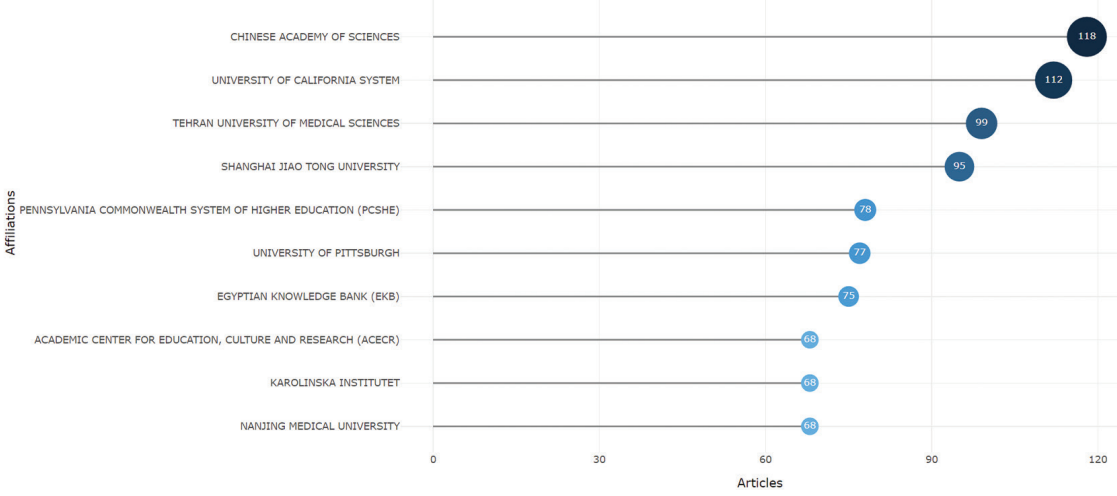

Figure 7. Top 10 publishing institutions in the field

University of Medical Sciences followed with 99 publications, ranking third. Other active institutions include Shanghai Jiao Tong University, the Pennsylvania Commonwealth System of Higher Education, and the University of Pittsburgh.

Publication Distribution by Country and International Cooperation Analysis

Figure 8 presents the distribution of corresponding authors' countries, comparing single country publications (SCP, turquoise) and multiple country publications (MCP, red). China and the United States lead in total output, with China favoring SCPs and the United States showing a higher MCP ratio. Iran ranks third mostly for its contribution of SCPs. Other countries follow in sequence, as shown in Figure 8.

Global Distribution of Scientific Research Output

Figure 9 shows a world map of global scientific production, where color intensity indicates output levels-dark blue for the highest, followed by blue, light blue, and grey. The United States and China, marked in dark blue, lead in scientific research and publications. Iran appears in shades of blue, reflecting moderate output. Countries with lower productivity are shown in lighter tones.

Term Usage Trends by Years

Figure 10 shows the frequency of specific terms in scientific research over time. The horizontal axis represents years, and the vertical axis lists popular terms. Between 2009 and 2011, terms such as "germ cell apoptosis", "human testicular tissue", and "embryo" were more common, while between 2015 and 2021, focus shifted, to "stromal cells", "expression", and "proliferation".

Citation Network Visualization and Scientific Impact Analysis

Figure 11 illustrates citation relationships and scientific impact among publications. Each node represents a study, with connecting lines indicating citation relationships. Node colors indicate different research clusters, grouping studies by topic. Larger, bold-labeled nodes such as "Brinster and Zimmermann (20) 1994" represent highly cited, influential works. Numerous lines from a node-for example, "Brinster and Zimmermann (20) 1994"-highlight that this study has been widely referenced cited.

Geographical Distribution of Scientific Cooperation Networks between Countries

Figure 12 presents a bibliometric map of global scientific collaboration. Lines represent country-to-country collaborations, with thickness indicating their strength. The United States, China, Germany, and the United Kingdom show the most extensive networks, highlighting their central role in global research.

Discussion

Infertility is a significant global health issue, affecting millions and arising from diverse genetic, hormonal, and environmental factors (17). Recently, stem cell-based therapies have emerged as promising alternatives to conventional treatments. With their self-renewal and differentiation abilities, stem cells offer potential for regenerating reproductive tissues (18). This

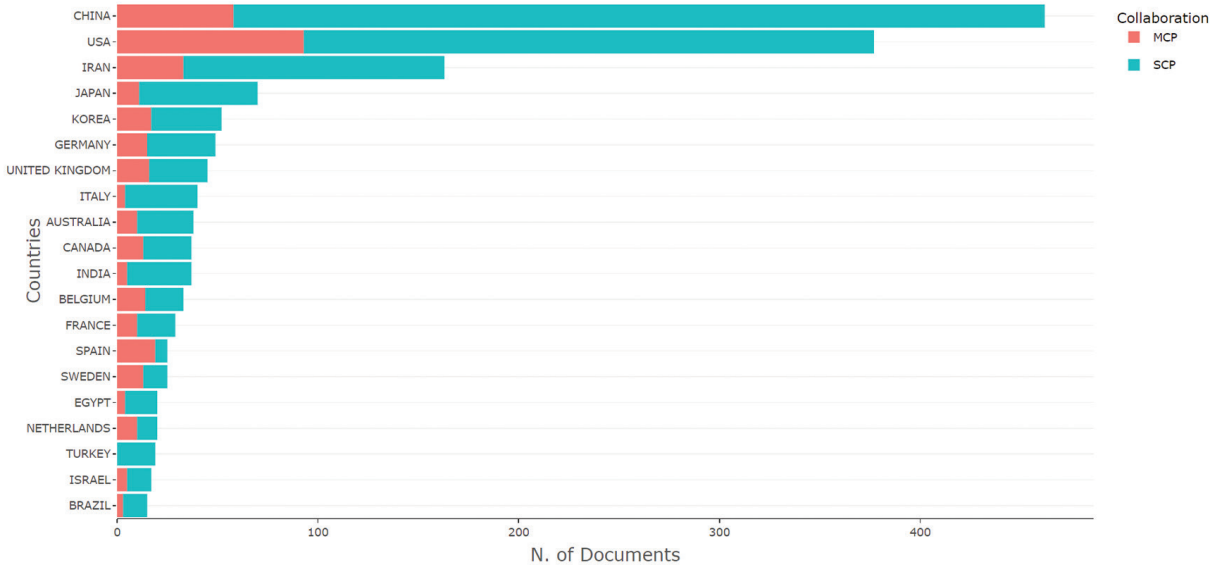

Figure 8. National (SCP) and international (MCP) distribution of scientific publications made by countries

SCP: Single country publications, MCP: Multiple country publications

therapeutic potential has increased scientific interest in the field. Bibliometric analyses offer key insights into research trends in stem cell-based infertility treatments, identifying influential studies, emerging topics, and research gaps to guide future work.

This study examines the role of stem cell therapies in infertility treatment through bibliometric analysis. Results show a notable rise in related research, thus highlighting its growing potential in reproductive medicine. Stem cell studies have gained broad national and international attention, with increased collaboration accelerating scientific progress in this field.

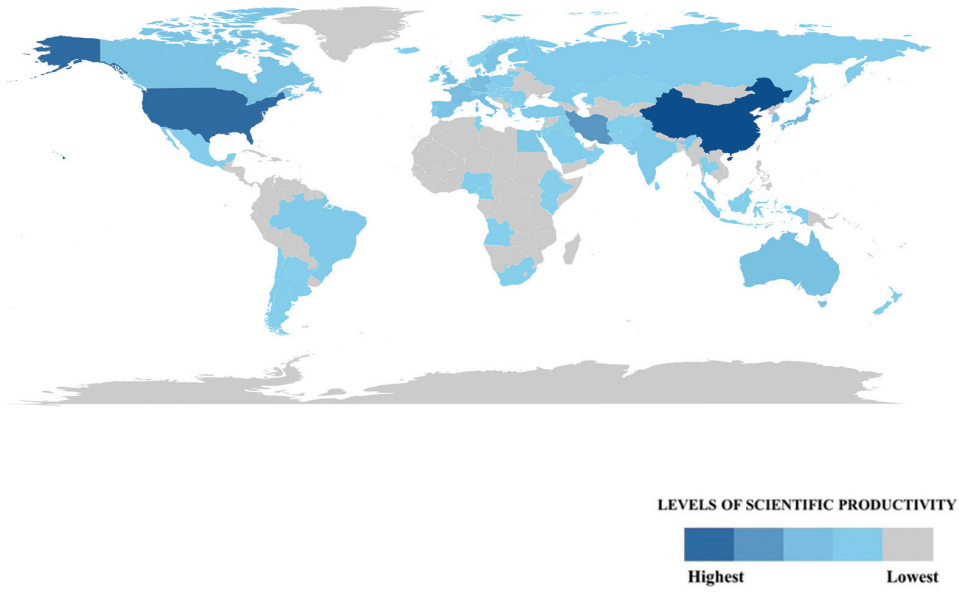

Figure 9. A color-coded world map showing the amount of scientific production of countries

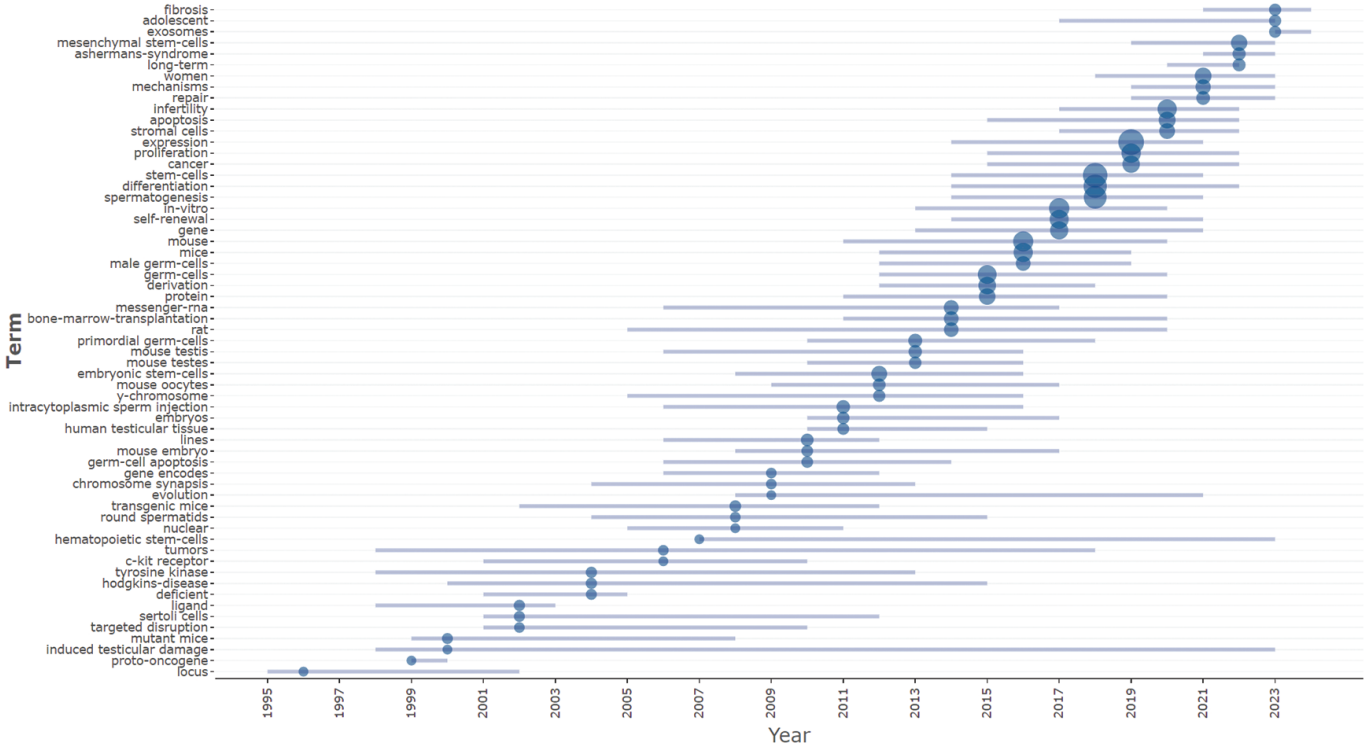

Figure 10. Popular topics and keywords in infertility and stem cell research from 1982 to 2024. The lines indicate the emergence of keywords, while the size of the bubbles represents the frequency of their usage over the years

The distribution of publications over the years shows that stem cell research, which began in 1982, remained limited until the 1990s. A marked increase followed, likely reflecting the growing recognition of stem cell therapy as a promising approach for infertility treatment. The sharp rise in the 2000s suggests a peak in scientific interest in this field (Figure 1).

The analysis of citation counts shows notable fluctuations over the years. A significant increase occurred in 1997, indicating heightened attention from the scientific community. However, this was followed by a period of stabilization, and a decline has been noted in more recent years (Figure 2). This decrease is likely due to the limited time these newer studies have had to gain academic visibility. In biomedical research, it often takes time for new findings to accumulate citations. Moreover, open-access policies and shifts in publishing practices have likely influenced citation dynamics. While open access increases article availability, it may also alter citation patterns. Changes in research priorities have also played a role. For instance, the transition from classical stem cell therapies

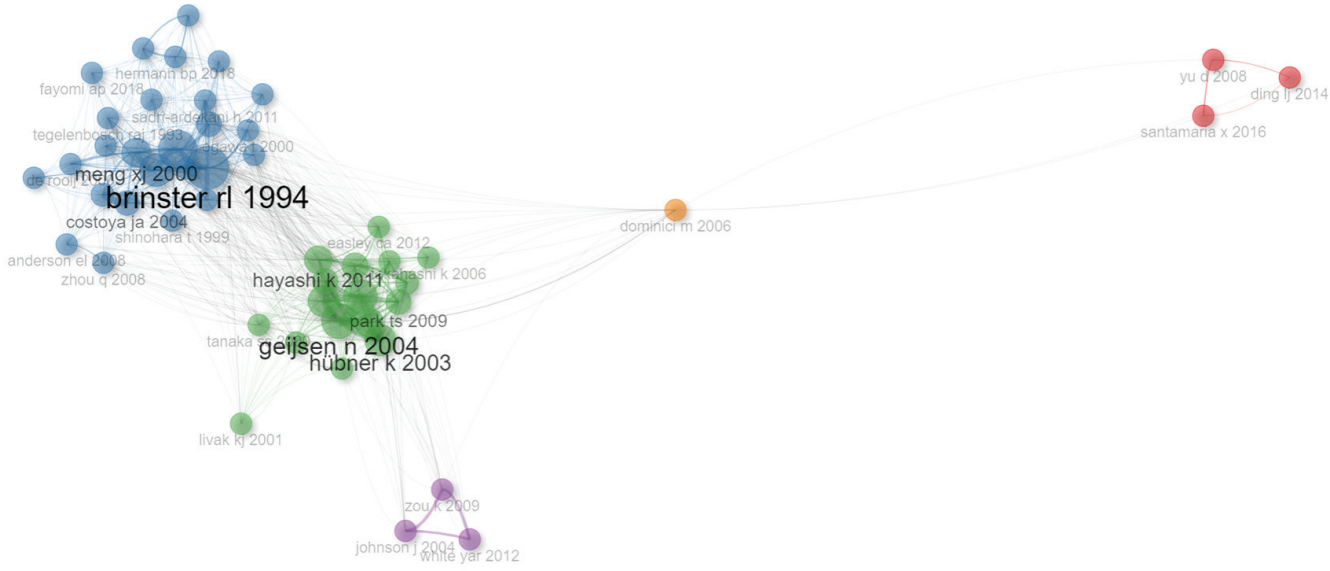

Figure 11. A network visualization depicting citation relationships and scientific impact among academic publications

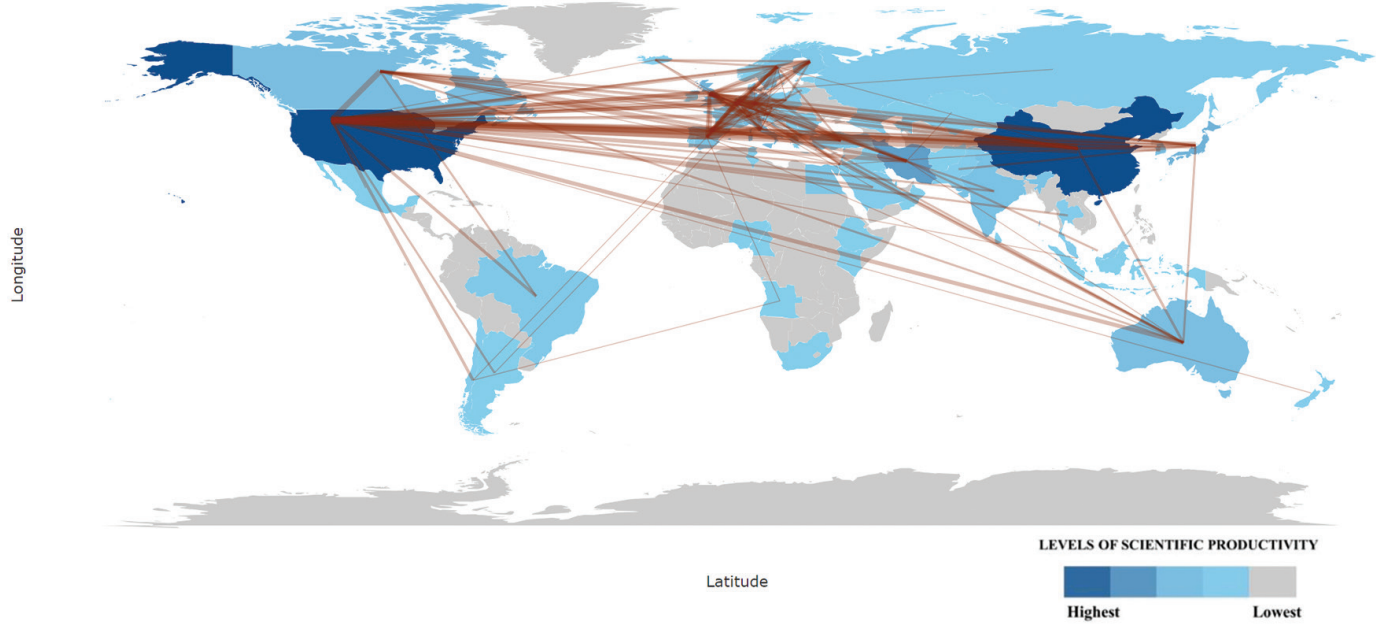

Figure 12. Global collaboration networks among authors

to newer biotechnological approaches may have reduced interest in certain areas, contributing to the observed decline. These trends underscore the need for deeper evaluation of the academic impact of recent studies (19). Citation network analyses further reveal that some works have become foundational in the field. Notably, Brinster and Zimmermann's (20) 1994 study is frequently cited in research on stem cells and infertility (Figure 11) (20). Brinster and Zimmermann's (20) 1994 study introduced one of the first experimental findings on SSC transplantation, offering a pioneering approach in the fields of stem cell biology and infertility treatment. By providing key insights into the functional integration of germ cells during spermatogenesis, the study has become a foundational reference both conceptually and methodologically. As an early and influential contribution to the field, the study continues to receive frequent citations.

The Sankey diagram analysis visually illustrates the active researchers, key topics, and foundational elements of the literature on stem cells and infertility. This method reveals how the research network is structured and highlights influential studies and authors in the field (21). It enables researchers to map existing knowledge, position their work within this framework, and plan future studies accordingly. Among the frequently associated terms, SSC stand out. The analysis also shows that Orwig KE holds a central position in this research area (Figure 3). The rising interest in SSCs reflects a growing focus on regenerative strategies for male infertility. SSCs are particularly promising for restoring spermatogenesis in prepubertal cancer survivors and patients with non-obstructive azoospermia. Recent advances in cell isolation, *in vitro* expansion, and transplantation techniques have strengthened the foundation for personalized fertility treatments. Nonetheless, several challenges remain, including safety concerns, ethical issues, and regulatory limitations. Future research should aim to bridge the gap between experimental data and clinical application, with attention to both efficacy and long-term safety.

Bradford's law is used to examine how scientific publications on a specific topic are concentrated around a core group of sources. It also identifies journals that publish fewer articles, offering insights into the distribution and relevance of sources within the field (22). This analysis helps determine the most cited and influential core journals in the literature. According to this principle, research on stem cells and infertility is clustered in specific journals. The "Core Sources" section of the figure, shown in grey, highlights these key journals. Notably, *Human Reproduction*, *Biology of Reproduction*, and *Fertility and Sterility* appear as the most prolific and influential sources (Figure 4). Their high publication volume reflects both the academic importance and the focused interest in this area.

An analysis of international collaboration networks shows that the United States and China lead in scientific output and are highly involved in global partnerships. In contrast, countries like Iran appear to focus more on national-level research, with limited international engagement (Figures 8 and 9). This highlights both the importance of global scientific collaboration and the unequal distribution of research activity. The concentration of output in the United States and China may limit the generalizability of findings. Studies conducted in specific geographic, genetic, or socioeconomic contexts may not fully reflect broader population needs. This imbalance also points to a lack of diverse perspectives and may constrain innovation in stem cell therapies for infertility. Promoting equity in research funding and fostering collaboration with underrepresented regions are essential for a more inclusive understanding of the field. Additionally, the global map of scientific output reveals disparities in research productivity and the dominant influence of certain countries (Figure 9). For bibliometric studies, such visualizations help explore geographic patterns and the underlying factors, including differences in funding, education systems, and economic development.

Bibliometric analyses tracking term frequency over time reveal shifts in research trends and highlight topics that gain prominence during specific periods. These analyses examine how the use of key terms evolves, offering insight into changing focus areas within the field. In recent years, terms such as stromal cells, expression, and proliferation have appeared more frequently, suggesting increased interest in these topics (Figure 10). Such data can inform future studies by identifying emerging areas that warrant further investigation.

Citation networks illustrate the relationships, connections, and scientific impact among academic publications (Figure 11). These maps help identify pioneering studies, track the evolution of specific research areas, and reveal links between different disciplines. They also point to influential works and highlight areas needing further exploration, offering opportunities for new research and collaboration. Similarly, the global collaboration map shows that international partnerships in this field are widespread and not limited by geographic proximity, emphasizing the global nature of scientific research (Figure 12).

