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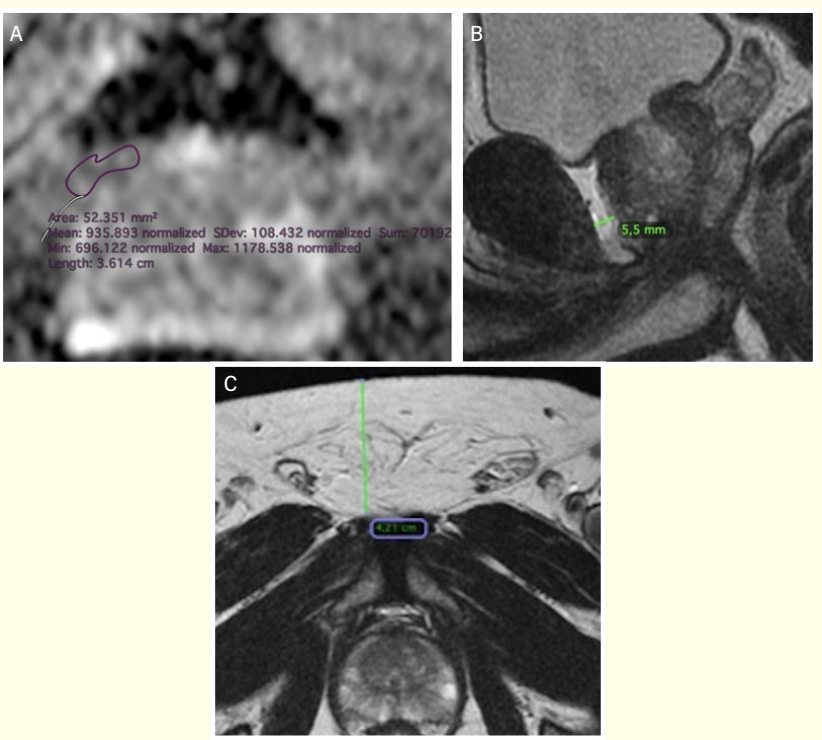

A) Measurement of the mean ADC value of periprostatic fat, using a ROI placed in the anterior periprostatic fat. B) Linear measurement of periprostatic fat thickness in the T2WI sagittal plane, and C) Linear measurement of subcutaneous fat thickness in the T2WI axial plane. (*e20240318*)

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DISCLAIMER

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EDITORIAL
IN THE ISSUE

Vol. 51 (1): e20250101, January - February, 2025
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2025: The year in which the International Brazilian Journal of Urology will be able to consolidate itself as one of the most important in urology

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In 2024 there was a small drop in the journal's impact factor, which nevertheless remained above 3. In 2025 we expect the impact factor to reach a very significant level, consolidating our journal as one of the most important in urology. The January-February number of Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Infertility, Endourology, Priapism, Bladder function, Climacturia and Overactive bladder. The papers came from many different countries such as Brazil, China, Indonesia and USA, and as usual the editor ´s comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Tobing and collegues from Indonesia, presented in page e20240356 (1) a nice systematic review comparing the external ureteral catheter and double-J stent as drainage methods for tubeless percutaneous nephrolithotomy (PCNL) and concluded that the external ureteral catheter (EUC) demonstrated fewer stent-related symptoms than the DJ-stent in tube- less PCNL, while both methods showed comparable safety and efficacy. The choice between EUC and DJ-stent should consider patient preferences and surgeon expertise. Further randomized controlled trials (RCTs) with larger sample sizes are needed to affirm these results.

Dr. Ferrão and collegues from Brazil, presented in page e20240406 (2) a nice systematic review about the prevalence of climacturia in patients after radical prostatectomy and concluded that climacturia is a frequently underestimated complication by urologists. Given its significant impact on quality of life, it warrants greater attention from specialists following radical prostatectomy.

Dr. Badia and collegues from the group of Dr. Allen Morey - USA, presented in page e20240497 (3) a important review about the surgical management of ischemic priapism and concluded that the while upfront penile prosthesis placement was previously considered the procedure-of-choice for cases of severe refractory priapism, there has more recently been a paradigm shift towards the utilization of tunneling procedures in the acute setting. The high efficacy of these maneuvers and the potential for sexual function recovery, potentially allow penile prostheses to be avoided in some patients; further studies are needed to investigate this hypothesis. For those ultimately requiring delayed penile prosthesis placement, the increased complication rates should be acknowledged, although multiple techniques exist to facilitate device placement. Ultimately, there is no proven algorithmic approach to the management of this challenging condition; interventional approach remains a nuanced one that depends on both patient and surgeon factors.