In recent years, although there has been a noticeable increase in studies focusing on SSCs and stromal cells, further research is needed to translate experimental approaches into clinical applications. In particular, there is a significant lack of long-term follow-up studies that evaluate the safety, efficacy, and ethical dimensions of stem cell-based infertility treatments. Additionally, the geographic imbalance in research productivity highlights the need for studies with broader inclusivity and regional diversity. Future research is also encouraged to explore the integration of stem cell-based approaches with gene editing

technologies and assisted reproductive platforms. Addressing these gaps and achieving comprehensive progress in the field will require interdisciplinary and multicenter studies conducted through global collaborations.

Study Limitations

This study has several limitations that should be acknowledged. First, it is limited to English-language publications indexed in the WoS database. This may introduce a language and indexing bias, potentially excluding relevant research published in other languages or included in different academic databases, thus underrepresenting the diversity of global perspectives and findings. Additionally, while the analysis relied solely on published literature, excluding grey literature and unpublished data, the latter may contain valuable insights and contribute to a more comprehensive understanding of the field.

Another inherent limitation of bibliometric analysis is its inability to assess the methodological rigor or clinical applicability of the included studies. While this study successfully identifies influential authors, research trends, and key publication outlets, it does not evaluate the scientific quality, experimental validity, or translational relevance of the cited works. Therefore, the results should be interpreted as a macro-level overview of the research landscape, rather than a critical appraisal of individual studies.

Moreover, the notable concentration of scientific output in a few countries, particularly the United States and China, highlights an imbalance in global research contributions. This geographic concentration may limit the generalizability of findings and underscores the need for more inclusive international collaboration and support for underrepresented regions. Addressing these limitations in future research through systematic reviews, meta-analyses, and broader database coverage will strengthen the transparency, inclusivity, and analytical depth of bibliometric studies in this domain.

Conclusion

This study highlights the potential of stem cell therapies in infertility treatment and provides a bibliometric analysis of the scientific literature. While the United States and China dominate research output, this geographic concentration underscores the need for greater inclusivity and contributions from underrepresented regions to achieve a globally relevant understanding of stem cell therapies.

Key themes like spermatogonial and stromal stem cells highlight a focus on therapeutic applications. However, gaps remain in addressing diverse populations and generating long-term safety data, limiting the generalizability of results. Limited input from underrepresented regions also restricts innovation diversity.

Tackling these issues requires balanced funding, inclusive policies, and global collaboration. Supporting studies with neutral or negative results and prioritizing underrepresented regions can reduce publication bias and promote more equitable progress in stem cell therapies for infertility.

Ethics

Ethics Committee Approval: Not necessary.

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

Concept: O.A.A., Ç.G., F.A., Design: O.A.A., Ç.G., Data Collection or Processing: Ç.G., Analysis or Interpretation: O.A.A., Ç.G., F.A., Literature Search: O.A.A., Ç.G., F.A., Writing: O.A.A., Ç.G., F.A.

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

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ORIGINAL RESEARCH
General Urology

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J Urol Surg 2025;12(4):237-242

The Efficacy of the Biopsy Chip Used in the Delivery of Prostate Biopsy Samples on Time Saving

Uğur Aferin[1], Göktuğ Kalender[2], Birgi Ercili[3], Sinharib Çitgez[4], Nil Urgancı[5], Selçuk Cin[6], İclal Gürses[6], Bülent Önal[4]

[1]*İstanbul Florance Nightingale Hospital, Demiroğlu Bilim University, Department of Urology, İstanbul, Türkiye*
[2]*İstanbul Beykoz State Hospital, Clinic of Urology, İstanbul, Türkiye*
[3]*Diyarbakır Memorial Hospital, Clinic of Urology, Diyarbakır, Türkiye*
[4]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Urology, İstanbul, Türkiye*
[5]*Memorial Sloan Kettering Cancer Centre, Department of Pathology, New York, USA*
[6]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pathology, İstanbul, Türkiye*

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

Traditional prostate biopsy methods require multiple containers, increasing handling time and potential tissue fragmentation. Innovations like the biopsy chip aim to streamline this process by consolidating samples onto a single platform, improving efficiency. Our study confirms that using a biopsy chip significantly reduces preparation, sectioning, embedding, and microscopic analysis times. While the biopsy procedure itself takes slightly longer, overall workflow efficiency is enhanced. These findings highlight the biopsy chip as a practical tool to optimize pathology processing, reduce workload, and improve diagnostic efficiency in prostate cancer evaluations.

Abstract

Objective: To reduce the workload, it is important to evaluate the prostate biopsy materials separately and in a shorter time. The aim of this study was to align and transfer the prostate biopsy materials taken by urologists on the same chip and to investigate whether the pathologist evaluates the tissues on this chip in a shorter time.

Materials and Methods: This was a prospective, non-randomized, comparative study including patients scheduled for 12-core transrectal ultrasound-guided prostate biopsy. Patients were assigned to one of two groups based on the biopsy specimen delivery method: The BxChip™ group (n=34), in which cores were aligned on a grooved gel-based matrix, and the conventional group (n=31), where each core was placed in a separate tube. The preparation time before biopsy and the total procedure time were recorded by urologists. Pathologists documented macroscopic assessment, sectioning, embedding, and microscopic examination times for each method.

Results: There was no statistically significant difference between the two groups in terms of demographic data and patient characteristics. While the biopsy procedure duration was longer in group 1, the duration of pre-biopsy preparation, macroscopic examination, sectioning, embedding, and microscopic examination was statistically lower in group 1 than in group 2.

Conclusion: In our study, the biopsy chip method is effective and provides time advantages in terms of taking, transferring, and analysing prostate biopsies.

Keywords: Prostate cancer, prostate biopsy processing, multiplex tissue processing, time saving

Correspondence: Bülent Önal MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Urology, İstanbul, Türkiye
E-mail: bulonal@yahoo.com **ORCID-ID:** orcid.org/0000-0003-0540-2693
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Introduction

Prostate cancer ranks as the second most prevalent form of cancer and the fifth highest contributor to cancer-related deaths in males globally (1).

The primary diagnostic tool for prostatic cancer is the histopathologic analysis of prostate core needle biopsy specimens. Ultrasound (US)-guided and/or magnetic resonance imaging (MRI)-targeted biopsies are part of the standard approach according to clinical necessity. A prostate biopsy can be performed by the transperineal or the transrectal approach (2).

For systematic biopsies without prior imaging for targeting, it is recommended to take cores from both sides of the prostate, and the apex to the base in the peripheral gland, reaching as posterior and lateral as possible. As demonstrated by a systematic review published in 2006, a systematic biopsy requires at least 12 cores (3). In the presence of suspicious areas determined by digital rectal examination (DRE) or MRI before biopsy (with more than one core from each MRI-visible lesion) and in cases where saturation repeat biopsy is required (>20 cores), it is recommended to take additional cores (4).

Since the conventional biopsy technique is thought to be time-consuming, new methods are needed. The BxChip™ is one of the techniques developed for this purpose. The BxChip™ technique aims to more quickly and reliably generate multiplex biopsy arrays using a matrix material and to use the arrays in histological procedures (5).

Preliminary data on the impact of the BxChip™ technique considers that it is easy to implement, has a rapid learning curve, and reduces the processing time of the ever-increasing number of cores per patient collected during prostate biopsy (6).

In this study, we aimed to evaluate the chip method using multiplex biopsy in prostate biopsies performed by urologists in our clinic and the time advantages it provides in the pre- and post-biopsy diagnostic periods.

Materials and Methods

This was a prospective, non-randomized, comparative study. The study was conducted in accordance with the principles of the Declaration of Helsinki, after obtaining approval from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (IRB number: 83045809-604.01.02, date: 17.05.2019) and detailed informed consent from all patients. An a priori power analysis revealed that a sample size of n=28 per group was needed to detect a significant difference [two-sided α=0.05, power (1-β)=90%, effect size=0.8].

Patients were included in the study if they were scheduled for a 12-core transrectal US (TRUS)-guided prostate biopsy between January 1, 2020, and January 31, 2023, undergoing the procedure for the first time, had negative multiparametric prostate MRI findings (Prostate Imaging Reporting and Data System ≤2), but still considered at clinical risk for prostate cancer based on serum prostate-specific antigen (PSA) level, PSA density, DRE findings, or family history,

Patients were assigned to one of two groups according to the technique used to deliver biopsy specimens to the pathology department. This allocation was non-randomized and was based on the availability of biopsy chips at the time of the procedure. Due to the differences in specimen handling, blinding of urologists and pathologists was not feasible.

In 34 patients (group 1), a multidirectional grooved matrix made of Biopsy Chip, a tissue surrogate gel, was used by the urologist to align the biopsy cores. The samples were then delivered to the pathology laboratory using this chip. In 31 patients (group 2), each biopsy core was placed in a separate standard biopsy container, and the samples were transferred to the pathology department using the conventional method. This was a prospective, non-randomized comparative study.

Biopsy Procedure

Biopsies were performed in the endoscopy suite of our institution with a team of one experienced urologist who had more than five years of experience in prostate biopsies, one nurse, and one ancillary staff member. Patients in both groups were started on antibiotic prophylaxis the day before the procedure and were directed to self-administer a sodium phosphate enema the night before. Just before the procedure, urine culture results, blood coagulation parameters, antiaggregant or anticoagulant drug use, and the presence of specific infection symptoms (e.g., fever, chills, urgency, frequent urination, or suprapubic tenderness) were thoroughly reviewed by urologists.

The patients were placed in the left lateral decubitus position, and lubricant sterile gel with lidocaine (Lubagel Plus, Yasemin Medika, İstanbul, Türkiye) was applied via the rectal route. A DRE was performed. The urologists used TRUS with a multiplanar 6.5 MHz probe attached to the US scanner (Siemens Medical Systems, Inc., Issaquah, WA, USA). A periprostatic block was applied under the guidance of TRUS, with a combination of lidocaine and bupivacaine using a 20-cm long, 22-gauge needle (Chiba Biopsy Needle with Echogenic Tip, Argon Medical Devices Inc., Dallas, USA), for both sides. Prostate volume was calculated using the prostate ellipsoid formula: volume (V)=0.52 x (L x W x H), where L is the cephalocaudal diameter, W is the width, and H is the anteroposterior diameter. TRUS-guided prostate biopsy was performed with a disposable 18-gauge×25-cm biopsy needle (Argon Pro-Mag Biopsy Needle, Argon Medical Devices Inc., Dallas, USA). Twelve cores were taken and put into separate containers in the

conventional biopsy arm (Figure 1) and placed in two separate containers in the BxChip™ arm (Figure 2).

1. Conventional Preembedding Method

Traditionally, the recommended method for processing biopsy samples is by embedding them individually in a supporting material such as a paraffin block. The individual samples' paraffin blocks are then divided into thin sections using a microtome. These thin sections are then placed on a microscope slide, stained as necessary, and examined under a microscope. One runs the risk of failing to include the tissue sample when sectioning the paraffin blocks and losing too much of the sample before a complete section is produced. The standard biopsy technique results in a large number of paraffin blocks, necessitating numerous sections and slides, high costs for consumables, processing labor, and pathologists' time to interpret the slides.

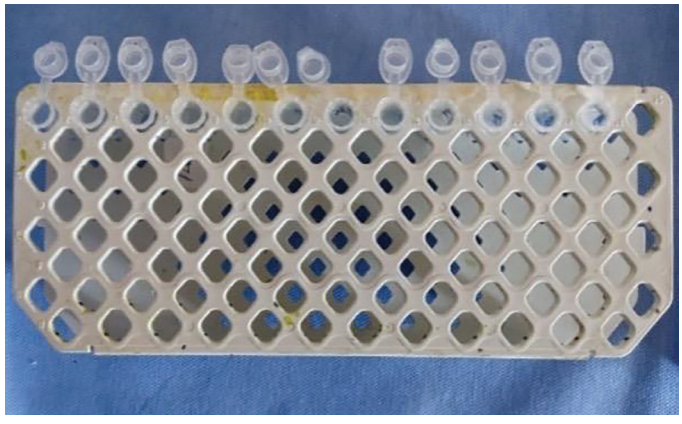

Figure 1. Twelve separate containers in conventional biopsy procedure

2. BxChip™ Method, Histologic Work-up and Diagnosis

The BxChip™ consists of a custom-made matrix that easily receives and holds multiple tissue cores. This block of matrix material is used to create a multiplex biopsy array, a histological preparation, with cell or tissue samples arranged within it. The chip is a proprietary biomimetic protein polymer that has a grooved, sectionable 2 mm, matrix. During both grossing and biopsy procedures, it can be utilized to align the specimens. One individual sectionable matrix can accommodate up to 12 core biopsies for simultaneous processing and sectioning. The chip, loaded with cores, is sandwiched between two foam pads in a tissue cassette to prevent any movement during processing. The biomimetic polymer shrinks during processing to the same extent as the cores themselves, which provides immobilization. Upon tissue processing, the chip is embedded and the paraffin block is sectioned.

Statistical Analysis

Statistical analysis of all data was performed using SPSS Statistics (Version 21.0, IBM Corp.). The suitability of the quantitative data for normal and non-normal distributions was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare non-normally distributed data, while the independent samples t-test was applied for normally distributed variables. A p-value of <0.05 was considered statistically significant for all analyses. An a priori power analysis was conducted using G*Power software (version 3.1.9.7, Düsseldorf, Germany). Assuming a two-tailed $\alpha=0.05$, power $(1-\beta)=0.90$, and an effect size of Cohen's $d=0.8$, the analysis revealed that a minimum of 28 participants per group was required to detect a statistically significant difference.

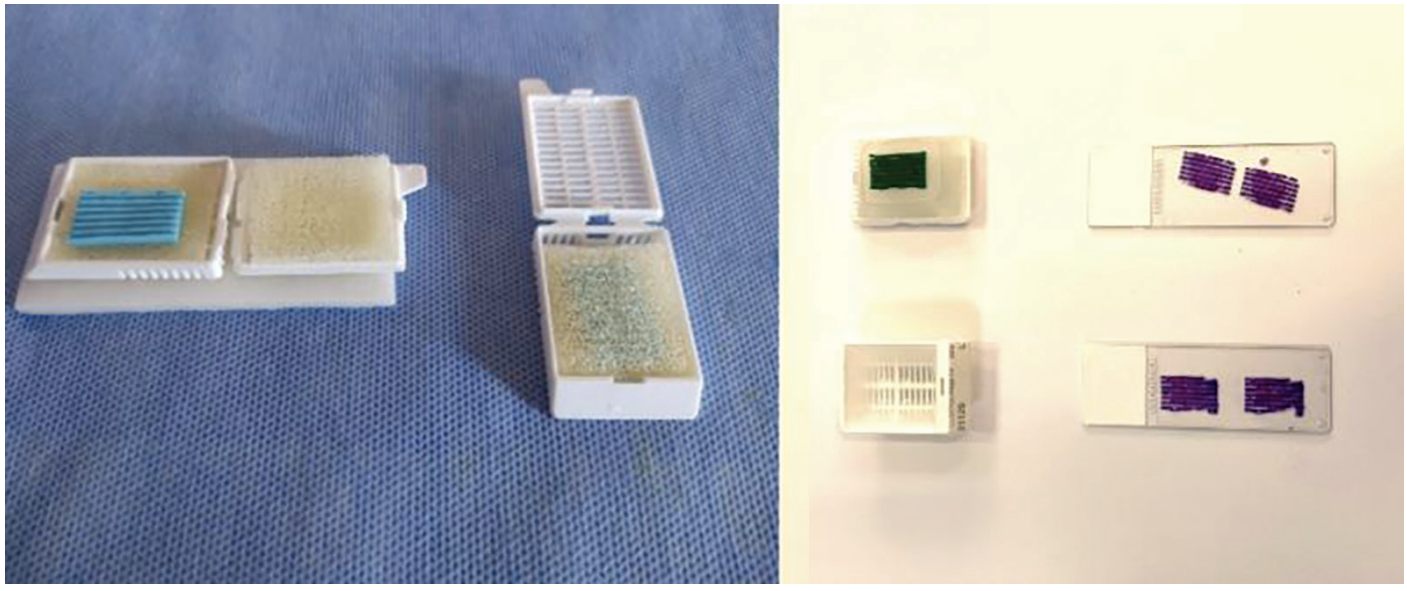

Figure 2. BxChip™ container allows to align 6 biopsy cores

Results

TRUS-guided biopsy has been successfully performed in 65 cases. Prostate biopsy samples were collected using the biopsy chip and the traditional method in 34 and 31 patients, respectively.

Groups were similar in terms of median age, PSA, PSA density, and prostate volume. The median age was 66.5 years and 69 years for group 1 and group 2, respectively. The median PSA levels were 7.27 ng/mL for group 1 and 7.5 ng/mL for group 2; PSA densities were 0.16 for group 1 and 0.13 for group 2, respectively. The median prostate volumes were 52 and 56 cc for groups 1 and 2, respectively (Table 1).

The median duration of pre-biopsy preparation was 3.5 (3.2-3.7) minutes and 4.3 (3.5-5.8) minutes in groups 1 and 2, respectively (p<0.001). The median duration of the biopsy procedure was 4.25 (3.7-5.2) and 3.96 (3.3-4.6) minutes in group 1 and 2, respectively (p<0.05). After the biopsy materials were delivered to the department of pathology, the median duration of macroscopic examination was 2.25 (1.5-2.2) and 5.27 (4.5-6.1) minutes in group 1 and group 2, respectively (p<0.001). The median duration of sectioning was 5.29 (3.5-7.9) and 12 (10-12.4) minutes in groups 1 and 2, respectively (p<0.001). The median duration of embedding is 2.2 (1.3-9.0) and 11 (9.2-16.2) minutes in groups 1 and 2, respectively (p<0.001). The median duration of microscopic examination was 12.29 (6.9-15.3) and 15 (9.4-17.3) minutes in group 1 and 2, respectively. There was no statistically significant difference in the median duration of microscopic examination between the groups (p=0.143) (Table 2).

Discussion

TRUS-guided prostate biopsy represents the benchmark procedure in pathological diagnosis of prostate cancer (2). The conventional method involves the placement of each biopsy sample in a distinct container. Following this procedure, each core must be examined individually by the pathologist. All these processes are considered time-consuming. In a study that evaluated the use of multicompartment microcassette in prostate biopsy, 88 patients underwent TRUS-guided prostate biopsy. The time saved per case was determined to be 20 minutes (72%) on average (7). Our study demonstrated similar results, as the overall average time saved per case was 21.75 minutes (42%).

In another study, the evaluation of the test time involved 48 prostate specimens. Two sets of sextant biopsies were obtained *ex vivo*. For each specimen, one set was obtained with the standard protocol which involves fixing each biopsy core in separate containers, and the other one was acquired using a multiplex chip. Time reduction was observed in the multiplex chip arm of the study (8). One notable distinction between our study and the aforementioned study is that the latter, was *ex vivo*.

These two studies mentioned above assessed the duration of tests from the perspective of pathologists (7,8). Especially

Table 1. Patient characteristics

Variables	Entire cohort		
	Chip (n=34)	Control (n=31)	p-value
Age (year)	66.5 (62.5-71)	69 (64-73)	0.274
PSA (ng/dL)	7.27 (6.4-10.8)	7.5 (6-11)	0.768
PSA density (ng/mL)	0.16 (0.09-0.28)	0.13 (0.09-0.19)	0.105
Prostate volume (cc)	52 (36.5-72)	56 (36-75.8)	0.768

Data were expressed as median (interquartile range). Differences between patient groups assessed by Mann-Whitney U test and independent samples t-test. PSA: Prostate-specific antigen

Table 2. Comparison of chip and control group

Variables	Entire cohort		
	Chip (n=34)	Control (n=31)	p-value
Duration of pre-biopsy preparation (minute)	3.5 (3.2-3.7)	4.3 (3.5-5.8)	**<0.001**
Duration of biopsy procedure (minute)	4.25 (3.7-5.2)	3.96 (3.3-4.6)	**<0.05**
Duration of macroscopic examination (minute)	2.25 (1.5-2.2)	5.27 (4.5-6.1)	**<0.001**
Duration of sectioning (minute)	5.29 (3.5-7.9)	12 (10-12.4)	**<0.001**
Duration of embedding (minute)	2.2 (1.3-9.0)	11 (9.2-16.2)	**<0.001**
Duration of microscopic examination (minute)	12.29 (6.9-15.3)	15 (9.4-17.3)	0.143

Data were expressed as median (interquartile range). Bold values are statistically significant. Differences between patient groups assessed by Mann-Whitney U test and independent samples t-test

during the microscopic examination phase, it is significantly time-saving for the pathologist as BxChip™ allows 6 cores to be examined at the same time (Figure 3). Additionally, we wanted to evaluate the test time from the perspective of the urologists who conducted the biopsy. The chip arm demonstrated a statistically significant reduction in preparation time prior to biopsy. The observed time savings may be attributed to the increased efficiency in preparing two chip containers rather than twelve individual containers. However, the duration of biopsy procedures using the chip was notably extended in the experimental group. This observation may be ascribed to inserting the biopsy cores into the grooves requiring a period of learning and being comparatively more challenging than inserting them into the container.

Study Limitations

Although the study was designed prospectively, it was neither randomized nor blinded. Group allocation was based on chip availability, and due to the distinct specimen handling procedures, blinding of urologists and pathologists was not feasible. Additionally, our study did not assess cost-effectiveness or sample quality. Some studies demonstrated that using a multiplex biopsy chips is quite cost-effective (7-9). Nevertheless, the utmost significance lies in the conservation of tissue integrity and length, as well as enhancing detection rates. In this context, multiple studies have shown the advantages of using a multiplex biopsy chip (7,8,10).

Conclusion

In this research, we examined the time difference between the standard prostate biopsy processing method and the BxChip™ approach, which enables the simultaneous processing of prostate biopsy specimens. Within the BxChip™ group, we observed a significant decrease in the duration needed, particularly when it came to the pathological assessment procedure. We consider the BxChip™ technique to be very useful in terms of time savings in clinical use, but larger-scale prospective randomized studies are needed in the future to assess cost-effectiveness, time saving, and sample quality.

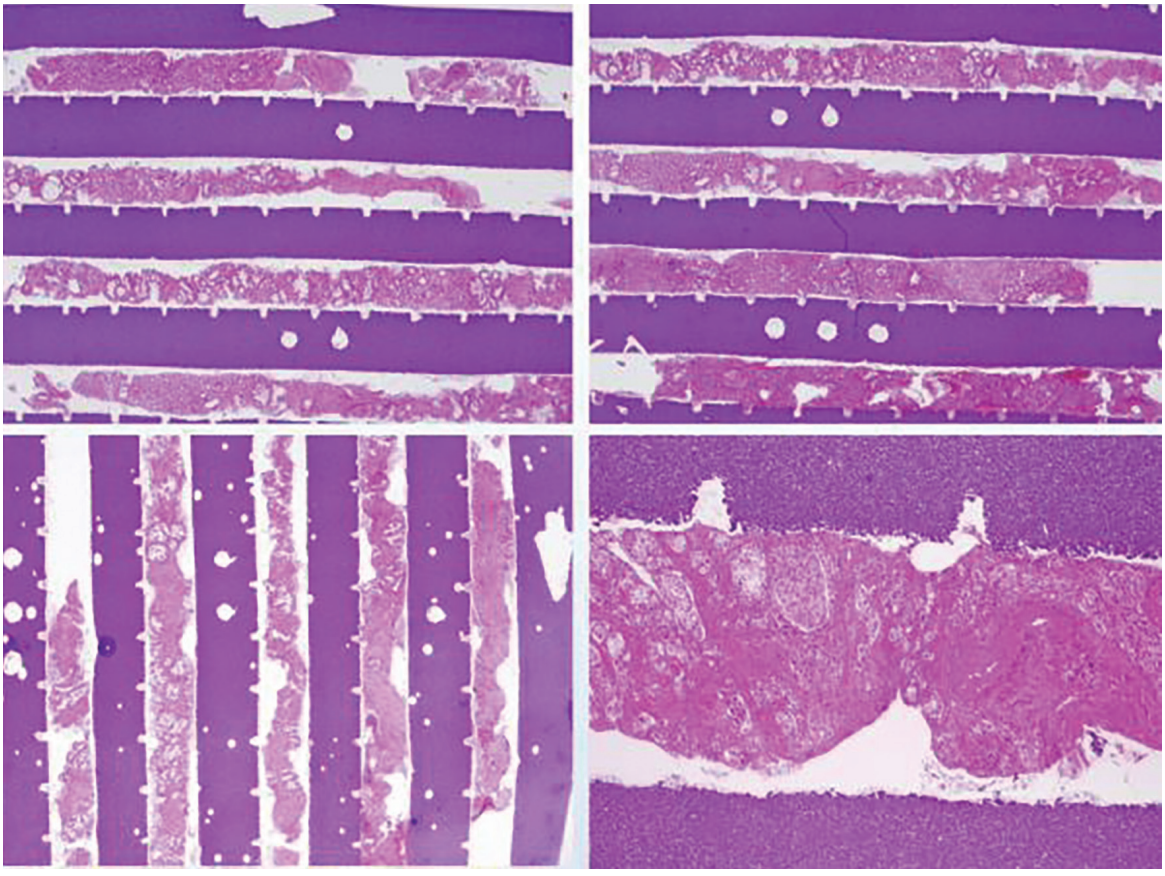

Figure 3. Microscopic examination of BxChip™

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki, after obtaining approval from the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (IRB number: 83045809-604.01.02, date: 17.05.2019). detailed informed consent from all patients.

Informed Consent: Detailed informed consent from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ö., İ.G., Concept: B.Ö., İ.G., U.A., Design: B.Ö., İ.G., U.A., Data Collection or Processing: G.K., N.U., S.C., Analysis or Interpretation: U.A., G.K., Literature Search: S.Ç., B.E., Writing: U.A., G.K., İ.G., B.Ö.

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ORIGINAL RESEARCH
Urooncology

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Comparison of Laparoscopic and Open Partial Nephrectomy in Early-stage Kidney Masses

Turker Altuntas, Mohammad Yasir Sahak, Mehmet Umut Kutukoglu, Yiloren Tanidir, Ilker Tinay, Yusuf Senoglu, Tarik Emre Sener

Marmara University Faculty of Medicine, Department of Urology, İstanbul, Türkiye

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

Partial nephrectomy is preferred in early-stage renal tumors because it provides oncological outcomes similar to radical surgery while preserving kidney function. In this study, we aimed to demonstrate the impact of the choice between open and laparoscopic surgery on perioperative and postoperative parameters, as well as long-term effects, in partial nephrectomy procedures performed in our clinic.

Abstract

Objective: The aim of this study was to demonstrate our clinical experience on the impact of the choice between open partial nephrectomy (OPN) and laparoscopic partial nephrectomy (LPN) on achieving optimal oncological outcomes, perioperative parameters, postoperative recovery and patient comfort, and long-term kidney function in patients undergoing these surgical methods.

Materials and Methods: Data from 127 patients who underwent partial nephrectomy between December 2020 and March 2024 were retrospectively reviewed, with 47 patients in the LPN group and 80 in the OPN group. The patients' demographic information, tumor sizes, complications, and perioperative and postoperative data were compared.

Results: It was found that patients undergoing OPN had larger tumor sizes and higher PADUA scores compared to the LPN group ($p<0.001$ and $p=0.011$, respectively). LPN showed an advantage in terms of lower average blood loss ($p<0.001$), while OPN was advantageous in terms of shorter warm ischemia time ($p=0.001$). Patients in the LPN group had shorter hospital stays and required fewer transfusions ($p<0.001$ and $p=0.021$, respectively). When complications and pathology results were evaluated, outcomes were similar in both groups. The decrease in glomerular filtration rate was found to be less in the LPN group compared to the OPN group ($p=0.008$).

Conclusion: LPN offers advantages over OPN, including less perioperative bleeding, lower morbidity, and shorter hospital stays. However, the longer warm ischemia time in LPN should be considered alongside these benefits.

Keywords: Pathology, radiology, urooncology

Introduction

Radical nephrectomy has long been considered the gold standard in the treatment of renal cell carcinoma. However, the emergence of minimally invasive approaches such as conservative treatments active surveillance, partial nephrectomy, and ablation techniques (cryotherapy, radiofrequency ablation) has gained prominence, especially for small masses, and due to the increased morbidity associated with radical surgery (1). It has been shown that partial nephrectomy, when applied to patients with stage T1 and appropriately located stage T2 tumors, provides similar oncological outcomes to radical nephrectomy while better preserving kidney function and reducing the risk of postoperative cardiovascular events (2). When evaluating the suitability for partial nephrectomy, the size, location, depth of the tumor, and its proximity to the hilum and collecting system, are considered. The surgical approaches for partial nephrectomy (open, laparoscopic, or robotic) depend

Correspondence: Tarik Emre Sener MD, Marmara University Faculty of Medicine, Department of Urology, İstanbul, Türkiye
E-mail: dr.emresener@gmail.com **ORCID-ID:** orcid.org/0000-0003-0085-7680
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on the tumor characteristics, as well as the surgeon's expertise and experience.

Laparoscopic partial nephrectomy (LPN) is considered to offer certain advantages over traditional open partial nephrectomy (OPN) in terms of oncological and surgical principles for kidney tumors. Studies have demonstrated that this method offers similar oncological efficacy and superior renal functional outcomes compared to laparoscopic radical nephrectomy. The main advantages of LPN include reduced blood loss, less postoperative pain, quicker postoperative recovery, better cosmetic outcomes, and more nephron-sparing results compared to other methods (3).

In this study, we reviewed the data of patients who underwent partial nephrectomy through either open or laparoscopic approaches in our clinic, aiming to evaluate the impact of the surgical method for achieving optimal oncological outcomes, perioperative parameters, postoperative patient comfort, and long-term kidney function.

Materials and Methods

Prior to the study, approval was obtained from the Marmara University Clinical Research Ethics Committee with protocol number 09.2023.554 and dated 30.05.2023. Data from 156 patients who presented with kidney masses to the Urology clinic of Marmara University Hospital between December 2020 and March 2024 and underwent either OPN or LPN by experienced surgeons according to the indications in the European Association of Urology Guidelines were retrospectively reviewed. Of the 156 patients, 29 were excluded due to preoperative chronic kidney disease, solitary kidney, multiple or bilateral tumors, metastatic disease, or loss of follow-up. A total of 80 patients who underwent OPN and 47 patients who underwent LPN were included in the study.

OPN was performed retroperitoneally. The laparoscopic procedure was performed transperitoneally. In all patients, two-layer renorrhaphy was performed after tumor excision. 2-0 and 3-0 V-Loc sutures were used for the renorrhaphies.

The preoperative demographic information of the patients, including age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, and Charlson comorbidity index (CCI) score, was recorded. For kidney mass evaluation, tumor size, tumor side, RENAL nephrometry score, and PADUA score were used. To compare surgical methods, perioperative parameters such as blood loss, operative time, warm ischemia time, perioperative transfusion requirements, and perioperative complications were recorded. Postoperative parameters included length of hospital stay, postoperative transfusion requirements, and postoperative complications. Postoperative complications were identified within 30 days after the surgery, and the Clavien-Dindo classification was used for complication assessment. For kidney function evaluation, preoperative and postoperative (3rd month), estimated glomerular filtration rate (eGFR), hemoglobin (Hgb), and hematocrit (Hct) values were used. The modified diet in renal disease formula was employed to calculate the eGFR. Pathology results of the patients' surgical specimens and rates of positive surgical margins were also recorded.

Statistical Analyses

Statistical analysis was conducted using IBM SPSS version 25.0. The Shapiro-Wilk test was initially applied to test the normality of the distribution between patients. Since the data did not show normal distribution, non-parametric methods were used. Nominal data were presented in tables as numbers and percentages, while numerical data were presented as medians, minimum, and maximum values. The comparison of the OPN and LPN groups was performed using the chi-square or Fisher's exact test for nominal data. The Mann-Whitney U test was used for the statistical analysis of numerical data, as the assumption of normality was not met. A p-value of 0.05 was considered statistically significant.

Results

A total of 80 patients who underwent OPN and 47 patients who underwent LPN were included in the study. The two groups were initially compared in terms of demographic information and tumor characteristics. There was no significant difference between the groups regarding age, gender, BMI, ASA score, CCI, side, and RENAL nephrometry score. When comparing the tumor size between the two groups, the median value in the OPN group was 37 mm (12-110 mm), while in the LPN group, it was 22 mm (10-68 mm) ($p<0.001$). When comparing the PADUA score, the OPN group scored 7 (5-12) and the LPN group scored 6 (5-9) ($p=0.011$) (Table 1).

Additionally, perioperative data were compared. The median blood loss in the OPN group was 600 mL (50-3300 mL), while in the LPN group, it was 200 mL (50-3200 mL). Blood loss was significantly lower in the LPN group ($p<0.001$). In terms of warm ischemia time, the OPN group had a median ischemia time of 23 minutes (5-40 minutes), whereas the LPN group had 34.5 minutes (18-66 minutes). The ischemia time was significantly lower in the OPN group ($p=0.001$). In contrast, although the operative time was longer in the LPN group, no significant difference was observed ($p=0.663$). Regarding perioperative transfusion requirements, 17 patients (21.25%) in the OPN group and 4 patients (8.51%) in the LPN group required transfusion ($p=0.062$) (Figure 1).

Figure 1. Perioperative parameters

LPN: Laparoscopic partial nephrectomy, OPN: Open partial nephrectomy

Table 1. Demographic information and tumor characteristics

	OPN (n=80)	LPN (n=47)	p-value
Age (years) median (min-max)	57.5 (31-86)	61 (24-78)	>0.05
Sex n (%)			
Men	53 (66.25%)	26 (55.31%)	>0.05
Women	27 (33.75%)	21 (44.69%)	
BMI (kg/m^2) median (min-max)	29.23 (20.52-44.92)	28.12 (21.56-43.6)	>0.05
ASA score median (min-max)	1 (1-3)	2 (1-3)	>0.05
CCI median (min-max)	3 (2-9)	3 (2-7)	>0.05
Side n (%)			
Right	39 (48.75%)	27 (57.44%)	>0.05
Left	41 (51.25%)	20 (42.56%)	
Tumor size (mm) median (min-max)	37 (12-110)	22 (10-68)	**<0.001**
RENAL score median (min-max)	5 (4-11)	5 (4-9)	>0.05
PADAU score median (min-max)	**7** (5-12)	6 (5-9)	**<0.05**

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, ASA: American Society of Anesthesiologists, BMI: Body mass index, CCI: Charlson comorbidity index, min: Minimum, max: Maximum

When postoperative complications were evaluated, patients in the OPN group had a median hospital stay of 5 days, (3-27 days), while patients in the LPN group had a stay of 4 days, (2-16 days) (p=0.001). In terms of postoperative transfusion rates, 15 patients (18.75%) in the OPN group and 2 patients (4.3%) in the LPN group required transfusion (p=0.021). Although significant differences were found in the length of hospital stay and postoperative transfusion requirements, no statistically significant difference was found in postoperative complications (p=0.358) (Table 2).

The groups were then compared based on pathological results. There was no significant difference when comparing the pathology results based on malignant or benign status and

Table 2. Postoperative comparison and complications			
	OPN (n=80)	**LPN (n=47)**	**p-value**
Duration of hospital stay (days) median (min-max)	5 (3-27)	4 (2-16)	**<0.001**
Transfusion n (%)	15 (18.75%)	2 (4.25%)	**<0.05**
Complications n (%)	16 (20%)	6 (12.76%)	>0.05
Minor complications[a]			
Fever	6	1	
Deep vein thrombosis	3	1	
Hematoma	0	1	
Pulmonary embolism	1	0	
Pleural effusion	2	0	
Drainage increase	2	0	
Hepatitis	1	0	
Hematuria	0	1	
Fat necrosis	1	0	
Major complications[b]			
Ex	0	2	

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, min: Minimum, max: Maximum
[a]: Clavien-Dindo 1,2
[b]: Clavien-Dindo 3,4,5

Table 3. Pathology results			
	OPN (n=80)	**LPN (n=47)**	**p-value**
Surgical margin positivity n (%)	0	2 (4.25%)	>0.05
Pathology result n (%)			>0.05
Malignant			
Clear cell carcinoma	50 (62.5%)	28 (59.57%)	
Papillary carcinoma	5 (6.25%)	2 (4.25%)	
Chromophobic cell carcinoma	9 (11.25%)	5 (10.63%)	
Benign	15 (18.75%)	12 (25.53%)	

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy

subtypes (p=0.661) (Table 3). No recurrence was observed during the long-term follow-up of the patients. When the pathology data of the patients included in the study were reviewed, the results showed that the outcome was benign in 27 out of 127 patients, and malignant in 100 patients. Among these 100 patients, 2 had positive surgical margins. No patient in the OPN group had a positive surgical margin, while 2 patients (4.25%) in the LPN group had positive margins (p=0.133). In the follow-up of these 2 patients, no recurrence was observed in the long term. These 2 patients were closely monitored. However, during the one-year oncological follow-up, no recurrent masses were detected in either the patients with positive surgical margins or those with other malignant pathologies.

Finally, the groups were analyzed in terms of preoperative, postoperative GFR at 3 months GFR, Hgb, and Hct values, as well as the changes in these values. There was no significant difference between the OPN and LPN groups in terms of preoperative GFR, Hgb, Hct, postoperative GFR, Hgb, Hct, or changes in Hgb and Hct. However, when comparing the GFR change between the groups, the GFR in the OPN group was -11.76 (-68.36 to -32.78) mL/min/1.73 m², while in the LPN group, it was -2.6 (-59.18 to -29.37) mL/min/1.73 m². A statistically significant difference was found between the two groups (p=0.008) (Table 4).

Discussion

With recent advancements in surgical techniques, partial nephrectomy, a minimally invasive procedure, has become the preferred primary method for treating clinical stage T1 renal masses. Studies have shown that there is no difference in cancer-specific survival between partial nephrectomy and radical nephrectomy in terms of oncological control (4-7).

In our study, the demographic data, preoperative, perioperative, and postoperative outcomes of patients who underwent

partial nephrectomy using either laparoscopic or open methods were evaluated. No difference was observed between the two groups in terms of demographic data. The four most commonly used scoring systems for surgical planning are the C-index, RENAL score, PADUA score, and D.A.P score (8). The RENAL score has the best correlation with surgical outcomes (9). When preoperative data were examined, it was found that the tumor size and PADUA score of patients who underwent OPN were higher than the LPN group. When comparing perioperative data, LPN was advantageous with lower average blood loss, while OPN offered shorter warm ischemia time. Although not statistically significant, OPN had a shorter operative time. Postoperatively, it was found that patients in the LPN group had a shorter hospital stay and required fewer transfusions. The complications and pathology results were similar in both groups. In terms of kidney function assessment, the decrease in GFR change values, obtained by subtracting the preoperative GFR value from the GFR recorded at 3 months postoperatively, was lower in the LPN group, compared to the OPN group. There was no difference between preoperative and postoperative GFR, Hgb, and Hctvalues. No difference was observed between the two methods in terms of Hgb and Hct changes.

Schiff et al. (10) found that, similar to our study, the average tumor size was higher in the OPN group compared to the LPN group when looking at the literature. The tendency towards open surgery in patients with larger tumor sizes could explain this.

In contrast to our study, Beasley et al. (11) suggested that OPN and LPN caused similar amounts of blood loss. Similar to our findings, Schiff et al. (10) found that, blood loss was lower in the LPN group, although not statistically significant.

Warm ischemia time is one of the factors affecting the preservation of kidney function and is one of the goals of partial nephrectomy. In our study, we found that the warm ischemia time was significantly longer in the LPN group. Similarly, a study conducted by Gill et al. (12) involving 1800 patients found that warm ischemia time was significantly longer in the LPN group than in the OPN group. A study by Porpiglia et al. (13) showed that a warm ischemia time of >30 minutes increased kidney damage. Therefore, we have concluded that we need to reduce the warm ischemia time in LPN surgeries.

In the literature, there are studies showing that the operation times are similar in both surgical methods (14,15). the study by Beasley et al. (11) found that the operative times of patients who underwent LPN were significantly longer. Although not statistically significant, we found that LPN took longer in our study. Conversely, there are studies in the literature that show LPN takes less time (10,12). These differences may be influenced by the level of surgical experience.

In our study, although the warm ischaemia period and operation time were shorter in OPN, the transfusion requirement was higher in this group compared to the laparoscopic group, likely due to increased bleeding inherent in the open surgical method.

When comparing hospital stay durations, Beasley et al. (11), similar to our study, showed that hospital stays were shorter in the LPN group.

In the literature, there are many studies comparing LPN and OPN in terms of complication rates. Similar to our study, Beasley et al. (11) showed that both OPN and LPN could be performed with similar complication rates. Contrary to our results, there are also publications, such as the study by Gill et al. (14), showing that the complication rates in laparoscopic procedures are higher.

When creatinine measurements were made between the groups to assess postoperative kidney function, Schiff et al. (10) found no difference in their study. In our study, we found that the decrease in GFR was significantly higher in the OPN group

Table 4. Evaluation of kidney functions

	OPN (n=80)	LPN (n=47)	p-value
Preoperative GFR (mL/min/1.73 m²) median (min-max)	92.29 (33.06-187.04)	87.98 (46.11-154.1)	>0.05
Postoperative GFR (mL/min/1.73 m²) median (min-max)	86.47 (11.72-151.25)	83.34 (39.23-130.83)	>0.05
ΔGFR (mL/min/1.73 m²) median (min-max)	-11.76 (-68.36-32.78)	-2.6 (-59.18-29.37)	**<0.05**
Preoperative Hgb (g/dL) median (min-max)	14 (10-17.7)	13.85 (10.4-18.4)	>0.05
Postoperative Hgb (g/dL) median (min-max)	13.55 (8.9-16.6)	13.25 (9.8-17.3)	>0.05
ΔHgb (g/dL) median (min-max)	-0.4 (-5.3-3)	-0.5 (-3.6-1.3)	>0.05
Preoperative Htc (%) median (min-max)	42 (30.8-50.8)	42.85 (33.6-56.8)	>0.05
Postoperative Htc (%) median (min-max)	39.7 (25.7-49.4)	40-8 (31.6-54.3)	>0.05
ΔHtc (%) median (min-max)	-1 (-17.2-6.9)	-0.95 (-9.2-5.7)	>0.05

OPN: Open partial nephrectomy, LPN: Laparoscopic partial nephrectomy, GFR: Glomerular filtration rate, Hgb: Hemoglobin, Htc: Hematocrit, min: Minimum, max: Maximum

compared to the LPN group, while there was no significant difference between preoperative and postoperative creatinine values. Considering this result, OPN is suggested to be more disadvantageous than LPN in terms of preserving kidney function.

Additionally, considering that the procedure was performed using a retroperitoneal approach in the OPN patients and a transperitoneal approach in the LPN patients, the OPN method provides both a lower risk of bowel injury and a reduced risk of postoperative ileus. None of our patients developed ileus.

Study Limitations

When evaluating the limitations of the study, its retrospective nature is a major limitation. Including a cost analysis in the comparison of these two methods would provide a more accurate assessment. The differences in tumor size and PADUA scores between patients who underwent partial nephrectomy via open and laparoscopic methods also constitute a limitation, as they may have an impact on surgical outcomes. Additionally, having all surgeries performed by a single surgeon could help obtain more homogeneous data. Higher-level evidence could be obtained from future prospective, double-blind, randomized studies.

Conclusion

LPN, when compared to OPN, provides similar oncological outcomes while offering less perioperative bleeding, lower morbidity, and shorter hospital stays. Although LPN should be prioritized and encouraged over OPN, performing this procedure in experienced centers, considering the longer warm ischemia time, would be more appropriate for the long-term preservation of kidney function.

Ethics

Ethics Committee Approval: Prior to the study, approval was obtained from the Marmara University Clinical Research Ethics Committee with protocol number 09.2023.554 and dated 30.05.2023.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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ORIGINAL RESEARCH
Urooncology

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Cultural Adaptation and Validation of the Turkish Version of the Expanded Prostate Cancer Index Composite

Sahin Kabay

İzmir Bozyaka Training and Research Hospital, Clinic of Urology, İzmir, Türkiye

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

With the tests and imaging methods developed in the field of health, prostate cancer (PCa) can be diagnosed at an early stage. PCa detected at an early stage can be successfully treated, and life expectancy is extended after treatment. Quality of life (QoL) is an important aspect in terms of PCa due to the various treatment options after diagnosis and urinary, bowel, hormonal, and sexual dysfunctions that develop depending on the characteristics of each treatment option. These complications occurring in these systems affect the QoL in the patient's social and functional life. Today, QoL scales are used in many countries of the world to evaluate functional disorders that develop due to PCa treatment, and new ones are being developed. There are very few scales that have been validated and are reliable for this purpose in our country. The aim of this study was to culturally adapt the Turkish version of the EPIC questionnaire.

Abstract

Objective: This study aimed to culturally adapt the Turkish version of the expanded prostate cancer index composite (EPIC) questionnaire form, which evaluates post-treatment functions in prostate cancer (PCa) patients, to investigate whether it is reliable, valid, and usable, and to evaluate the quality of life (QoL) characteristics of patients who have used different treatment methods.