Dr. Vieira and collegues from Brazil, presented in page e20240318 (4) a nice study about themorphological (linear measurements) and functional (ADC value) assessments of periprostatic fat can predict the aggressiveness of prostate cancer (PCa) over a 5-year follow-up period. This study is the cover of the present edition. The authors topic concluded that the ADC value of periprostatic fat may serve as an additional tool for PCa risk stratification, correlating with poorer outcomes such as systemic recurrence and overall survival. If validated by external, prospective, multicenter studies, these findings could impact future therapeutic decisions.

Dr. Ferreira and collegues from Brazil, presented in page e20240375. (5) a interesting study about the long-term follow-up of patients undergoing nephrectomy for urolithiasis and concluded that type 2 diabetes mellitus and age were predictors of chronic kidney disease progression, while higher preoperative eGFR was protective. Hypercalciuria and contralateral kidney stones increased the risk of kidney stone formation and/or growth post-nephrectomy for urolithiasis.

Dr. Macedo and collegues from Brazil, presented in page e20240453 (6) a nice study about the management of children and adolescents with overactive bladder refractory to treatment with parasacral transcutaneous electrical nerve stimulation and concluded that children with OAB refractory to pTENS who received structured subsequent treatments showed partial response in all cases, with complete symptom resolution in half of the patients. More intensive urotherapy, medications, or repeat pTENS in combination with oxybutinin can be effective for managing this challenging condition.

Dr. Osório and collegues from Brazil, presented in page e202409922 (7) a interesting research comparing the Gleason 7 (3+4) and (4+3) prostatic adenocarcinomas with prognostic criteria and immunohistochemical profiles of AMCR, PSA and Ki-67 and concluded that differences in the Gleason score 7 (3+4) and Gleason score 7 (4+3) of PC when comparing prognostic criteria. Anti-Ki 67 and anti-PSA antibody immunostaining showed a positive correlation as the Gleason score 7 increased from (3+4) to (4+3).

Dr. Yang and collegues from China, presented in page e20240311 (8) a interesting study about the effect of detethering surgery on the bladder function and psychology of children with primary tethered cord syndrome and concluded that detethering surgery (DS) could not considerably ameliorate pre-existing bladder dysfunction and patients exhibiting non-progressive bladder dysfunction could be treated conservatively with close observation. Tethered cord syndrome (TCS) plagues patients all the time even if detethering. Psychological counseling for children with TCS should be strengthened after DS.

The Editor-in-chief expects everyone to enjoy reading.

CONFLICT OF INTEREST

None declared.

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EDITORIAL

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Reviewers are fundamental to success of the International Brazilian Journal of Urology

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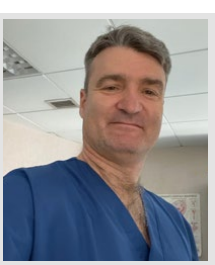
In 2024 the International Brazilian Journal of Urology maintained the impact factor above 3 and this fact was possible because the serious peer review process of our Journal (1). In this year we received more than 650 papers. The Editor-in-Chief would like to thanks all the reviewers and specially to the Doctors: Alexandre Danilovic (Hospital das Clínicas da Faculdade de Medicina da USP -São Paulo, SP, Brasil); Arnold P. Achermann (Universidade Estadual de Campinas - UNICAMP); Daniele Castellani (Ospedali Riuniti di Ancona, Italy); Eduardo Mazzucchi (Universidade de São Paulo - USP, SP, Brasil); Henry H. Woo(Sydney Adventist Hospital Clinical School,); Evangelos Liatsikos (Hospital of Patras, Greece); José C. Truzzi (Universidade Federal de São Paulo - UNIFESP); José de Bessa (Universidade Estadual de Feira de Santana - UEFS); Ricardo Miyaoka (Universidade Estadual de Campinas - UNICAMP); Wilmar Azal Neto (Universidade Estadual de Campinas - UNICAMP); who reviewed more than 3 articles during the year and strictly within the deadline,

Thanks a lot!!!!!


Alexandre Danilovic


Arnold Acherman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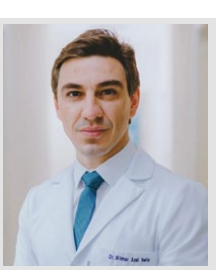
Wilmar A. Neto

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CONFLICT OF INTEREST

None declared.