Materials and Methods: To create the Turkish version of the EPIC questionnaire form, we used cultural adaptation for language translation and conducted exploratory and confirmatory factor analysis to determine its validity and reliability.

Results: A total of 423 patients diagnosed with PCa who underwent radical retropubic prostatectomy, laparoscopic radical prostatectomy, or robot-assisted laparoscopic radical prostatectomy, and received radiotherapy and/or hormonal treatment in addition to surgery were included in this study. In our study, Cronbach's alpha coefficients were calculated as 0.919 for urinary function, 0.901 for bowel habits, 0.930 for sexual function, 0.940 for hormonal function, and 0.813 for the general questionnaire form.

Conclusion: The EPIC questionnaire was successfully translated into Turkish and was culturally adapted. The resultant Turkish version has high reliability and validity and will be an important tool for QoL research in the population. EPIC was successfully translated, culturally adapted, and validated with high reliability and validity into Turkish. It will be a valuable QoL tool for physicians in clinical and research settings, and for patients in decision-making. It can also be considered an objective reference to compare various treatment modalities related to PCa.

Keywords: Basic science, general urology, urooncology

Introduction

The World Health Organization defines quality of life (QoL) as encompassing individual perception, goals, expectations, concerns, physical health, mental state, level of freedom, individual communication, and beliefs in one's life. QoL for health includes comments and evaluations regarding the functional ability of the patient, the effect on the patient's physical and mental state, the patient's feelings, and their social relationships related to the treatment applied for different diseases, as well as the results of different treatment approaches that impact

Correspondence: Sahin Kabay MD, İzmir Bozyaka Training and Research Hospital, Clinic of Urology, İzmir, Türkiye
E-mail: skabay@yahoo.com **ORCID-ID:** orcid.org/https://orcid.org/0000-0002-4657-9818
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QoL (1,2). The increase in life expectancy due to the early diagnosis of prostate cancer (PCa) has made QoL important in cancer treatment. The variety of treatment methods and some treatment methods are not superior to each other in some cases bring the patient's QoL expectations to the fore in choosing treatment. Different types of questionnaire scales have been created for this purpose. The expanded prostate cancer index composite (EPIC) questionnaire was developed by researchers at the University of Michigan and University of California, Los Angeles (UCLA). The UCLA PCa index was expanded to reflect the symptoms of PCa treatment and their negative effects. The EPIC questionnaire consists of 32 questions in four sections questioning urinary system, bowel, sexual, and hormonal symptoms, and includes a 5-point Likert-type scale (3). Since its development, the EPIC questionnaire has been widely accepted as a useful, systematic and comprehensive tool.

The hypotheses of the study are as follows: a) It is important to evaluate the patient's QoL expectations when choosing a treatment because of the variety in PCa treatment methods, the fact that some treatments are not superior to others in some cases, and the problems related to treatments, b) It is important to make ethical evaluations in the use and development of QoL scales in the field of health, c) While QoL scales provides positive contributions from an ethical perspective, they can cause ethical problems in some areas, d) With the evaluations, the dysfunctions experienced by patients during and after receiving PCa treatment can be determined, e) Different dysfunctions experienced during the PCa treatment process affect the QoL.

This study aimed to culturally adapt the Turkish version of the EPIC questionnaire form, which evaluates post-treatment functions in PCa patients, to investigate whether it is reliable, valid and usable, and to evaluate the QoL characteristics of patients who have used different treatment methods.

Materials and Methods

A total of 423 patients diagnosed with PCa who underwent radical retropubic prostatectomy (RRP), laparoscopic radical prostatectomy (LRP), or robot-assisted laparoscopic radical prostatectomy (RLRP) and received radiotherapy (RT) or hormonal treatment (HT) in addition to surgery were included in this study. Patients who were admitted to Eskişehir Osmangazi University, Faculty of Medicine, Department of Urology between March 2015 and December 2018, and were followed up and treated for a diagnosis of PCa were included in this study. In all patient groups, patients receiving treatment with a diagnosis of PCa were asked to complete the self-administered EPIC questionnaire in the hospital in the 3rd month after starting treatment. Approval was obtained from Eskişehir Osmangazi University Ethics Committee (approval number: 02, date: 19.02.2015) and informed consent was obtained for all interviews. Permission for the Turkish validation of the EPIC questionnaire form was obtained from the original authors and the institutions responsible for its development (3). The inclusion criteria included patients with a history of biopsy-proven PCa, a localized PCa diagnosis or clinical stage T1-T3, no previous treatment for PCa, and who had a therapeutic indication for retropubic radical prostatectomy. Patients with a history of chemotherapy, recent surgery, radiation, initiation of androgen deprivation therapy within 4 weeks or who do not fully speak and understand Turkish were excluded from the study. As stated below, our study was translated with the internationally recommended cultural adaptation (4). The methods of translation into Turkish, validity, and reliability were completed in four stages: first translation, translation synthesis, expert committee review, and back translation. The initial translation was done by two independent translators, one of whom, a native English speaker, was informed about the aims of the study. During the translation synthesis phase, two translated versions were evaluated by the researchers, preserving the same basic features of the original query form. The expert committee review board was composed of five urologists who were fluent in English. The committee evaluated semantic, idiomatic, cultural, and conceptual similarities between the original and translated versions of each question. During the back translation, the questionnaire form was translated from Turkish to English by two independent translators who were fluent in English and were blind to the aims and objectives of the study. Inconsistencies between the two languages were evaluated.

Cronbach's alpha coefficient was calculated for reliability analyses. Alpha (α) coefficient $0.60 \leq \alpha \leq 0.80$ was considered reliable, and $0.80 \leq \alpha \leq 1.00$ was considered highly reliable (5).

In our study, exploratory factor analysis (EFA) and confirmatory factor analysis (CFA as a model), as well as one-factor, first-level multi-factor, and second-level multi-factor models, were examined separately by CFA (6). Kaiser-Meyer-Olkin (KMO) and Bartlett's tests were performed to evaluate the suitability of factor analysis of the data. In CFA, a chi-square test was performed to evaluate the goodness of fit. Also, goodness of fit index (GFI), root mean square error of approximation, standardized root mean square residual, and comparative fit index were calculated.

Statistical Analyses

SPSS (22.0, SPSS, Chicago, IL, USA) was used for all statistical analyses of the study. The Amos program (IBM SPSS Amos v27), was used for CFA and EFA. Pearson correlation coefficients were calculated to evaluate each scale in terms of the domain, problem scales, and conceptual independence of each area. With confirmatory factor analysis, the multiple correlation square

(r2) value, which determines the strength of the relationship between each item and the latent variable regarding the scale items, and the t values, which show the relationship and GFIs for the factor structure of the scale items, were calculated.

Results

A total of 423 patients treated with PCa were included in the study. The mean age of the patients was 63.1±6.75. The mean PSA value of all patients was 6.90±4.97 ng/mL. Two hundred and twenty (52%) of the patients received RRP, 39 (9.2%) LRP, 12 (2.8%) RLRP, 66 (15.6%) RT, 86 (20.4%) RT&HT and hormonotherapy. When the correlation analysis results of the significant relationship between the EPIC measurement data averages are examined; there is a linear and statistically significant weak relationship between urinary function measurement data and bowel habits measurement data ($r=+0.102$, $p<0.05$). These data show that the improvement in urinary function also improves bowel habits. It is seen that there is a linear and statistically significant relationship between the bowel habits measurement data and the sexual function measurement data ($r=+0.264$, $p<0.01$). These data show that the sexual function of patients whose bowel habits improve also improves. It is seen that there is an inverse and statistically significant relationship between the sexual function measurement data and the hormonal function measurement data ($r=-0.156$, $p<0.01$) (Table 1). This analysis shows that hormonal dysfunctions cause a decrease in sexual function.

When the one-way analysis of variance results regarding the means of urinary function, bowel habits, sexual function, and hormonal function measurement data were examined according to the treatment groups, it was found that urinary function [$F_{(3, 419)}=0.665$, $p>0.05$], sexual function [$F_{(3, 419)}=2.387$, $p>0.05$] and hormonal function [$F_{(3, 419)}=1.604$, $p>0.05$] did not show a significant difference according to the operation variable. On the other hand, bowel habits measurement scores [$F_{(3-419)}=7.277$, $p<0.05$] showed a significant difference according to the operation variable (Table 2). Tukey honestly significant difference (HSD) was performed to determine which groups caused the significant differences among the factors. The Tukey HSD analysis results indicated an increase in favor of the RRP and RLRP groups when bowel habits measurement data were assessed according to the type of surgery. These results show that open surgery, LRP, and RLRP are better in terms of affecting bowel habits (Table 3).

When the one-way analysis of variance results related to the means of urinary function, bowel habits, sexual function and hormonal function measurement data according to treatment satisfaction are examined, urinary function measurement data [$F(4-418)=1.718$, $p>0.05$], hormonal function measurement data [$F(4-418)=1.035$, $p>0.05$] do not show a significant difference according to the satisfaction variable. On the other hand, bowel habits measurement data [$F(4-418)=28.310$, $p<0.05$] and sexual function measurement data [$F(4-418)=26.900$, $p<0.05$] show a significant difference according to the satisfaction variable (Table 4). Tukey HSD was performed to determine the groups from which the domains, that showed significant differences, originated. When the Tukey HSD analysis results were examined, it was seen that patient satisfaction was not sufficient regarding bowel habits according to the satisfaction variable in the bowel habits measurement data, but patients were satisfied with sexual function (Table 5).

In our study, before performing EFA and CFA, the assumption of multivariate normality in the database (n=423) was checked. According to these results, the data (n=67) were found not to comply with multivariate normality. After excluding these data, the analysis continued with (n=356). In line with the suggestions of Tabachnick and Fidell (7), the number of items was selected with a minimum of 5 and a maximum of 20. Among the 356 data points randomly selected, 191 were used for EFA and 165 for CFA. The reliability analysis results of our study appear to be reliable. The KMO value was found to be high at 0.90, and the Bartlett test was significant. These values show that the EPIC data are very suitable for factor analysis (Table 6).

When the factor rotation results were examined, it was concluded that it was a valid measurement tool with four factors with high loading values consisting of n=7 (0.679-0.857) items in the urinary function domain, n=9 (0.644-0.771) items in the bowel habits domain, n=9 (0.670-0.795) items in the sexual function domain and n=6 (0.824-0.916) items in the hormonal function domain. In this study, the coefficient of determination was calculated as 2.95E-011 and this value was found to be greater than 0.00001.

Table 1. Evaluation of the relationship between urinary function, bowel habits, sexual function, hormonal function

		(Y_1)	(Y_2)	(Y_3)	(Y_4)
Urinary function (Y_1)	Correlation (r)	1			
Bowel habits (Y_2)	Correlation (r)	0.102*	1		
Sexual function (Y_3)	Correlation (r)	0.017	0.264**	1	
Hormonal function (Y_4)	Correlation (r)	0.053	0.073	-0.156**	1

*: The relationship is significant at $p<0.05$, **: The relationship is significant at the $p<0.01$ level

Table 2. Results of one-way analysis of variance associated with urinary function, bowel habits, sexual function, hormonal function and treatment groups

		N	$\bar{X}$	S	F	p
Urinary function	RRP	220	29.43	6.34	0.665	0.574
	LRP&RLRP	51	28.94	6.02		
	RT&HT	85	29.88	6.76		
	RT	67	30.48	7.50		
Bowel habits	RRP	220	28.12	5.22	7.277	**0.000***
	LRP&RLRP	51	28.37	5.47		
	RT&HT	85	31.72	8.60		
	RT	67	28.52	5.92		
Sexual function	RRP	220	41.41	6.79	2.387	0.068
	LRP&RLRP	51	40.41	6.60		
	RT&HT	85	39.41	8.56		
	RT	67	42.12	5.80		
Hormonal function	Rv RP	220	33.04	6.40	1.604	0.188
	LRP&RLRP	51	33.57	6.71		
	RT&HT	85	34.78	7.18		
	RT	67	32.87	6.48		
	RRP	220	29.43	6.34		
	LRP&RLRP	51	28.94	6.02		
	RT&HT	85	29.88	6.76		
	RT	67	30.48	7.50		

*: The relationship is significant at p<0.05, RRP: Radical retropubic prostatectomy, LRP: Laparoscopic radical prostatectomy, RT: Radiotherapy, HT: Hormonal treatment, RLRP: Robot-assisted laparoscopic radical prostatectomy

Table 3. Multiple comparison Tukey HSD analysis results associated with urinary function, bowel habits, sexual function, hormonal function and treatment groups

			AD	SD	p
Bowel habits	RRP	RLRP	-0.25437	0.95974	0.993
		RT&HT	-3.59947*	0.78867	0.000
		RT	-0.40421	0.86170	0.966
	RLRP	RRP	0.25437	0.95974	0.993
		RT&HT	-3.34510*	1.09380	0.013
		RT	-0.14984	1.14758	0.999
	RT&HT	RRP	3.59947*	0.78867	0.000
		RLRP	3.34510*	1.09380	0.013
		RT	3.19526*	1.00888	0.009
	RT	RRP	0.40421	0.86170	0.966
		RLRP	0.14984	1.14758	0.999
		RT&HT	-3.19526*	1.00888	0.009

*: The relationship is significant at p<0.05 significance level, RRP: Radical retropubic prostatectomy, LRP: Laparoscopic radical prostatectomy, RT: Radiotherapy, HT: Hormonal treatment, RLRP: Robot-assisted laparoscopic radical prostatectomy, AD: Average difference, SD: Standard deviation, HSD: Honestly significant difference

Table 4. Results of one-way analysis of variance associated with urinary function, bowel habits, sexual function, hormonal function and treatment satisfaction

		N	$\bar{X}$	S	F	p
Urinary function	Extremely dissatisfied	30	28.50	4.58	1.718	0.145
	Dissatisfied	30	30.07	7.14		
	Uncertain	32	31.72	8.54		
	Satisfied	77	28.47	4.77		
	Extremely satisfied	254	29.80	6.85		
Bowel habits	Extremely dissatisfied	30	33.77	9.82	28.310	**0.000***
	Dissatisfied	30	30.30	6.08		
	Uncertain	32	35.91	9.52		
	Satisfied	77	30.47	7.20		
	Extremely satisfied	254	26.86	3.22		
Sexual function	Extremely dissatisfied	30	35.73	5.97	26.900	**0.000***
	Dissatisfied	30	37.13	4.60		
	Uncertain	32	34.59	9.01		
	Satisfied	77	39.27	7.25		
	Extremely satisfied	254	43.41	5.81		
Hormonal function	Extremely dissatisfied	30	34.57	7.30	1.035	0.389
	Dissatisfied	30	33.53	6.53		
	Uncertain	32	34.94	7.30		
	Satisfied	77	33.84	6.64		
	Extremely satisfied	254	32.96	6.46		

*: The relationship is significant at $p<0.05$ significance level

To test the validity of the scale used in our study, multifactor CFA (level I) was performed. When the GFI data for the multifactor first level scale, GFI data were evaluated, the p value was found to be statistically significant. The value of X^2 (527.021)/df (415) being between 0 and 2 indicates a good fit. The analysis result (X^2/df=1.270) indicates a good fit. It was observed that all comparative fit indices, absolute fit indices, and residual based fit indices fit well (Figure 1).

As a result of multi-factor CFA (level II), the p-value was found to be significant. The value of X^2 (536.635)/df (417), being between 0 and 2, is a good fit. The analysis result (X^2/df=1.287) indicates a good fit. All comparative fit indices, absolute fit indices, and residual-based fit indices have good fit values (Figure 2). In our study, when we look at the model fit criterion GFI reference ranges for level I and level II, we observe that the goodness of fit is quite good.

Discussion

The perception of QoL may show individual differences and also change in the same patient at different times. While the symptoms of the disease seriously impair the QoL in some patients, they are seen as unimportant in others. This situation may also show similarities the treatments applied.

QoL after PCa treatment is an important issue. Moreover, since approximately 16% of patients treated for localized PCa are dissatisfied with their treatment choice, they should be informed as comprehensively as possible before choosing their treatment (8). Although there are many questionnaires evaluating cancer patients, more specific methods are needed to examine the QoL of PCa patients who have received multiple treatment regimens. These cancer scales are unable to fully reflect the severity of symptoms, are inadequate in measuring the life limitations caused by the disease, and have limitations in evaluating QoL due to PCa; despite this, they are still used for these evaluations. In contrast, the EPIC questionnaire attempts to reveal the physical and mental aspects of QoL by systematically asking questions about areas related to frequently seen symptoms (9). Another important feature is that it includes symptom areas related to hormonal status, which are not included in other questionnaires on QoL. The study conducted for the original form of EPIC reported Cronbach alpha coefficients the Cronbach's alpha coefficients for urinary function, bowel habits, sexual function, and hormonal function were reported as 0.88, 0.92, 0.93, and

Table 5. Multiple comparison Tukey HSD analysis results associated with urinary function, bowel habits, sexual function, hormonal function, and treatment satisfaction

			AD	SD	p
Bowel habits	Extremely dissatisfied	Dissatisfied	3.46667	1.45248	0.121
		Uncertain	-2.13958	1.42960	0.565
		Satisfied	3.29913	1.21071	0.052
		Extremely satisfied	6.90446*	1.08602	0.000
	Dissatisfied	Extremely dissatisfied	-3.46667	1.45248	0.121
		Uncertain	-5.60625*	1.42960	0.001
		Satisfied	-0.16753	1.21071	1.000
		Extremely satisfied	3.43780*	1.08602	0.014
	Uncertain	Extremely dissatisfied	2.13958	1.42960	0.565
		Dissatisfied	5.60625*	1.42960	0.001
		Satisfied	5.43872*	1.18317	0.000
		Extremely satisfied	9.04405*	1.05523	0.000
	Satisfied	Extremely dissatisfied	-3.29913	1.21071	0.052
		Dissatisfied	0.16753	1.21071	1.000
		Uncertain	-5.43872*	1.18317	0.000
		Extremely satisfied	3.60533*	0.73182	0.000
	Extremely satisfied	Extremely dissatisfied	-6.90446*	1.08602	0.000
		Dissatisfied	-3.43780*	1.08602	0.014
		Uncertain	-9.04405*	1.05523	0.000
		Satisfied	-3.60533*	0.73182	0.000
Sexual function	Extremely dissatisfied	Dissatisfied	-1.40000	1.63191	0.912
		Uncertain	1.13958	1.60620	0.954
		Satisfied	-3.53939	1.36027	0.072
		Extremely satisfied	-7.67612*	1.22018	0.000
	Dissatisfied	Extremely dissatisfied	1.40000	1.63191	0.912
		Uncertain	2.53958	1.60620	0.510
		Satisfied	-2.13939	1.36027	0.516
		Extremely satisfied	-6.27612*	1.22018	0.000
	Uncertain	Extremely dissatisfied	-1.13958	1.60620	0.954
		Dissatisfied	-2.53958	1.60620	0.510
		Satisfied	-4.67898*	1.32933	0.004
		Extremely satisfied	-8.81570*	1.18558	0.000
	Satisfied	Extremely dissatisfied	3.53939	1.36027	0.072
		Dissatisfied	2.13939	1.36027	0.516
		Uncertain	4.67898*	1.32933	0.004
		Extremely satisfied	-4.13672*	0.82223	0.000
	Extremely satisfied	Extremely dissatisfied	7.67612*	1.22018	0.000
		Dissatisfied	6.27612*	1.22018	0.000
		Uncertain	8.81570*	1.18558	0.000
		Satisfied	4.13672*	0.82223	0.000

*: The relationship is significant at p<0.05 significance level, HSD: Honestly significant difference, AD: Average difference, SD: Standard deviation

Table 6. Results of reliability and factor analysis suitability tests for the EPIC form			
Scale dimention	**Original proposition number**	**Number of remaining propositions**	**Cronbach's alfa coefficient**
Urinary function	7	7	0.919
Bowel habits	9	9	0.901
Sexual function	9	9	0.930
Hormonal function	6	6	0.940
General	31	31	0.813
Kaiser-Meyer-Olkin and Bartlett's test			
Kaiser-Meyer-Olkin measure of sampling adequacy			0.901
Bartlett's test of sphericity	Approx. chi-square		3705.816
	df		465
	Sig.		0.000
EPIC: Expanded prostate cancer index composite			

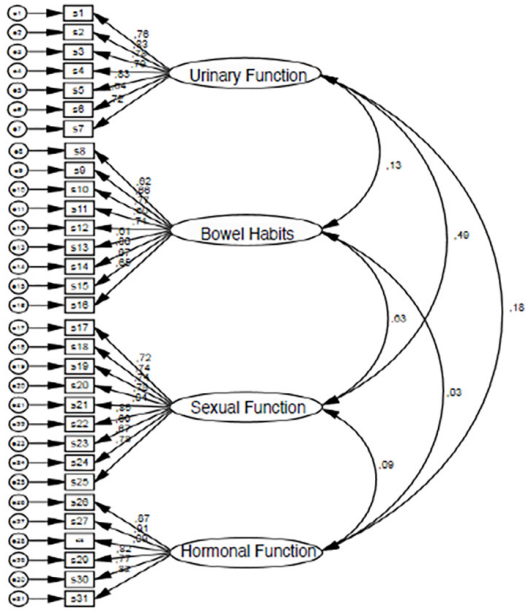

Figure 1. Multifactor confirmatory factor level I model and multifactor level I scale goodness of fit indices

Scale model*	ΔX²	SD	p	ΔX²/SD	GFI	CFI	RMSEA	RMR
Level II	527.021	415	0.000	1.270	0.852	0.970	0.038	0.002
GFI: Goodness of fit index, RMSEA: Root mean square error of approximation, RMR: Standardized root mean square error root mean square residual, CFI: Comparative fit index, X2: Chi-square, SD: Standard deviation								

0.82, respectively. In the reliability and validity study in the Korean study, Cronbach's alpha coefficients were calculated as 0.86 for urinary function, 0.84 for bowel habits and sexual function, and 0.82 for hormonal function; in the Spanish study, the values were 0.73 for urinary function, 0.75 for bowel habits, 0.89 for sexual function, and 0.66 for hormonal function; in the French study, the values were 0.88 for urinary function, 0.92 for bowel habits, 0.93 for sexual function, and 0.82 for hormonal function; and in the Punjabi study, the values of the urinary, bowel, sexual, and hormone function were 0.88, 0.91, 0.91, and 0.95, respectively. In our study, the internal consistency of all functions and domains was very high according to Cronbach's alpha coefficients, and when compared with the literature, this was consistent with the literature (3,10-15).

Hormonal therapy for PCa also significantly affects QoL. Erectile dysfunction is reported to be present in 50-100% of these patients, gynecomastia in 13-70%, and hot flashes in 55-80% (16). Although there are numerous scales to assess QoL, such as FACIT, short form-36, and functional assessment of cancer therapy (FACT)-G for chronic diseases or cancer patients, a more specialized approach to examine the QoL of patients with PCa treated with multimodality has not been found. These

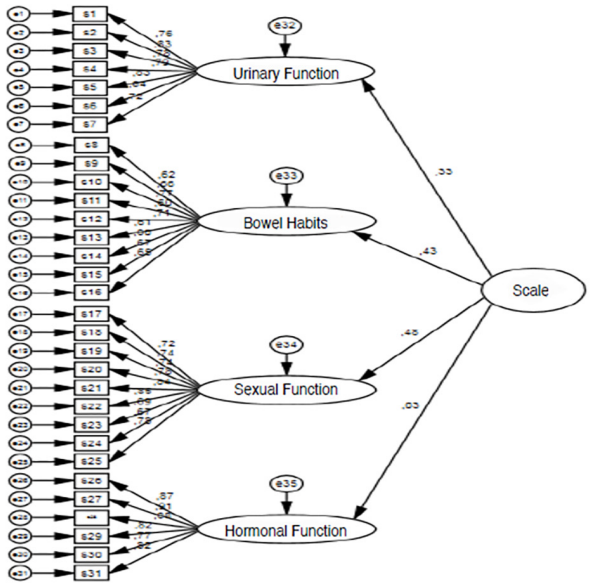

Figure 2. Multifactor confirmatory factor level II model and multifactor level II scale goodness of fit indices

Scale model*	ΔX^2	sd	p	ΔX^2/sd	GFI	CFI	RMSEA	RMR
Level II	536.635	417	0.000	1.287	0.851	0.968	0.039	0.002

GFI: Goodness of fit index, RMSEA: Root mean square error of approximation, RMR: Standardized root mean square error root mean square residual, CFI: Comparative fit index, X^2: Chi-square, SD: Standard deviation

approaches have been used to investigate QoL despite the lack of evaluation of symptom severity, disability, life-limiting issues, and QoL specifically after PCa treatments. FACT-P, a questionnaire developed to overcome this limitation, was intended to provide objective and consistent data on cancer treatment by enhancing FACT-G with prostate-related symptoms. However, this scale did not provide sufficiently detailed information on QoL related to symptoms after PCa treatment. The EPIC questionnaire, on the other hand, systematically organizes areas related to common symptoms and attempts to separate physical and mental aspects of QoL.

Our study also shows that when the data of the EPIC questionnaire form, is evaluated, the sexual function of patients whose bowel habits are not affected is good. Hormonal dysfunctions cause a decrease in sexual function. While there is no difference between urinary and hormonal functions according to age groups, the bowel habits of patients aged 69 and over are more affected. On the other hand, in the sexual function measurement data, the data show that the 48-58 age group has better sexual function compared to other age groups. No difference was found in terms of urinary, hormonal, and sexual functions according to the type of operation. However, LRP & RLRP surgeries show a better outcome in terms of affecting bowel habits. When patients' satisfaction with the treatments they received is examined, there is no difference in terms of urinary function and hormonal functioning. It was observed that satisfaction with bowel habits was not sufficient, but satisfaction with sexual function was. A small number of patients who filled out the Turkish version of the EPIC questionnaire said that they had difficulty answering some questions. However, when these patients were examined, it was understood that the reason was not because of linguistic and cultural problems. It was observed that symptoms resulting from different treatment methods were not present in these patients. For example, patients who only received surgical treatment had difficulty answering the questions because they did not experience symptoms related to HT (10-14).

Schroeck et al. (17) concluded that there was a high correlation between the scores of the International Index of Erectile Function (IIEF-5) and the EPIC questionnaire the sexual function subgroup in their comparative study, and that these results may help in the interpretation of sexual function outcomes in patients with PCa (17).

Acar et al. (18) reported that 144 patients with low-risk PCa who were followed for at least one year were divided into brachytherapy, RRP, and active surveillance groups, and their QoL was examined. All patients were asked to complete the European Organization for Research and Treatment of Cancer-quality of life questionnaire (EORTC-QLQ)-C30, EORTC-QLQ-prostate module 25, IIEF-5 and ICIQ-SF scales at baseline

and 12 months. During the follow-up periods, patients who received brachytherapy treatment had significantly lower QoL scores in terms of urinary and sexual function. In the RLRP group, significant changes were observed in sexual function, urinary incontinence, and erectile dysfunction parameters. The deterioration in sexual function was found to be 71% in the RLRP arm and 59% in the brachytherapy arm. It was found to be 30% in the active surveillance arm. However, in the measurements of QoL, no significant decrease in QoL scores was found among the RLRP, brachytherapy and AS groups during the follow-up period (18).

Study Limitations

The study's limitations concern the general use of the EPIC questionnaire form, which is used by urologists and oncologists, but it does not seem to have found adequate space yet. This situation can be explained by the large number of questions and the advanced age of the patient. The large number of questions in the EPIC questionnaire may make it difficult for some elderly or debilitated patients who have difficulty maintaining concentration and complying with the questionnaire. In addition, a pilot study was not conducted in our study.

Conclusion

The Turkish validity and reliability study of the EPIC questionnaire form was developed to reflect the original version. It was adapted to Turkish culture and language. Since its reliability and validity have been established, it can be used to assess treatment-related QoL in Turkish-speaking PCa patients. In addition, it can be considered an objective reference to compare various treatment methods for PCa. The results obtained in this study are compatible with the original form, show equivalence with the Turkish version, and have sufficient reliability and high sensitivity.

Ethics

Ethics Committee Approval: Approval was obtained from Eskişehir Osmangazi University Ethics Committee (approval number: 02, date: 19.02.2015).

Informed Consent: Informed consent was obtained for all interviews.

Footnotes

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

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ORIGINAL RESEARCH
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Effects of Diabetes and Antidiabetics on the Obesity Paradox in Renal Cell Cancer: A Single-center Experience

Moustafa Elleisy[1], Heike Zettl[2], Desiree Louise Dräger[1], Oliver W. Hakenberg[1]

[1]Department of Urology, University Medical Center Rostock, Rostock, Germany
[2]Clinical Cancer Registry, University Medicine Rostock, Rostock, Germany

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

The prevalence of type 2 diabetes mellitus is increasing rapidly worldwide, and there is strong evidence suggesting that cancer incidence is increased in individuals with diabetes. In this study, the effects of different antidiabetic drugs and body weight on the treatment of renal cell carcinoma were investigated.

Abstract

Objective: To determine the effect of diabetes and anti-diabetic treatments on the obesity paradox in renal cell cancer (RCC). We report preliminary results from a single centre study.

Materials and Methods: We retrospectively collected data from 294 patients treated between 2018 and 2023 for radical nephrectomy (RN) or partial nephrectomy (PN) for RCC. Age at diagnosis, histopathological data (pathological T-stage, lymph node involvement), tumor size, body mass index, length of hospital stay, death, recurrence, as well as type 2 diabetes mellitus and antidiabetic drugs were recorded and analyzed. A total of 232 (81%) patients were non-diabetic and 55 (19%) were diabetic patients. Patient data were assessed for differences related to bodyweight and the use of antidiabetics.

Results: In the diabetic cohort, a higher age at diagnosis of RN was observed when comparing patients treated with dipeptidyl peptidase-4 inhibitors to those treated with sodium glucose cotransporter 2 inhibitors (81 vs. 59 years, $p<0.01$), as well as when comparing patients treated with metformin to those treated with sulfonylureas (SU) (67 vs. 81 years, $p<0.05$). Furthermore, in diabetic patients with PN, compared to those treated with insulin, treated with metformin, no deaths occurred, which was significant (0% vs. 50%, $p<0.05$). The length of stay after PN for diabetic patients treated with metformin was significantly shorter than that of diabetic patients treated with insulin or SU ($p<0.05$).

Conclusion: In our study, an obesity paradox was observed for obese patients with RCC. However, the beneficial effects of certain antidiabetics should be considered as a potential cause of this paradox.

Keywords: Renal cell cancer, pathological outcomes, diabetes, metformin, antidiabetics

Introduction

Renal cell carcinoma (RCC) accounts for 3% of all cancer incidence and is the 14th most prevalent oncological disease worldwide (1). In Europe, 138,611 diagnoses of RCC and 54,054 deaths were reported in 2020, with the deaths accounting for 30% of all RCC-related deaths worldwide. An increase in the RCC incidence rate in Europe was reported between 1990 and 2013, reflecting a 23% increase in the age-standardized incidence rate per 100,000 people (1).

Diabetes Mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (2). [The specific disease] is emerging as one of the most prevalent human diseases after cardiovascular

Correspondence: Moustafa Elleisy MD, Department of Urology, University Medical Center Rostock, Rostock, Germany
E-mail: elleisy.moustafa@gmx.at **ORCID-ID:** orcid.org/0000-0001-7375-5357
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conditions and is the sixth leading cause of death worldwide (World Health Organization - WHO). The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly worldwide (2). In 2019, 11% of women and 12.3% of men in Germany had a documented diagnosis of diabetes, one of the highest prevalence rates in Europe. T2DM accounts for about 90% of the total diabetes cases and its prevalence increases with age (3).

There is strong evidence suggesting that cancer incidence is increased in patients with T2DM (2,4). The pathophysiological hypotheses to explain the link between diabetes or hyperglycemia and cancers rely on biological, particularly endocrine mechanisms involving insulinresistance. Indeed, in the genesis of T2DM, reduced insulin sensitivity plays a key role, inducing compensatory hyperinsulinaemia, with an increased level of circulating insulin-like growth factors (IGF). These are well known to stimulate cell proliferation in many organs, including the liver, pancreas, colon, ovary, and breast, all of which are organs with an increased risk of cancer in type 2 diabetic patients (2). T2DM may be considered a specific and independent risk factor for various forms of cancer, due to its particular metabolic characteristics of glucose intolerance and hyperinsulinemia (2,3).

Diabetes has also been significantly linked with an elevated risk of kidney cancer in a meta-analysis of 11 cohort studies (3). Women were observed to have a slightly greater risk ratio (3). Diabetes has also been associated with higher mortality after cancer, and survivors of some cancers have a higher incidence of developing subsequent diabetes (5). Finally, cancer and diabetes treatments have been shown to influence the relationship between diabetes and cancer-associated outcomes (5).

The Effect of Antidiabetic Drugs on Cancer Risk

Metformin is an oral biguanide that is well established as the first-line treatment of T2DM (6). In a retrospective study, a significant association between metformin use and decreased RCC risk was described. Moreover, a decreased risk of RCC was reported with increased cumulative duration of metformin use (inverse dose-response pattern) (1).

Sulfonylureas (SU) are among the oldest drugs available for the treatment of T2DM. Although SU have been in clinical use for many years, their associations with cancer remain uncertain (6).

There was initially a concern that exogenous insulin was associated with an increased risk of cancer (5). After methodological concerns were carefully considered, however, more recent epidemiological studies have not consistently found an association between insulin, particularly insulin analogues, and cancer (5).

The role of thiazolidinediones (TZDs) in cancer treatment and prevention is uncertain (7). TZDs have been shown to be associated with approximately 20% to 40% lower prostate-specific antigen levels among patients with prostate cancer (6).

Incretin-based drugs include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (5). While there were initial concerns about an increased risk of pancreatic cancer with incretin-based drugs and medullary thyroid cancer with GLP-1 receptor agonists, these effects have not been confirmed in recent studies (5).

Sodium glucose cotransporter 2 inhibitors (SGLT2-I) are the newest class of oral diabetes medications (5). In animal models, certain SGLT2-I have been associated with mammary, adrenal, testicular, and renal neoplasms. As SGLT2-I are relatively new in clinical practice, their effects on cancer incidence and mortality should be further elucidated in large-scale studies, with longer durations of follow-up (3,5,6).

Obesity Paradox

Obesity is a well-known risk factor for RCC incidence. Nonetheless, in several studies, a favourable RCC prognosis in terms of survival benefit was reported in patients with elevated body mass index (BMI), and this phenomenon is known as the "obesity paradox" (7). According to this paradox, obesity is associated with an increased risk of developing RCC, but after treatment, obese patients have better survival rates than their non-obese counterparts (7). The exact mechanisms behind this paradox are not fully understood, but might include differences in tumour biology, immune response or treatment response in obese patients (1). The risk of RCC was shown to increase by 4% to 6% per unit increase in BMI (per 1 kg/m^2). Early adult obesity and especially abdominal obesity (observed more frequently in males than females) have also been identified as risk factors of RCC (1).

The aim of this retrospective analysis was to assess the association between antidiabetic treatments as a potential protective factor and the obesity paradox in RCC, in patients treated at the Department of Urology, University of Rostock, between January 2018 and December 2023.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University Medical Center Rostock (approval number: A 2023-0174, date: 24.01.2025). The need for informed consent was waived by the Ethics Committee of the University Medical Center Rostock.

Institutional review board approval was obtained before the initiation of the study. This study included a total of 294 patients treated for nmRCC. We identified all patients newly

diagnosed with RCC at our institution according to the Clinical Cancer Registry (CCR) using the International Classification of Diseases, 10th Revision code C64 for renal cancer. The CCR also provided information on age at diagnosis and tumor stage (TNM classification). The OPS Classification of Interventions and procedures version 2023, an administrative dataset covering all procedural episodes in German hospitals, was used to identify specific procedures. The 5-554 code was used to identify patients who underwent radical nephrectomy (RN) and the 5-553 code was used for partial nephrectomy (PN). Patients who underwent either open or laparoscopic surgery were included. Age at diagnosis, histopathological data (pathological T-stage, lymph node involvement), tumor size, BMI, length of hospital stay (LOS), death, and recurrence were recorded and analyzed. T2DM status was considered, if patients were under medical treatment prior to admission for surgical treatment. Patients with incomplete data were excluded.

Statistical Analysis

We analyzed a BMI-based cohort according to the WHO's BMI categories: normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), obesity class 1 (BMI 30-34.9), obesity class 2 (BMI 35-39.9), and obesity class 3 (BMI ≥40). All patients were newly diagnosed with RCC at our institution between 1 January 2018 and 31 December 2023. Data were analyzed using SPSS (Version 29, IBM Corp., Armonk, NY, USA). Categorical variables were reported as absolute numbers and proportions, while continuous variables were reported as medians with interquartile ranges or means with standard deviations as appropriate. Comparisons of categorical variables between the cohorts were made using Pearson's chi-squared test, and Fisher's exact test and were reported according to the smallest theoretical frequency, with Fisher's exact test used if less than 5 and Pearson's chi-squared test if greater than 5. According to the distribution of the data, assessed by the Kolmogorov-Smirnov test, the t-test and the Mann-Whitney U test were used for group comparisons for continuous variables. A one-way ANOVA with Bonferroni multiple comparison test, was used for continuous variables. A p-value of $p<0.05$ was considered statistically significant.

Results

A total of 287 (98%) patients were included in the study, while 7 (2%) were excluded due to missing diabetes status and/or incomplete data, as shown in Figure 1. Of the included patients, 232 (81%) were non-diabetic and 55 (19%) were diabetic. Antidiabetic treatments included metformin in 16 (29%) patients, insulin in 15 (27%) patients, diet in 9 (16%) patients, SLGT2-I in 6 (11%) patients, SU in 3 (5,5%) patients, DPP-4 in 3 (5,5%) patients, and glinide in 1 (1,8%) patient. In Figure 2, the patients are shown with their respective BMI cohorts.

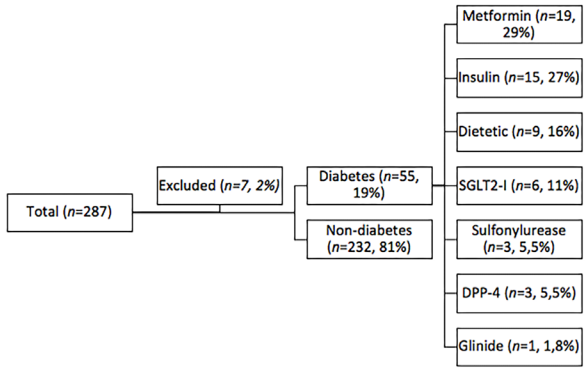

Figure 1. A graphic showing the treatment of patients and their antidiabetic medication

SGLT2-I: Sodium-glucose cotransporter type 2 inhibitors, DPP-4: Dipeptidyl peptidase-4 inhibitor

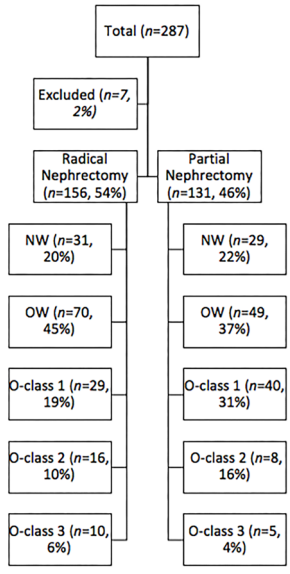

Figure 2. A graphic showing the patients with their respective BMI cohorts

BMI: Body mass index, NW: Normal weight (BMI: 18.5-24.9 kg/m²), OW: Overweight (BMI 25-29.9 kg/m²), O: Obesity (class 1: BMI 30-34.9 kg/m², class 2: BMI 35-39.9 kg/m², class 3: BMI ≥40 kg/m²)

Radical Nephrectomy

Overall, 156 patients underwent RN. Of these, 124 (79%) were non-diabetics and 32 (21%) were diabetics (Table 1). Fourteen patients (43.8%) were treated with metformin, 9 (28%) with insulin, 9 (28%) with dietary measures, 2 (6.3%) with SGLT2-I, 3 (9.4%) each with DPP-4 or SU, and only 1 (3.1%) patient with glinide. Additionally, a higher age at diagnosis was found in the diabetic cohort when comparing DPP-4 and SGLT2-I (81 vs. 59 years, $p<0.01$, as shown in Table 2), as well as when comparing metformin and SU (67 vs. 81 years, $p<0.05$). Of note, the diabetic cohort did not have a significantly higher BMI ($p>0.05$, data not shown).

Table 1. Descriptive characteristics for the cohort of 156 patients treated with radical nephrectomy between January 2018 and December 2023

Variables	NW	OW	O-class 1	O-class 2	O-class 3	p-value
Number of patients, n (%)	31 (19.9)	70 (44.9)	29 (18.6)	16 (10.3)	10 (6.4)	
Diagnosis age, median (IQR), years	69 (59-79)	68 (62-77)	65 (59-70)	63 (51-76)	59 (56-65)	0.4[a,b]/0.6[c]/0.3[d]
Gender, n (%)						
Female	15 (48)	23 (33)	7 (24)	7 (44)	4 (40)	0.1[a]/0.5[b,d]/0.8[c]
Male	16 (52)	47 (67)	22 (76)	9 (56)	6 (60)	
Diabetes, n (%)	4 (13)	14 (20)	5 (17)	5 (31)	4 (40)	0.5[a]/0.9[b]/0.3[c]/0.1[d]
Length of stay, mean (SD), days	7.7 (3.7)	7.9 (5.7)	7.9 (4.9)	6.1 (1)	7.5 (2.2)	0.4[a]/0.5[b]/0.09[c]/0.7[d]
Histology, n (%)						
Clear cell RCC	21 (68)	54 (77)	23 (79)	15 (94)	8 (80)	0.9[a]/0.1[b]/0.5[c]/0.7[d]
Papillary RCC	1 (3)	9 (13)	4 (14)			
Chromophobe RCC	3 (10)	3 (4)		1 (6)	1 (10)	
Sarcoamtoid RCC	2 (6)					
Others	2 (6)	4 (6)	2 (7)		1 (10)	
Unknown	1 (3)					
Pathological tumor stage, n (%)						
pT1a	3 (10)	6 (9)	1 (3)	4 (25)	1 (10)	0.2[a,c]/0.1[b]/0.09[d]
pT1b		9 (13)	5 (17)	2 (13)	2 (20)	
pT2a	4 (13)	5 (7)	2 (7)		1 (10)	
pT2b	1 (3)	2 (3)				
pT3a	18 (58)	42 (60)	19 (66)	9 (56)	4 (40)	
pT3b	3 (10)	6 (9)	1 (3)	1 (6)		
pT3c			1 (3)		1 (10)	
Unknown	2 (6)				1 (10)	
Nodal tumor stage, n (%)						
N0	23 (74)	56 (80)	27 (93)	14 (88)	9 (90)	0.7[a]/0.1[b]/0.2[c,d]
N1	6 (19)	9 (13)	1 (3)			
NX	2 (6)	5 (7)	1 (3)	2 (13)	1 (10)	
Recurrence, n (%)	3 (10)	12 (17)	2 (7)	2 (13)	3 (30)	0.4[a]/0.9[b,c]/0.1[d]
Death, n (%)	10 (32)	20 (29)	4 (14)	6 (38)	2 (20)	0.7[a]/0.09[b]/0.7[c,d]
Tumor site, n (%)						
Right	15 (48)	35 (50)	19 (66)	11 (69)	4 (40)	0.9[a,d]/0.2[b,c]
Left	16 (52)	35 (50)	10 (34)	5 (31)	6 (60)	
Tumor size, mean (SD), cm	7.8 (4.5)	7.1 (3.1)	6.7 (2.3)	5.8 (2.2)	6 (3.4)	0.3[a,d]/0.2[b]/0.07[c]

(*) Statistically significant difference. (a) NW vs. OW, (b) NW vs. O-Class 1, (c) NW vs. O-Class 2, (d) NW vs. O-Class 3, BMI: Body mass index, RCC: Renal cell carcinoma, NW: Normal weight (BMI: 18.5-24.9 kg/m²), OW: Overweight (BMI 25-29.9 kg/m²), O: Obesity (class 1: BMI 30-34.9 kg/m², class 2: BMI 35-39.9 kg/m², class 3: BMI ≥40 kg/m²), IQR: Interquartile range, SD: Standard deviation

Table 2. Descriptive characteristics of the diabetes cohort of 29 patients treated with radical nephrectomy between January 2018 and December 2023

Variables	Metformin	Insulin	DPP-4	SU	p-value
Number of patients, n (%)	14 (48)	9 (31)	3 (10)	3 (10)	
Diagnosis age, median (IQR), years	67 (63-76)	65 (63-81)	59 (57-62)	81 (78-84)	0.7[a,d]/0.08[b]/<0.05*[c]/0.09[e]/<0.01*[f]
Gender, n (%)					
Female	4 (29)	3 (33)		2 (67)	0.9[a]/0.5[b,c,d,e]/0.3[d,e]/0.4[f]
Male	10 (71)	6 (67)	3 (100)	1 (33)	
BMI, mean (IQR), kg/m^2	30 (27-35)	33 (28-38)	35 (23-41)	27 (24-28)	0.3[a,b,f]/0.2[c]/0.8[d]/0.1[e]
Length of stay, mean (SD) days	6.7 (2)	8.3 (4.8)	7.3 (1.5)	6.3 (1.5)	0.3[a]/0.6[b]/0.8[c]/0.7[d]/0.5[e,f]
Histology, n (%)					
Clear cell RCC	11 (79)	8 (89)	3 (100)	3 (100)	0.3[a]/0.8[b,c]/0.2[d,e]/0.9[f]
Papillary RCC		1 (11)			
Chromophobe RCC	1 (7)				
Others	2 (14)				
Pathological tumor stage, n (%)					
pT1a		1 (11)		1 (33)	0.5[a,e]/0.1[b,d]/0.2[c]/0.3[f]
pT1b	3 (21)	2 (22)			
pT2a	1 (7)		1 (33)		
pT2b					
pT3a	8 (57)	6 (67)	1 (33)	2 (67)	
pT3b	2 (14)				
pT3c			1 (33)		
Nodal tumor stage, n (%)					
N0	12 (86)	9 (100)	3 (100)	3 (100)	0.5[a]/0.8[b,c]/0.9[d,e,f]
N1	1 (7)				
NX	1 (7)				
Recurrence, n (%)	5 (36)	3 (33)	0	0	0.9[a,f]/0.5[b,c,d,e]
Death, n (%)	5 (36)	3 (33)	0	2 (67)	0.9[a]/0.5[b,c,d,e]/0.4[f]
Tumor site, n (%)					
Right	9 (64)	5 (56)	2 (67)	3 (100)	0.9[a,b,d,f]/0.5[b,c,e]
Left	5 (36)	4 (44)	1 (33)		
Tumor size, mean (SD), cm	8.3 (3.8)	6 (2.9)	6.6 (3.2)	6.7 (2.5)	0.1[a]/0.5[b,c]/0.8[d]/0.7[e]/0.9[f]

(*) Statistically significant difference. (a) Metformin vs. Insulin, (b) Metformin vs. DPP-4, (c) Metformin vs. SU, (d) Insulin vs. DPP-4, (e) Insulin vs. SU, (f) DPP-4 vs. SU, BMI: Body mass index, RCC: Renal cell carcinoma, SGLT2-I: Sodium-glucose cotransporter type 2 inhibitor, DPP-4: Dipeptidyl peptidase-4 inhibitor, SU: Sulfonylureas, IQR: Interquartile range, SD: Standard deviation

Table 3. Descriptive characteristics for the cohort of 131 patients treated with partial nephrectomy between January 2018 and December 2023

Variables	NW	OW	O-Class 1	O-Class 2	O-Class 3	p-value
Number of patients, n (%)	29 (22.1)	49 (37.4)	40 (30.5)	8 (6.1)	5 (3.8)	
Diagnosis age, median (IQR), years	75 (64-81)	69 (62-77)	66 (61-74)	75 (62-80)	61 (59-65)	0.7[a]/0.4[b]/0.9[c]/0.3[d]
Gender, n (%)						
Female	12 (41.4)	16 (32.7)	10 (25)	4 (50)	2 (40)	0.4[a]/0.2[b]/0.7[c]/0.9[d]
Male	17 (58.6)	33 (67.3)	30 (75)	4 (50)		
Diabetes, n (%)						
Negative	24 (82.8)	38 (77.6)	33	5 (62.5)	1 (20)	0.7[a]/0.4[b]/0.1[c]/<0.001*[d]
Positive	5 (17.2)	10 (20.4)	(82.5)	2 (25)	1 (20)	
Unknown		1 (2)	5 (12.5) 2 (5)	1 (12.5)	3 (60)	
Length of stay, mean (SD), days	7.2 (3.6)	6.7 (2)	6.8 (2.7)	5.9 (1.5)	9 (6.7)	0.9[a]/0.7[b]/0.3[c]/0.4[d]
Histology, n (%)						
Clear cell RCC	18 (62)	28 (57.1)	32 (80)	8 (100)	4 (80)	0.6[a]/0.1[b]/0.2[c]/0.5[d]
Papillary RCC	8 (27.6)	16 (32.7)	3 (7.5)			
Chromophobe RCC	2 (6.8)	1 (2)	4 (10)		1 (20)	
Others	1 (3.4)	3 (6.1)	1 (2.5)			
Unknown		1 (2)				
Pathological tumor stage, n (%)						
pT1	1 (3.4)	1 (2)				0.7[a]/0.6[b,c]/0.4[d]
pT1a	15 (51.7)	31 (63.3)	20 (50)	7 (87.5)	1 (20)	
pT1b	5 (17.2)	6 (12.2)	10 (21)		3 (60)	
pT2			1 (2.5)			
pT2a	1 (3.4)					
pT3		1 (2)				
pT3a	5 (17.2)	5 (10.2)	7 (17.5)	1 (12.5)	1 (20)	
pT4		1 (2)	1 (2.5)			
Unknown	2 (6.9)	4 (8.2)	1 (2.5)			
Nodal tumor stage, n (%)						
N0	27 (93.1)	40 (81.6)	35 (87.5)	8 (100)	5 (100)	0.2[a]/0.6[b]/0.9[c,d]
N1			1 (2.5)			
NX	2 (6.9)	9 (18.4)	4 (10)			
Recurrence, n (%)	2 (6.9)	7 (14.3)	2 (5)	0	0	0.5[a]/0.9[b,c,d]
Death, n (%)	6 (20.7)	4 (8.2)	10 (25)	0	1 (20)	0.2[a]/0.7[b]/0.3[c]/0.9[d]
Tumor site, n (%)						
Right	12 (41.4)	22 (44.9)	17 (42.5)	5 (62.5)	3 (60)	0.8[a]/0.9[b]/0.4[c]/0.6[d]
Left	17 (58.6)	27 (55.1)	23 (57.5)	3 (37.5)	2 (40)	
Tumor size, mean (SD), cm	3.5 (2.2)	3.3 (2.4)	3.5 (1.3)	2.5 (0.6)	3.9 (1.7)	0.6[a,d]/0.9[b]/0.2[c]

(*) Statistically significant difference. (a) NW vs. OW, (b) NW vs. O-Class 1, (c) NW vs. O-Class 2, (d) NW vs. O-Class 3, BMI: Body mass index, RCC: Renal cell carcinoma, NW: Normal weight (BMI: 18.5-24.9 kg/m²), OW: Overweight (BMI 25-29.9 kg/m²), O: Obesity (class 1: BMI 30-34.9 kg/m², class 2: BMI 35-39.9 kg/m², class 3: BMI ≥40 kg/m²), IQR: Interquartile range, SD: Standard deviation

Table 4. Descriptive characteristics of the diabetes cohort of 22 patients treated with partial nephrectomy between January 2018 and December 2023

Variables	Metformin	Insulin	SGLT2-I	p-value
Number of patients, n (%)	12 (55)	6 (27)	4 (18)	
Diagnosis age, median (IQR), years	70 (64-77)	75 (56-84)	70 (63-79)	0.8[a]/0.9[b]
Gender, n (%)				
Female	2 (16.7)	3 (50)		0.3[a]/0.9[b]/0.2[c]
Male	10 (83.3)	3 (50)	4 (100)	
BMI, mean (IQR), kg/m^2	29 (25-31)	29 (22-36)	28 (26-29)	0.9[a]/0.5[b]/0.8[c]
Length of stay, mean (SD) days	5.3 (0.8)	8.7 (5.2)	8.7 (4.7)	<0.05*[a,b]/0.9[c]
Histology, n (%)				
Clear cell RCC	8 (66.7)			0.9[a]/0.6[b]/0.2[c]
Papillary RCC	2 (16.7)	6 (100)	3 (75)	
Chromophobe RCC	2 (16.7)		1 (25)	
Pathological tumor stage, n (%)				
pT1a	5 (41.7)	2 (33.3)	2 (50)	0.3[a]/0.6[b]/0.4[c]
pT1b	3 (25)	2 (33.3)		
pT2a	1 (8.3)			
pT3a	3 (25)	2 (33.3)	2 (50)	
Nodal tumor stage, n (%)				
N0	10 (83.3)			0.9[a,b,c]
NX	2 (16.7)	6 (100)	4 (100)	
Recurrence, n (%)	1 (8.3)	2 (33.3)	1 (25)	0.07[a]/0.5[b]/0.9[c]
Death, n (%)	0	3 (50)	1 (25)	<0.05*[a]/0.3[b]/0.6[c]
Tumor site, n (%)				
Right	6 (50)	4 (66.7)	1 (25)	0.7[a]/0.6[b]/0.5[c]
Left	6 (50)	2 (33.3)	3 (75)	
Tumor size, mean (SD), cm	3.7 (1.9)	3.9 (1.7)	3.4 (0.9)	0.8[a]/0.7[b]/0.6[c]

(*) Statistically significant difference. (a) Metformin vs. Insulin, (b) Metformin vs. SGLT2-I, (c) Insulin vs. SGLT2-I, BMI: Body mass index, RCC: Renal cell carcinoma, SGLT2-I: Sodium-glucose cotransporter type 2 inhibitor, IQR: Interquartile range, SD: Standard deviation

Partial Nephrectomy

Overall, 131 patients underwent PN. Of these, 108 (82%) were non-diabetic and 23 (18%) were diabetic (Table 3). Twelve patients (52%) were treated with metformin, 6 (26%) with insulin, 4 (17%) with SGLT2-I, and 1 (4%) with a DPP-4 inhibitor. A significant difference in T2DM rates was found between normal weight and obesity class 3, but this is most likely due to a lack of data (Table 4). Interestingly, in the diabetic cohort undergoing PN, patients treated with metformin showed a significantly lower death rate compared to those treated with insulin (0% vs. 50%, p<0.05). Furthermore, the LOS for diabetic patients treated with metformin was significantly shorter than that of diabetic patients treated with insulin or SU (p<0.05). No differences in terms of pathological features or other baseline characteristics were found. Here, as well, the diabetic cohort did not show a significantly higher BMI (p>0.05, data not shown).

Discussion

In this study, RCC patients were differentiated according to body weight and associated antidiabetic medications. For RN, a significantly higher age at diagnosis, was observed in the diabetic cohort, when comparing DPP-4 inhibitors and SGLT2-I inhibitors. Furthermore, patients with diabetes treated with metformin experienced no deaths, a result significantly different from those taking insulin. This corresponds to studies, which have shown that diabetics treated with metformin have a reduced risk of PCa by 44% (8). A Scottish study reported that people with diabetes taking metformin had a 23% lower overall risk of cancer compared to those not taking metformin. The study observed and reported a risk reduction for the longest metformin treatment period (8).

A number of factors have been proposed to contribute to the increased risk of cancer development and mortality in the setting of obesity and T2DM. These include hyperglycemia,

insulin resistance, hyperinsulinemia, increased IGF-1 levels, dyslipidemia, inflammatory cytokines, increased leptin, and decreased adiponectin (6). Insulin resistance in metabolic tissues, such as fat, liver, and skeletal muscle, results in increased production of insulin from pancreatic β-cells, which leads to circulating hyperinsulinemia. Pancreatic β-cells eventually decompensate, and hyperglycemia develops. Hyperglycemia also develops as a result of increased hepatic glucose production secondary to insulin resistance in the liver and decreased uptake into skeletal muscle and adipose tissue (6). Endogenous insulin acting on the liver increases IGF-1 synthesis and leads to decreased concentrations of IGF-binding proteins 1 and 2, thus potentially increasing local concentrations of bioavailable IGF-1. Adipose tissue inflammation occurs with insulin resistance, leading to the production of cytokines and changes in the circulating concentrations of adipokines, such as increased leptin and decreased adiponectin (6).

The mechanism by which obesity improves the survival of patients with RCC is not well understood. Patients with higher BMI may adequately preserve their fat and muscle mass, thus allowing a better nutritional status and a potential survival advantage, delaying the onset of cachexia. Another possible explanation is that RCCs arising in obese patients may be more indolent than those in normal-weight patients; they have favorable clinical and pathologic conditions at diagnosis when compared with normal-weight patients (lower stage, lower Fuhrman grade, smaller tumor size and absence of symptoms and distant metastasis) (9,10). Although patients with obesity are characterized by a higher rate of tumor growth, they may have more indolent tumors, probably because they are diagnosed at earlier stages as they are at a higher likelihood of being screened for other diseases (10).

An alternative explanation for the obesity paradox may be a different gene expression involving fatty acid metabolism genes. Fatty acid synthase (FASN) is a gene that regulates de novo biosynthesis of fatty acids, an essential process for tumor growth. FASN is downregulated in patients with obesity, and higher FASN expression is associated with worse survival. The upregulation of FASN gives cancer cells a survival advantage, making it a potential metabolic oncogene. Lastly, obese and normal-weight patients could have different transcriptomic profiles: tumors of patients with obesity have a different molecular profile than those of normal-weight patients. The molecular profile of tumours of obese patients is characterized by the upregulation of genes associated with hypoxia, angiogenesis and epithelial-mesenchymal transition (10). Interestingly, Li et al. (11) also found an obesity paradox for lung cancer operations, where patients with higher BMI showed a significantly better long-term survival rate. Possible reasons for this are that obese patients have a greater ability to store nutrients to resist surgical interventions compared to normal/underweight patients. The protective effects of peripheral adipose tissues have been demonstrated in previous investigations, contributing to a better prognosis for surgical patients (11). Another conceivable cause could be that an increasing number of people are becoming obese at a young age with strong physiological functions and better recovery capabilities. Because obese patients are considered at higher risk of cardiovascular disorders, they are generally treated at an early age with medicines to control blood pressure and prevent hyperglycemia. This situation may be another important reason for the obesity paradox (11).

We hypothesize that obese patients usually present with diabetes as part of a metabolic syndrome. It is possible, however, that the use of metformin and SGLT2-I, for example, suppresses the mTOR signaling pathway by reducing the circulating levels of insulin and IGF-1 in peripheral blood and activating liver kinase B1 signaling pathways, thus leading to decreased cell proliferation, reduced protein translation, and lower insulin levels (7). Nevertheless, the obesity paradox has not yet been fully clarified.

BMI is used in most studies that evaluate the influence of obesity on RCC (12). However, BMI has limitations that impact its utility in elucidating the biology underlying the impact of obesity on RCC (12). BMI is an imperfect surrogate for biologically distinct body composition compartments, such as visceral adipose tissue and muscle mass, and inferences about the global metabolic state based on BMI are incomplete (12). However, in recent studies, the BMI range associated with the lowest risk of mortality varies depending on secular trends, ethnicity, and population (12). Furthermore, adiposity traits are known to be sexually dimorphic. Females have higher single nucleotide variants-based (SNV-based) heritability for waist-to-hip ratio (WHR) and larger effect sizes in more than 90% of WHR (adjusted for BMI)-associated SNVs, compared with males. Since female adiposity distribution is drastically different from that in males, the relatively higher abdominal obesity in males may explain the sex-specific difference in risk (13). A previous study found that the BMI-all-cause mortality association weakened with older age. A possible reason why the BMI–all-cause mortality association attenuates might be that nutritional reserves become more important with age. Another cause could be reverse causality, as there is increased prevalence of major disease among older individuals, some of which impact BMI through muscle mass loss (13). Body composition can be measured indirectly using anthropometric measurements, such as BMI and abdominal circumference, or directly using computed tomography or dual-energy X-ray absorptiometry (12).

However, research on the relationship between diabetes and cancer risk is limited. Most studies have poor sensitivity to detect small associations, especially for specific cancer types. The use of various antihyperglycemic drugs in diabetic patients also complicates research, as adjustments to medication over time make it challenging to evaluate long-term outcomes (3). Yet the link between diabetes and anti-diabetic medication, especially metformin, is compelling and well worth further exploration.

The prevention and early detection of cancer in diabetic patients should be a top priority in clinical practice. Additionally, hyperglycemia may create an environment that favors cancer cell growth. Healthcare providers should follow certain guidelines for the care of diabetic individuals, including medical therapy and regular cancer screenings based on each patient's unique risk factor profile. Through these measures, the early detection of cancer can be prioritized, leading to more effective treatment and improved outcomes for diabetic patients (3).

Many studies suggest a potential positive effect of certain antidiabetics; however, prospective studies are needed to validate these findings. Currently, the lack of large, randomized controlled trials makes it difficult to provide a general recommendation. Nevertheless, for diabetic patients with RCC, one could consider using metformin and SGLT2-I rather than DPP-4 or SU.

Study Limitations

This study is limited by its retrospective nature and single-center data collection, which restricts the generalizability of the findings. Other limitations are the relatively low number of diabetic patients and the lack of long-term follow-up. Further investigations with larger cohorts will be needed to establish the prognostic significance of DM and anti-diabetic medication in cancer patients. Although BMI is largely used to replace the term 'obesity' in clinical practice, BMI does not effectively reflect body fat distribution. Other parameters describing body fat distribution, such as abdominal circumference and subcutaneous fat thickness, may be included in future clinical trials to better assess body fat.

Conclusion

In this study, no significant differences were found regarding the obesity paradox in RCC. However, the findings indicate that certain antidiabetic treatments have beneficial effects on RCC for both RN and PN.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University Medical Center Rostock (approval number: A 2023-0174, date: 24.01.2025).

Informed Consent: The need for informed consent was waived by the Ethics Committee of the University Medical Center Rostock.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.L.D., O.W.H., Concept: M.E., Design: M.E., Data Collection or Processing: H.Z., M.E., Analysis or Interpretation: M.E., Literature Search: M.E., Writing: M.E.

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CASE REPORT
General Urology

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Brunn Cyst: A Rare Cause of Bladder Outlet Obstruction

Siddanagouda B. Patil, Santosh Patil, Vinay S. Kundargi, Basavesh S. Patil, Manoj K. Vaidya

BLDE (Deemed To Be University), Shri B. M. Patil Medical College Hospital and Research Centre, Department of Urology, Bijapur, India

Abstract

Von Brunn cysts are formed by pinching off of epithelial nests from urothelial buds and rarely cause bladder outlet obstruction, with only 10 such cases reported in the literature. A young man presented with new-onset obstructive voiding symptoms. Cystoscopy confirmed the ultrasound and computed tomography findings of a midline cystic lesion at the bladder neck, above the prostate parenchyma, located anteriorly spanning from 11 to 1 o'clock. A possible ball valve effect of the cyst at the bladder neck was causing obstruction. Transurethral reroofing and cyst resection resulted in complete resolution of the voiding symptoms.

Keywords: Bladder outlet obstruction, Von Brunn cyst, bladder neck cyst, endourology, pathology, radiology

Introduction

Bladder outlet obstruction is mostly attributable to benign prostatic hyperplasia (BPH) in elderly men and urethral stricture disease in young and middle-aged populations. Israel Franco, in 1988, first reported Brunn's cyst as a cause of bladder neck obstruction in a young male (1). These cysts form as a result of pinching off of epithelial nests from urothelial buds. They are seldom encountered in the bladder neck region, and when large, they may be a rare cause of bladder outlet obstruction. Von Brunn cysts are commonly found in the trigone but are not always visible on endoscopy or imaging. Histologically, they are characterized by solid nests of benign urothelial cells sequestered in the lamina propria or submucosa (2). Von Brunn's cyst causing bladder outlet obstruction is an infrequent entity, and less than 10 such cases have been reported in the literature till date, all of which were described in males.

Case Presentation

A healthy man in his mid-30s presented with recent onset predominantly obstructive voiding symptoms. He complained of weak stream, intermittency, incomplete emptying, hesitancy, nocturia, and occasional burning micturition in the past 2 months. His International Prostate Symptom score was 13 and his bother score was 4. No history of diabetes, hypertension, smoking, previous surgery or catheterization. The patient had a normal external urethral meatus, and systemic examination, including a focused neurological assessment, revealed no abnormality. Written informed consent was obtained from the patient prior to publishing the case-related information in this case report.

Urinalysis, urine culture, and renal function tests were normal. Uroflowmetry revealed a peak flow rate of 6 mL/s and an average flow rate of 2.7 mL/s in a voided volume of 279 mL.

Ultrasound of the kidneys, ureter, and bladder (Figure 1A) showed a round cystic lesion 1.5. 1 cm noted within the bladder, near the neck, without any prostatomegaly or hydronephrosis. However, the patient had an elevated post-void residual volume of 150 mL (Pre void- 450 mL).

Computed tomography (Figure 1B, C) showed a well-defined non-enhancing midline cystic lesion in the bladder neck region measuring 1.9*1.8*1.3 cm without any evidence of a solid enhancing component or calcification. The upper tracts were essentially normal.

The excretory phase of contrast-enhanced computed tomography, which showed a cystic lesion seen as a filling defect in the bladder neck region, helped us to rule out the possibility of an ectopic ureter with ureterocele. We proceeded with a working diagnosis of bladder neck or prostatic cyst. During cystoscopy, a normal prostatic urethra and intravesical

Correspondence: Manoj K. Vaidya MD, BLDE (Deemed To Be University), Shri B. M. Patil Medical College Hospital and Research Centre, Department of Urology, Bijapur, India
E-mail: vaidyamk@gmail.com **ORCID-ID:** orcid.org/0000-0002-5448-1327
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extension of the cystic lesion above the prostatic parenchyma helped us confirm the diagnosis of bladder neck cyst- "Von Brunn cyst".

Cystourethroscopy demonstrated a normal anterior and posterior urethra, non-obstructing prostate, with a bulge/spherical cyst at the bladder neck located anteriorly spanning from 11 to 1 o' clock position (Figure 2A). This cyst obstructs the bladder outflow possibly by a ball valve effect. The bladder wall showed mild trabeculation with normal urothelium and ureteric orifices. Transurethral reroofing and resection of the bladder neck cyst were performed, and a per urethral Foley catheter was maintained for 48 h.

Histopathological examination revealed few cystic dilated glands lined by transitional epithelium, along with chronic inflammatory cells in the lamina propria and foci of lymphocytic aggregates at places (Figure 2B). These features are suggestive of chronic non-specific inflammation with Cystitis Glandularis.

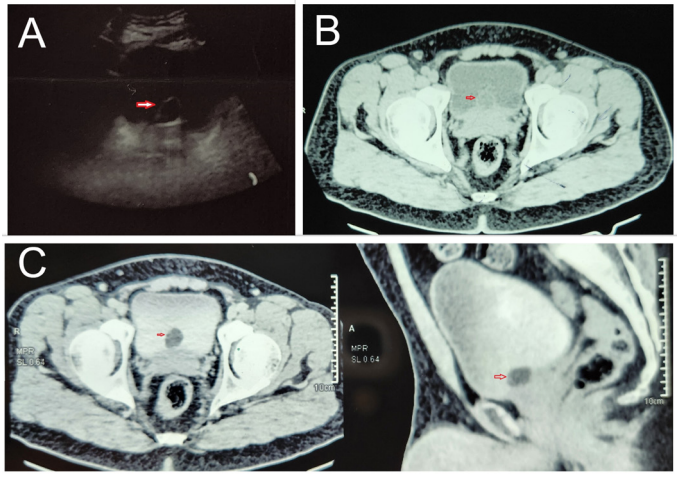

Figure 1. A. Ultrasound image showing a small cystic lesion (arrow) in the bladder neck region above the prostate. B. Midline cystic lesion measuring 1.9*1.8*1.3 cm at the level of the urinary bladder neck on plain computed tomography (CT). C. Contrast-enhanced CT showing bladder neck cyst as a filling defect, without any evidence of a solid-enhancing component or calcification

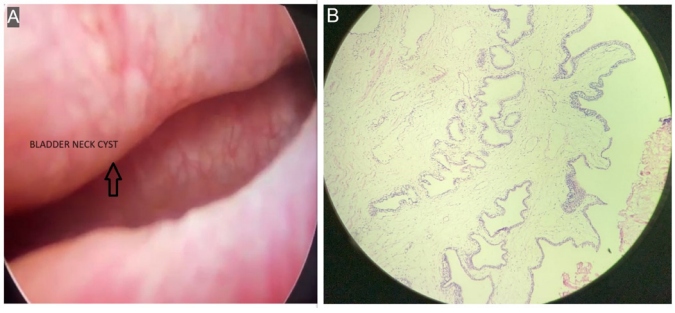

Figure 2. A. Cystoscopic evaluation of the patient's anterior cyst seen at the bladder neck. B. Histopathological microscopic image showing few cystic dilated glands lined by transitional epithelium along with chronic inflammatory cells and foci of lymphocytic aggregates in the lamina propria

At 1-month follow-up, the patient's voiding symptoms had resolved completely. There was no postvoid residual urine volume on ultrasound imaging. Uroflowmetry showed significant improvement with a peak flow rate of 30 mL/s and an average flow rate of 19 mL/s in a voided volume of 210 mL.

Discussion

This patient had a rare cause of benign lower urinary tract obstruction attributable to Brunn's cyst in the bladder neck, unlike commonly encountered causes like BPH in middle-aged or elderly patients and stricture in the young. A literature search revealed around 9 such cases of bladder neck cysts causing obstructive lower urinary tract symptoms, most of which were young or middle-aged males (Table 1). Further, as observed in similar cases reported in the literature, the lower urinary tract symptoms disappeared following transurethral resection of the cyst, thereby suggesting that a possible ball valve effect of the cyst at the bladder neck was responsible for the obstruction. Ultrasonography and endoscopy are sufficient to diagnose Brunn's cyst. However, other imaging modalities like intravenous urography or computed tomography, as performed in our case, may aid in the diagnosis (3).

The differential diagnosis of cystic lesions near the bladder neck includes prostatic cysts and ureterocele. Rarely, inflammatory conditions of the bladder-like cystitis cystica may lead to small filling defects in the bladder wall, which, under rare circumstances, manifest as large cystic lesions. Prostatic cysts are usually intraparenchymal and tend to originate from posterior structures like prostatic utricle or ejaculatory duct. Although rare, these infra-vesical cystic lesions of the prostate may be associated with lower urinary tract symptoms (4). Brunn's cyst in our case was located anteriorly at the bladder neck and above the prostatic parenchyma.

The other important diagnosis to be considered is ureterocele resulting from ectopic ureteric insertion. This can also appear as a cystic lesion near the neck of the bladder. However, ureteroceles are mostly congenital, associated with duplex collecting systems, and present at an early age (5). The von Brunn cyst is a benign condition with no reported recurrence in the current literature and needs no long-term follow-up.

Conclusion

Brunn's cyst should be considered as a rare benign cause of new-onset obstructive lower urinary tract symptoms in young patients, which can cause obstruction at the bladder neck by the ball valve effect. Ultrasound and computed tomography will aid in the diagnosis of this condition, which can be confirmed during cystoscopy. Transurethral reroofing and resection resulted

Table 1. Cases of bladder neck cyst causing lower urinary tract symptoms reported in the literature. A summary of the case details and treatment is provided

	Cases reported in literature	Case details	Treatment
1.	**Brunn cyst as a cause of bladder outlet obstruction: a case report** Insuan and Insuan (6)	• 45-year-old male. • Cystic lesion at the bladder neck, approximately 1.6x1.7x2.0.	Transurethral resection of the bladder neck cyst.
2.	**Bladder outlet obstruction secondary to Brunn's cyst: A rare presentation in a young man** Baarimah et al. (7)	• 21-year-old male. • Brunn's cyst was confirmed on ultrasonography and magnetic resonance imaging.	Managed by endoscopic de-roofing of the cyst.
3.	**Brunn's cyst: A rare cause of lower urinary tract symptoms** Ilyas et al. (8)	• 53-year-old male. • A 7 mm × 8 mm, small, well-defined cystic lesion at the bladder neck. • Intravenous urography revealed a small filling defect in the region of the bladder neck.	Transurethral de-roofing and cyst resection.
4.	**Transurethral resection of an uncommon Brunn's cyst: A resolution for lower urinary tract symptoms** Dongsu et al. (9)	• 44-year-old male. • Ultrasonography revealed an isolated cystic lesion, 1.12×0.72×0.73 cm in dimensions, at the bladder neck.	Bruun's cyst located in the bladder neck was excised using a cystoscopic approach.
5.	**Bladder Outlet Obstruction Secondary to a Brunn Cyst** Grimsby et al. (3)	• 43-year-old male. • Renal and bladder ultrasound revealed a cystic structure in the bladder.	Transurethral unroofing and resection of cystic lesion.
6.	**Brunn cyst causes obstructive LUTS** Ren et al. (10)	• 37-year-old male. • Ultrasound of the kidneys, ureter, and bladder showed a 1.7 cm thin-walled midline cystic structure in the bladder neck, abutting the ureteric orifice.	Transurethral resection of bladder neck.
7.	**Bladder Neck Obstruction Secondary to Brunn's Cyst** Franco et al. (1)	• 29-year-old male. • Cystogram showing a thickened and heavily trabeculated bladder.	Mass drain and unroofed using transurethral resection loop.
8.	**Brunn's Cyst Induces Persistent Lower Urinary Tract Symptoms in a Young Man: A Case Report** Lindner et al. (11)	• 46-year-old male. • Sonographic and cystoscopic examination revealed a cystic lesion located at the bladder neck.	Transurethral reroofing and cyst resection.
9.	**Brunn's Cyst: A Rare Cause of Bladder Outlet Obstruction in a Young Man** Sailo and Sailo (12)	• 27-year-old male. • Bladder ultrasound showed a 1.4×1.2 cm cystic mass at the bladder neck.	Transurethral de-roofing and resection of the cystic mass were performed using resection loop.

in complete resolution of voiding symptoms. Considering the benign nature of this entity, no long-term follow-up is recommended.

Ethics

Informed Consent: Written informed consent was obtained from the patient prior to publishing the case-related information in this case report.

Footnotes

Authorship Contributions

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

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

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CASE REPORT
Pediatric Urology

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Xanthine Stones in an Infant: A Case Report and Clinical Insights

Siddanagouda B. Patil[1], Vinay S. Kundargi[1], Santosh Patil[1], Basavesh S. Patil[1], Manoj K. Vaidya[1], Gurushantappa S. Kadakol[2]

[1]BLDE (Deemed To Be University), Shri B. M. Patil Medical College Hospital and Research Centre, Department of Urology, Bijapur, India
[2]BLDE (Deemed To Be University), Shri B. M. Patil Medical College Hospital and Research Centre, Department of Anatomy, Bijapur, India

Abstract

Xanthinuria is a rare autosomal recessive condition characterised by increased urinary xanthine excretion resulting from a derangement in purine metabolism, accounting for only 0.1% of pediatric stones. Incidence of inherited xanthinuria lies in the range of 1:6,000 to 1:69,000. A male baby in the latter part of infancy presented with a history of recurrent episodes of abdominal pain, fever, vomiting for 4 months, and a recent history of passage of calculi. On evaluation, radiolucent calculi were noted in the left renal pelvis and in the bilateral distal ureters, causing hydroureteronephrosis. During initial cystoscopy, a posterior urethral valve was incidentally noted and fulgurated. Ureteroscopic lithotripsy in two sessions cleared the stone burden. Crystallographic analysis of the stone was suggestive of a xanthine stone. Selective genetic analysis for *XDH1* gene targeting exons 6F, 8F, 10F, 16F, 21F, 23F, was done on samples from the index case, first and second degree relatives. Interestingly, no mutations were recorded in the index case, but a mutation was noted in one first-degree relative and one second-degree relative, respectively, in exons 21F [c. 2211C>T (p. I737I)] and 8F [g. 682G>C (p. T202T)]. As only targeted gene analysis was done, the possibility of mutations in other exons of the *XDH1* gene cannot be ruled out. A complete metabolic workup along with stone analysis helps in the early diagnosis of metabolic conditions like xanthinuria, which can be further confirmed with genetic studies. Diet and lifestyle changes can help in preventing recurrence of stones and avoiding further renal damage.

Keywords: Endourology, general urology, pediatric urology

Introduction

Radiolucent calculi in children represent 5-10% of kidney stones in developed countries and 27% of pediatric urolithiasis in underdeveloped countries. The majority of these cases are uric acid stones followed by xanthine stones and 2,8-dihydroxyadenine stones (1). Xanthinuria is a rare autosomal recessive condition characterised by increased urinary xanthine excretion resulting from a derangement in the purine metabolism. Essentially, the last two steps of purine degradation involving the conversion of hypoxanthine to xanthine, and xanthine to uric acid are affected. This results in increased accumulation of hypoxanthine and xanthine and their subsequent excretion in the urine. Three forms of xanthinuria have been described based on distinct mutation loci: type I (xanthine dehydrogenase/oxidase deficiency), and type II (xanthine dehydrogenase and aldehyde oxidase deficiency) are collectively referred to as "classical xanthinuria". A third clinical type, associated with molybdenum cofactor deficiency (deficiency of sulfite oxidase and aldehyde oxidase), has also been described (2). Xanthinuria is a rare cause of urolithiasis in children, accounting for about 0.1% of pediatric stones (3). It is estimated that the incidence of xanthinuria, which is inherited, lies in the range of 1:6.000 and 1:69.000 (4). Common presentation in the pediatric age group is abdominal pain (44%), hematuria (38%), fever (15%), and other urinary tract infection associated symptoms (5).

Apart from the patients with hereditary xanthinuria, another group of individuals who are frequently affected by xanthine stones is patients with Lesch-Nyhan syndrome, on allopurinol therapy. Lesch-Nyhan syndrome causes developmental delay in children. These children may find it difficult to express their symptoms, resulting in a delay in diagnosis. Hence, imaging becomes extremely important in these patients. As xanthine urolithiasis tends to recur in the majority of the cases, these

Correspondence: Manoj K. Vaidya MD, BLDE (Deemed To Be University), Shri B. M. Patil Medical College Hospital and Research Centre, Department of Urology, Bijapur, India
E-mail: vaidyamk@gmail.com **ORCID-ID:** orcid.org/0000-0002-5448-1327
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patients need to undergo multiple imaging studies throughout their lifetime (6).

Another rare cause of calculi in the pediatric population is cystinuria. About 6% of all pediatric urolithiasis is due to cystine. Cystinuria is an autosomal recessive disorder resulting in decreased reabsorption of cystine and other dibasic amino acids like ornithine, lysine, and arginine. However, these stones are radiopaque and may be identified on an X-ray (7).

Case Presentation

A male baby in later infancy born out of a third-degree consanguineous marriage presented with a history of recurrent episodes of abdominal pain, fever, vomiting and crying during micturition on and off for the past 4 months. There was a history of passage of 2 tiny calculi one week back (Figure 1A) associated with mild hematuria, following which the infant was referred to the urologist. The antenatal and post-natal periods were uneventful. The appropriate age-related developmental milestones were attained. The baby was being breastfed, and weaning had been started with a home-based cereal diet. Abdominal examination did not reveal any significant findings. Written informed consent for publication of the case details, including history, investigation reports, and other relevant information was obtained from the infant's parents.

The investigations revealed hemoglobin 9.7 mg%, mild leucocytosis (14,600 cells/cumm), serum creatinine (0.74 mg/dL), calcium 10.9 mg/dL, uric acid- 2.0 mg/dL (normal range 3-6 mg/dL) and vitamin D- 26.69 ng/mL (ref range 6.2-53.2 ng/mL). Urinalysis showed 10-15 pus cells and 8-10 red blood cells. Urinary pH- 6.5, calcium- 31.65 mg%, creatinine- 43.6 mg% and urine calcium creatinine ratio- 0.72 were in the normal range. Urine culture was sterile.

Ultrasonography showed bilateral 6 mm calculi in renal pelvis with grade I hydronephrosis. The X-ray of the kidney ureter bladder region (Figure 1B) did not show any radio-opaque shadow. Two days later the baby underwent a computed tomography (CT) abdomen (Figure 1C) which revealed 6.5 mm [402 Hounsfield unit (HU)] right distal ureter calculus just proximal to ureterovesical junction (UVJ) causing mild right hydroureteronephrosis (HUN), a 6 mm obstructive calculus (352HU) in left UVJ causing mild left HUN and a 10 mm (427 HU) non obstructive calculus in left renal Pelvis.

Differential diagnosis-CT scan ruled out any gross anatomic abnormality, and a metabolic workup was done considering the possibility of hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, hyperuricosuria, and Xanthinuria as potential causes of urolithiasis in this infant.

Treatment

The baby was scheduled for bilateral ureteroscopic lithotripsy (URSL) using a 4.5 Fr ureteroscope with a thulium fiber laser. During this procedure, both the lower ureter calculi were fragmented, and bilateral Double J stenting was done. Two weeks later, the baby underwent a second procedure, specifically, a left URSL for the 10 mm calculus in the left renal pelvis. The stone fragments were sent for crystallographic analysis (Figure 2A), which was suggestive of compact masses of rhombic crystals indicative of xanthine stones (xanthine 71%).

In view of the limited resources and available testing facilities, we did a targeted genetic analysis of the child and family members (parents and grandmother) to identify mutations in the *XDH1* gene, focusing on exons 6F, 8F, 10F, 16F, 21F, 23F, as these are the frequently reported mutation sites. Interestingly, no mutations were recorded in the index case, but a heterozygous mutation

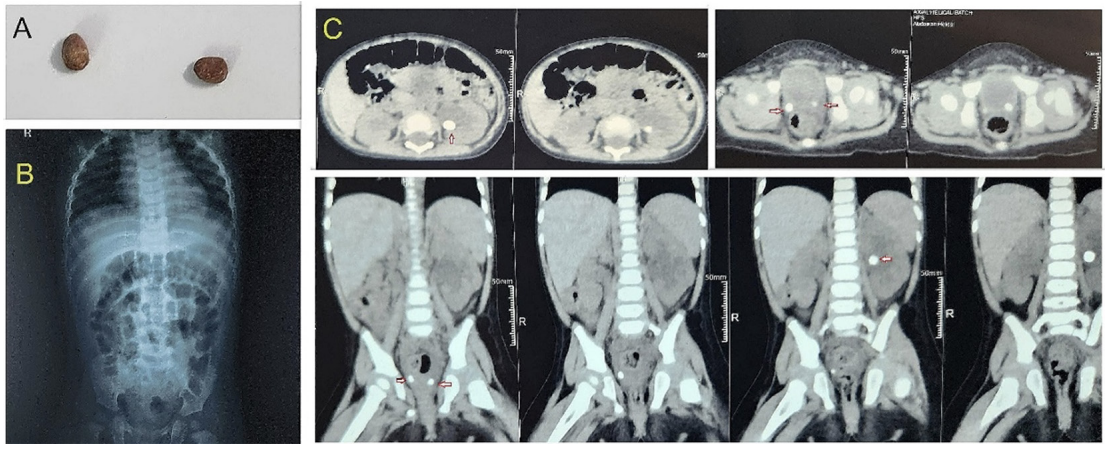

Figure 1. A. Two tiny calculi passed spontaneously. B. X-ray of the KUB region showing no evidence of any radio-opaque shadow. C. Axial and coronal CT images showing the 10 mm (427 HU) non obstructive calculus in left renal Pelvis, a 6.5 mm (402 HU) right distal ureter calculus, 6mm calculus (352 HU) at left UVJ (Calculi are Indicated by red arrows)

KUB: Kidney ureter bladder, CT: Computed tomography, HU: Hounsfield unit, UVJ: Ureterovesical junction

was noted in one first-degree relative (Father) and one second-degree relative (Grandmother) in exons 21F [c. 2211C>T (p. I737I)] and 8F [g. 682G>C (p. T202T)], respectively (Figure 2B, C). the relatives were asymptomatic and had no history of urolithiasis. Thus, a conclusion may be drawn that there may be mutation in one of the remaining 30 exons that were not analysed.

Complete clearance of the ureteric and renal pelvic stones was achieved. The parents were counselled to administer a low purine diet to the baby along with an alkalizer and to maintain adequate hydration. On being followed up for 6 months after the procedure, the baby was doing well and had no recurrence of abdominal pain and urolithiasis. A follow-up CT scan did not show any evidence of residual or new calculi.

Discussion

Hereditary xanthinuria is an uncommon condition that alters purine metabolism, leading to urolithiasis. As a result, these individuals can develop renal stones at any age, including infancy.xanthine stones or any urolithiasis in children should receive special attention, as they are associated with significant morbidity due to the propensity of the renal stones to recur (8,9).

The peculiar property of xanthine stones is their radiolucency, making it difficult to detect them on plain radiographs. The physical appearance of the calculus is round and brownish in color. They may be composed of pure xanthine or may contain a certain proportion of hypoxanthine. The urinary pH is a major factor affecting the solubility of oxypurines. The urinary supersaturation of oxypurines at acidic pH leads to precipitation and stone formation. The other differential diagnosis for radiolucent stones is uric acid stones. However, these are associated with hyperuricosuria (10,11). In our patient, the urine was also slightly acidic, and the stones were radiolucent and not evident on X-ray. Ultrasound helped in detecting the stones. CT gave the exact size and location of stones, which had a low density in the range of 400 HU, and helped in planning the management.

In humans, the activity of xanthine oxidase/xanthine dehydrogenase is predominant in the liver and small intestine. Hence, the conventional method to establish hereditary xanthinuria is by an allopurinol loading test or a liver biopsy. In the current context, the approach to diagnose the type of xanthinuria may be broadly divided into a three-step algorithm as shown below (Table 1) (12).

Establishing the diagnosis and characterising the exact phenotype (type I or II), based on clinical and biochemical tests alone, is difficult, thereby necessitating the use of molecular testing. Clinical tests include stone analysis, demonstration of an elevated urinary xanthine or hypoxanthine excretion, and measurement of XDH/xanthine oxidase activity in liver or intestinal biopsy samples (13). Biochemical tests to detect xanthinuria include estimating the level of uric acid in the blood, which is usually very low (below 2 mg/dL). Measurement of urinary xanthine and hypoxanthine requires high performance liquid chromatography and the normal 24-hour urine values are below 40 mol/L and 70 mol/L, respectively (14). In the current

Table 1. Approach to diagnose the type of xanthinuria

Laboratory tests	Urinary metabolites	Genetic studies
Extremely low level of serum/urinary uric acid	N1-methyl-2-pyridone-5-carboxamide	Molecular genetics
Stone composition analysis	N1-methyl-4-pyridone-5-carboxamide	
	These products are results of the oxidation of N1-methylnicotinamide by aldehyde oxidase	

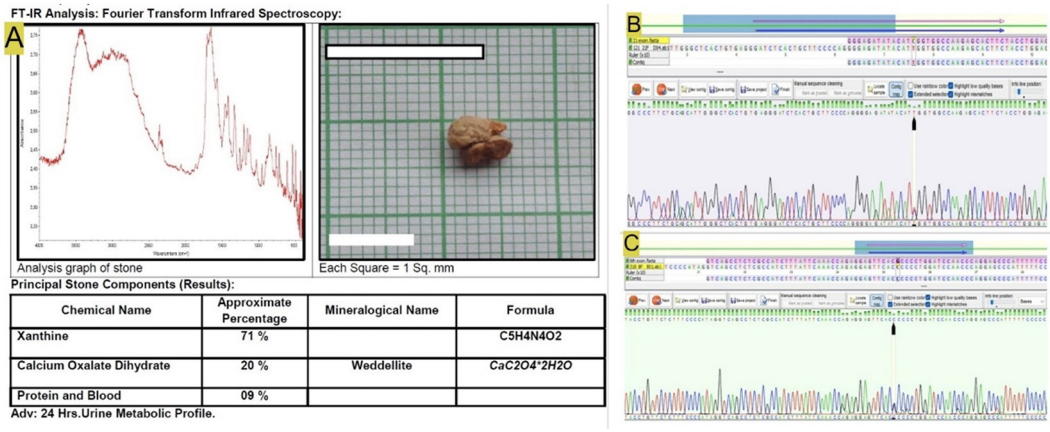

Figure 2. A. Stone analysis by FT-IR showing xanthine (71%) as the principal component. B. Heterozygous mutation in exon 21F [c. 2211C>T (p. I737I)] noted in first degree relative. C. Heterozygous mutation in exon 8F [g. 682G>C (p. T202T)] noted in second degree relative

FT-IR: Fourier transform-infrared spectroscopy

case, we observed that the serum uric acid levels were low, which was in line with our diagnosis of xanthinuria. Urinary xanthine and hypoxanthine levels were not estimated due to the unavailability of liquid chromatography.

The human *XDH* gene is located on chromosome 2p23.1. The *XDH* gene has 36 exons, which code for a 1.333 amino acid protein. Currently, there are about 18 mutations in the XDH coding region: 16 missense/non-sense, one small deletion, and one small insertion. Out of these mutations, 7 mutations are known to cause clinical xanthinuria (2,15). In our case, we performed genetic analysis using primers targeting a few specific coding regions (exons 6F, 8F, 10F, 16F, 21F, 23F) which are known to cause clinical xanthinuria. However, no mutation was detected in the index case, indicating that the mutation may be present in one of the remaining coding regions.

Most of the individuals with heterozygous mutations in the *XDH* gene do not demonstrate hypouricemia or symptoms of urolithiasis. In some rare instances, their urinary oxypurine excretion may increase and lead to stone formation. However, the incidence of urolithiasis in heterozygotes has not been estimated reliably (16). In the current family, too, we could identify a first-degree and a second-degree relative with heterozygous mutation in exon 21F and 8F, respectively, and both had no history suggestive of urolithiasis.

In the present case, we were able to achieve stone clearance with URSL alone. Other modalities for management of these calculi include Micro PCNL and retrograde intrarenal surgery. Shockwave lithotripsy can be used in the treatment of these stones but comes with the associated disadvantages of multiple sittings and need for general anaesthesia in pediatric patients (17,18).

Management of xanthinuria is primarily aimed at avoiding recurrence of stones and the subsequent complications. A strictly low purine diet (avoidance of seafood, alcohol, cheese, and chocolates) must be advised, along with adequate hydration, Alkalisers are commonly prescribed because the solubility of oxypurines is pH dependent. Excessive physical activity may cause renal or intramuscular deposition of xanthine crystals and hence must be avoided (19).

The best way to prevent recurrent urolithiasis in patients with xanthinuria is a low purine diet and an adequate intake of fluids, as per the current literature. However, there is ongoing research to identify new agents that can prevent the crystallisation of xanthine in the urine of recurrent xanthine stone formers. Grases et al. (20), in their *in vitro* studies, identified two metabolites of theobromine-7-methylxanthine and 3-methylxanthine, which can prevent crystallisation of xanthine. However, further clinical trials are necessary to establish the *in vivo* efficacy of theobromine metabolites in preventing xanthine nephrolithiasis (20).

Conclusion

Any pediatric patient presenting with urolithiasis must undergo complete metabolic evaluation. A stone analysis will further aid in diagnosis of certain rare conditions, like xanthinuria, which can be confirmed by genetic studies. In patients with xanthinuria, simple diet restrictions with lifestyle changes will help prevent the recurrence of stones and avoid further renal damage.

Ethics

Informed Consent: Written informed consent for publication of the case details, including history, investigation reports, and other relevant information was obtained from the infant's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.B.P., S.P., B.S.P., M.K.V., Concept: S.B.P., V.S.K., S.P., B.S.P., G.S.K., Design: S.B.P., V.S.K., M.K.V., Data Collection or Processing: B.S.P., G.S.K., Analysis or Interpretation: S.B.P., M.K.V., G.S.K., Literature Search: V.S.K., B.S.P., M.K.V., G.S.K., Writing: V.S.K., S.P., M.K.V.

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

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VIDEO ARTICLE
Pediatric Urology

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A Rare Vascular Anomaly Causing Left Hydroureteronephrosis

Dilşad Dereli[1], Çiğdem Öztunalı[2], Emrah Şişli[3], Baran Tokar[1]

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatric Urology, Eskişehir, Türkiye
[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatric Radiology, Eskişehir, Türkiye
[3]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatric Cardiovascular Surgery, Eskişehir, Türkiye

Abstract

In children, hydroureteronephrosis due to ureterovesical stenosis may develop from reflux or obstruction. In diagnostic cystoscopy, not only the findings of the ureteral orifice and ureteral tracing but also the findings of accompanying intra- and extravesical pathologies should not be overlooked. A five-year-old male patient had increased left hydroureteronephrosis on ultrasound follow-up and Mag-3 scintigraphy showed partial obstruction. Retrograde pyelography (RPG) was planned for diagnostic purposes. Cystoscopy showed pulsation in the subureteric area of the left ureteral orifice. RPG was performed. Distal passage problems and proximal hydroureteronephrosis were found on the left side. Postoperative abdominal computed tomography (CT) angiography was performed to investigate the cause of arterial pulsation. It was observed that the left iliac artery did not bifurcate at the normal level and was aberrant in the pelvis as an external iliac artery, single arterial structure that was tortuous and slightly wide. At this level, it extended into the posterior neighborhood of the bladder. This anatomical variation and the suburethral neighborhood of the artery caused marked intravesical arterial pulsation. No intervention was performed, and it was noted that if surgical intervention was necessary according to the follow-up, it should be performed in absolute extravesical exploration, considering the existing pathology. Pulsatile mass detected during cystoscopy for intravesical evaluation may be associated with rare extravesical vascular malformations. Following CT angiography, invasive interventions should be carefully planned if necessary. Expansion of invasive procedures without a thorough understanding of extravesical anatomy may lead to serious complications.

Keywords: Hydroureteronephrosis, ureterovesical stenosis, iliac artery, vascular pathologies, hydronephrosis

Introduction

In children, a ureter diameter greater than 7 mm is considered megaureter (1). Primary megaureter occurs due to a functional or anatomical abnormality of the ureterovesical junction. Primary megaureter is classified according to the presence or absence of reflux and obstruction (2).

Primary obstructive megaureter accounts for approximately 25% of childhood obstructive uropathies (3). It is frequently found in the left ureter and is bilateral in 10-15% of cases. Boys are affected more frequently than girls (4).

Primary megaureter is often diagnosed by ultrasonography. Patients may present with symptoms such as urinary tract infection, abdominal pain, hematuria, or uremia. Some cases are diagnosed incidentally. Associated ipsilateral ureteropelvic junction obstruction, contralateral vesicoureteral reflux, and renal hypoplasia/dysplasia may be observed. Surgical intervention is required in only 10-30% of cases diagnosed with primary obstructive megaureter. It is believed that ureteral dilatation in patients with primary obstructive megaureter may improve over time in the natural course of the disease (5-7).

Case Presentation

A five-year-old male patient had been referred to the pediatric urology outpatient clinic at the age of three due to left hydronephrosis. The patient was asymptomatic during follow-up. The table below outlines the ultrasound follow-up conducted for the patient after reaching three years of age.

At the age of 3 years, voiding examination revealed no vesicoureteral reflux. Mag-3 scintigraphy indicated reduced and delayed perfusion and concentration function in the left kidney, along with a partial response to diuretics. The left kidney's contribution to renal function was calculated at 51%.

During a follow-up Mag-3 scintigraphy at the age of 4.5 years, the patient exhibited increased hydroureteronephrosis

Correspondence: Dilşad Dereli MD, Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatric Urology, Eskişehir, Türkiye
E-mail: derelidilsad@gmail.com **ORCID-ID:** orcid.org/0000-0003-1261-3405
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on ultrasound. Activity retention was noted within dilated pelvicaliceal structures, followed by excretion post-diuretic injection. It was observed that the ureter became more prominent and tortuous during excretion. The left kidney's contribution was recalculated at 48%.

During the diagnostic cystoscopy of the patient, the ureters were observed to be in their normal anatomical location and structure. However, a pulsating formation protruding into the bladder was noticed superior to the left ureteral orifice. To address this, a 3 Fr ureteral stent was inserted into the left distal ureteral orifice, followed by retrograde pyelography (RPG). The RPG revealed mild stenosis of the ureteral orifice, characterized by significant tortuosity and a fold at the pelvic orifice (Figure 1).

Due to the significant pulsation observed, computed tomography (CT) angiography was scheduled for further evaluation and treatment.

Abdominal CT angiography revealed grade 4 hydronephrosis in the left kidney, with the left ureter exhibiting tortuosity along its course. Notably, the abdominal aorta was positioned on the right side inferiorly to the origin of the renal arteries, with its bifurcation occurring at the level of the L3 vertebra. The left common iliac artery appeared narrow in caliber and anteriorly situated compared to the right, with the inferior mesenteric artery arising from it. The left common iliac artery did not bifurcate at the usual level; instead, it as a single artery resembling the left external iliac artery, displaying an aberrant course within the pelvis. The left internal iliac artery was observed to originate from this aberrant common iliac artery in the posterolateral vicinity of the inferior part of the bladder. Furthermore, the left external iliac artery exhibited indentation in the posterior vicinity of the bladder during its abnormal course. At this level, it appeared tortuous and slightly dilated (Figures 2, 3, 4, 5, 6).

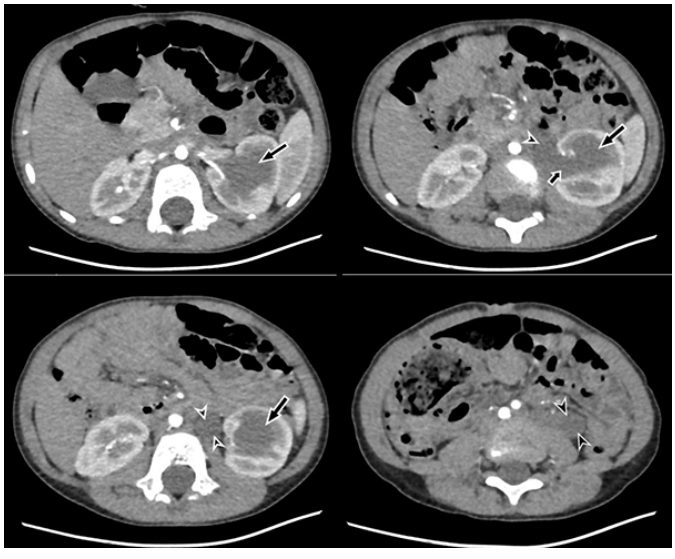

Figure 1. Retrograde pyelography

Discussion

Primary obstructive megaureter is a rare urinary system anomaly. The pathogenesis of primary obstructive megaureter has not been fully elucidated. It is attributed to delayed or abnormal

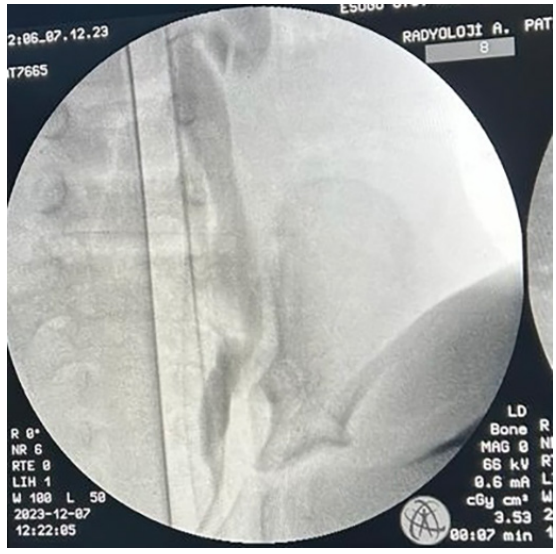

Figure 2. Axial CT angiography images show the left dilated calyces (arrows), pelvis (short arrow), and the proximal ureter (arrowheads)

CT: Computed tomography

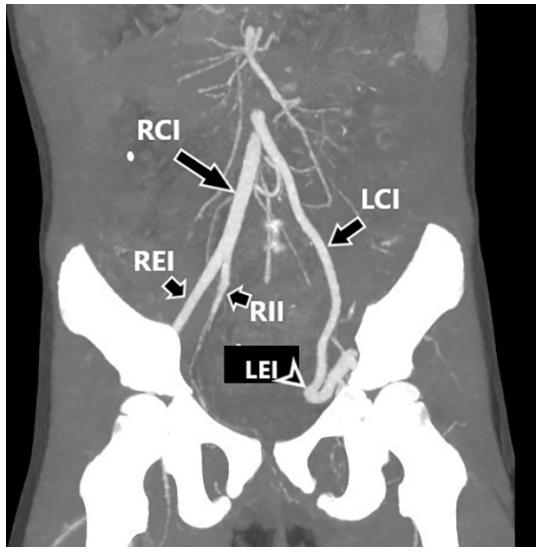

Figure 3. Coronal MIP CT angiography image shows normal bifurcation of the RCI into the REI and RII. The LCI does not bifurcate normally but continues distally into the pelvis as a single artery. LCI gives off LII in the pelvis (not shown), and continues as the LEI. The LEI is wide and tortuous in the pelvis, near the bladder

CT: Computed tomography, MIP: Maximum intensity projection, REI: Right external iliac, RII: Right internal iliac, RCI: Right common iliac, LCI: Left common iliac, LII: Left internal iliac, LEI: Left external iliac

Table 1. Follow-up of the patient's urinary system ultrasounds				
		3 years old	4 years old	4 years 6 months old
Kidney dimension	Right	61x25 mm	67x37 mm	69x42 mm
	Left	77x38 mm	78x40 mm	96x40 mm
Anterior-posterior diameter	Right			
	Left	13 mm	15 mm	19 mm
Degree of hydronephrosis	Right			
	Left	Grade 3	Grade 3-4	Grade 3-4
Parenchyma	Right	6 mm	9 mm	11 mm
	Left	6 mm	7 mm	9 mm
Ureteral dilatation	Right			
	Left	11 mm	15 mm	15 mm

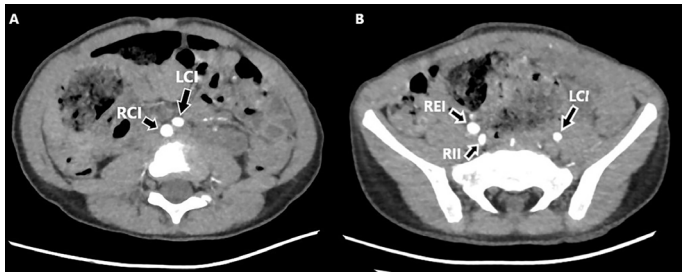

Figure 4. CT angiography images show the normal RCI bifurcating into the REI and RII arteries (A, B). The LCI is anterolateral to the RCI, just below the aortic bifurcation (A). LCI does not bifurcate at a normal level but continues distally into the pelvis as a single artery (B)

CT: Computed tomography, RCI: Right common iliac, LCI: Left common iliac, REI: Right external iliac, RII: Right internal iliac

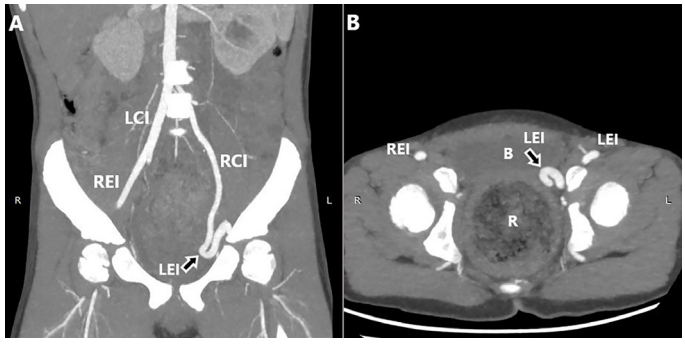

Figure 5. Coronal (A) and transvers (B) MIP

MIP CT angiography images show normal RCI and REI. The LCI does not bifurcate at a normal level, but continues distally into the pelvis as a single artery. The LCI branches off from the LII in the pelvis, and continues as a tortuous and dilated LEI artery. The LEI shows an indentation to the left posterolateral wall

B: Bladder, R: Rectum, REI: Right external iliac, RCI: Right common iliac, LCI: Left common iliac, LII: Left internal iliac, LEI: Left external iliac, MIP: Maximum intensity projection

muscle development in the distal ureter, which should occur in the first week of gestation (8). This leads to the formation of an aperistaltic segment causing functional obstruction. Rarely, megaureter occurs due to congenital ureteral stricture or valves (9,10). The prognosis is generally good for unilateral

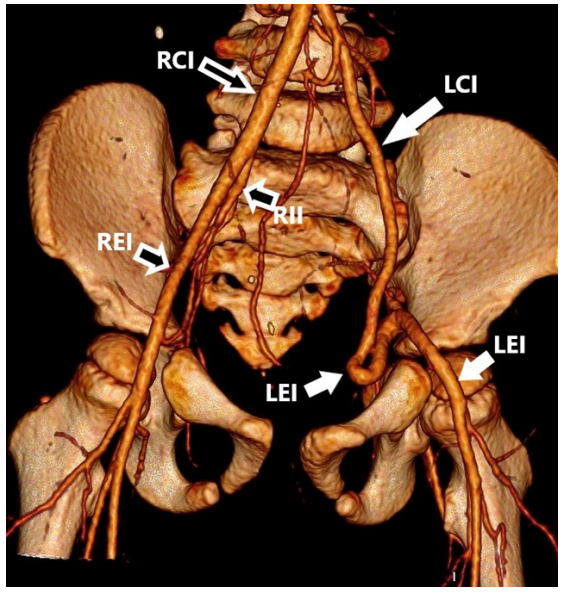

Figure 6. Volume-rendered 3D CT angiography image shows the normal RCI bifurcating into REI and RII arteries. LCI does not bifurcate at a normal level but continues distally into the pelvis as a single artery. The LCI gives off the LII in the pelvis and continues as a tortuous and dilated LEI artery. Based on these findings, if, depending on the patient's follow up, he requires a surgical intervention, laparoscopic extravesical exploration was considered the best option to expose the area and plan the surgery

CT: Computed tomography, REI: Right external iliac, RII: Right internal iliac, RCI: Right common iliac, LCI: Left common iliac, LII: Left internal iliac, LEI: Left external iliac

ureterovesical strictures diagnosed antenatally. There are no randomized studies indicating the optimal treatment for patients with primary obstructive megaureter. In many cases, hydroureteronephrosis regresses spontaneously (5,6). Spontaneous recovery occurs with segmental maturation. The spontaneous resolution time is prolonged in cases with severe hydroureteronephrosis. The chance of spontaneous resolution is lower in cases with scintigraphically demonstrated obstructive lesions. If there is no additional congenital renal abnormality, long-term results are favorable. Surgical treatment is indicated if hydronephrosis increases or renal function decreases during follow-up. Recurrent urinary tract infections, pyelonephritis,

persistent flank pain, or hematuria also require surgical intervention. Ten percent of cases with megaureter undergo surgery due to decreased renal function at the initial evaluation.

While complete resolution is observed in 34% of cases during conservative follow-up, 49% of cases remain stable (3). In some cases, increased dilatation, urinary tract infection, and decreased renal function necessitate surgical intervention within the first year. Reimplantation of the dilated ureter in small infants is technically challenging and can potentially lead to bladder dysfunction (11). Therefore, less invasive procedures such as endoscopic or open Double-J catheter placement are preferred (12,13). This approach helps to alleviate the obstruction and reduces the need for reimplantation (13,14). In the literature, endoscopic catheter placement has been successful in approximately 30% of cases (12). In our patient, we initially aimed to perform an examination for etiological investigation without placing a catheter. We believed that interventions could result in serious complications.

Conclusion

The pulsatile mass identified during cystoscopy in the intravesical assessment may be linked to significant extravesical vascular malformations. Invasive interventions should be carefully planned following CT angiography. Extending invasive procedures without a comprehensive understanding of the extravesical anatomy could lead to serious complications. Therefore, a thorough evaluation of the vascular anatomy is imperative to ensure safe and effective management of the patient's condition.

After diagnostic evaluation, open or laparoscopic extravesical exploration, and ureteral surgery can be planned if necessary, according to the findings.

Ethics

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

Footnotes

Authorship Contributions

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

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

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Video 1.

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LETTER TO THE EDITOR
Functional Urology

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J Urol Surg 2025;12(4):282-283

Letter to the Editor: "The Role of the Incontinence Severity Index in the Treatment of Stress Urinary Incontinence"

İbrahim Hacıbey

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Urology, İstanbul, Türkiye

Dear Editor,

I read with great interest the article by Öztürk and Atlıhan titled *"The Role of the Incontinence Severity Index in the Treatment of Stress Urinary Incontinence"* [J Urol Surg. 2025;12(1):34-39]. The authors provide valuable insight into the comparative efficacy of medical and surgical interventions for stress urinary incontinence (SUI) using the incontinence severity index (ISI) as a primary outcome. However, I aim to raise several critical methodological points that we believe merit further clarification or acknowledgment.

Firstly, although the authors acknowledge the retrospective design and short-term nature of the study, a crucial limitation remains unaddressed: the significant imbalance in baseline ISI severity among treatment groups. As seen in Table 2, patients in the medical treatment group had significantly milder disease at baseline, while those undergoing surgical procedures had more severe presentations (p-values for slight, moderate, and severe categories: 0.018, 0.044, and 0.032, respectively). This baseline heterogeneity introduces a confounding factor in interpreting treatment efficacy, particularly when ΔISI is compared between groups. Although designing and implementing a study based on a milder disease group may be more practical, a more robust analysis -such as adjusted comparisons or subgroup stratification- would help minimize this bias.

Secondly, the authors state that patients in the medical group received 20 mg/day of duloxetine. Although the recommended therapeutic dose of duloxetine for SUI is 80 mg/day (typically administered as 40 mg twice daily), it is common practice to initiate treatment at 40 mg/day and titrate the dose based on tolerability (1). In this study, the use of 20 mg/day remains below both the guideline-recommended and commonly initiated doses, potentially underestimating the drug's full therapeutic effect. This dosing deviation may affect the observed efficacy of medical treatment, and it could have been more explicitly acknowledged as a methodological limitation or justified with clinical rationale (e.g., tolerability concerns or prescribing practices specific to the study population).

Third, one underexplored implication of the short follow-up duration of the study is its impact on understanding the progression of patients in the medical treatment group who may ultimately require surgery. The transition from conservative to surgical treatment is common in real-world settings, particularly when pharmacologic management becomes insufficient (2). Without long-term data, the study cannot inform how many patients might have eventually opted for surgery, which weakens conclusions about the sustained value of medical therapy.

Beyond these critiques, I commend the authors for their pragmatic focus on the ISI as an accessible, patient-friendly tool. Unlike urodynamic tests, which are often costly and operator-dependent, ISI offers a low-burden method for monitoring treatment response, especially in resource-limited settings. The authors appropriately emphasize this point.

In conclusion, while the study offers meaningful contributions to the field, interpretation of comparative treatment outcomes should be tempered by the presence of baseline group imbalances, suboptimal medical dosing, and the absence of

Correspondence: İbrahim Hacıbey MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Urology, İstanbul, Türkiye
E-mail: drihacibey@gmail.com **ORCID-ID:** orcid.org/0000-0002-2212-5504
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long-term follow-up, needed to assess treatment sustainability and escalation. I hope these reflections will be useful for guiding future prospective and randomized research on this topic.

Sincerely,

Ethics

Informed Consent: Retrospective study.

Footnotes

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

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

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