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EDITORIAL

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Best videos of the year in 2024 for the International Brazilian Journal of Urology - IBJU

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Dear readers,

It has truly been an incredible privilege to see our cherished journal achieve new echelons as a top 10 ranked international urological journal (based on updated impact factors for 2022), with now the IBJU having an impact factor of 3.7 which is an incredible achievement due in large part of the excellent work and leadership of our editor-in-chief Dr. Luciano Favorito and the entire editorial team committed to publishing only the highest quality peer reviewed scientific work and as well of the commitment of our international clinical investigators and leaders committed to publish their quality work in our esteemed journal. In this regard, I anticipate our journal will continue to have incredible success as a leading scientific journal within the global urology community for many years to come. One of my greatest honors as the video section editorial of the IBJU is to highlight some of the high quality videos published which not only depict cutting edge surgical approaches but offer the potential to innovate and re-define the treatment paradigm in surgical care for many urological conditions all in an effort to optimize surgical outcomes both in terms of treatment efficacy, functional results, and reduced surgical morbidity.

In this regard, I am pleased to announce the first prize for best video of the year to Dr. Cannoletta and colleagues from the department of urology, University of Illinois at Chicago as part of an international collaboration with centers in Italy in the video and abstract submission entitled "**Single-port transvesical vesico-vaginal fistula repair: An initial experience**" IBJU volume 50(4): 502-503, July-August 2024 (1). In this report of 4 patients managed using this novel minimally invasive surgical technique, the authors repair not only highlight an innovative surgical technique which is meticulously depicted but also with persistent favorable results at 3 months. There is no question this approach and technique has the potential to redefine the current treatment standard. The selection for second prize for best video of the year is awarded to Dr .Gamal and colleagues from the group of Dr. Vipul Patel at the AdventHealth Global Robotics Institute in a collaboration with Stanford University and the University of Central Florida in their accepted video submission entitled "**Step-by-step peritoneal bladder flap bunching (PBFB) technique: An innovative approach following lymph node dissection in robotic radical prostatectomy**" IBJU volume 50(5): 657-658, September-October 2024 (2). As conveyed by the authors, the occurrence of post-operative lymphoceles following lymph node dissection at time of robotic radical prostatectomy (RRP) although rare, adds potential morbidity and a ne-

cessity for secondary interventions in a subset of patients. Using a modified PBFB technique completed at time of RRP, this approach minimizes this risk using an easily learned and reproducible technique completed by one the most experienced surgeons in robotic prostatectomy and his team hence allowing to learn and benefit from their surgical refinements. The third prize for best videos of the year is awarded to Dr Fan and colleagues from the department of urology at Peking University in their video publication entitled "**Totally intracorporeal robot assisted bilateral ileal ureter replacement for the treatment of ureteral strictures using Kangduo surgical robot 2000 Plus**" IBJU volume 50(6): 781-782, November-December 2024 (3). The authors are to be congratulated for completing this complex bilateral ileal ureter reconstruction using an innovative surgical technique and robotic platform. The expansion in robotic platforms is critical in the dissemination and adoption of minimally invasive techniques accessible to patients and families across the globe. It also pushes the envelope in the further development and refinement in surgical tools integrating cutting edge technology. We should never become complacent that we have the best tools at hand as we owe it to our patients to push the envelope in always seeking to improve their lives.

Lastly, I would like to thank all of you as dedicated readers and supporters of the video section of the IBJU in your commitment and dedication. It does not go unnoticed, and we are always seeking to promote and highlight advances in surgical technology and procedures which is at the fundamental basis of the field of urology. As we close out the present year, I want to wish each one of you and your families a very happy and healthy holiday season with best wishes in the year 2025.

Warmest regards,

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Comparison of External Ureteral Catheter and Double-J stent as Drainage Methods for Tubeless Percutaneous Nephrolithotomy: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: The external ureteral catheter (EUC) and double-J stent (DJ-stent) are frequently used for drainage in tubeless percutaneous nephrolithotomy (PCNL). This study aims to compare the outcomes and effectiveness of these two methods.

Materials and Methods: We conducted a detailed literature search using relevant key words on Google Scholar, Europe PMC, Medline, and Scopus databases. Continuous variables were combined using mean difference (MD), while binary variables were analysed using risk ratio (RR) with 95% confidence intervals through random-effects models.

Results: Our analysis included nine studies. The results showed that EUC was associated with a significantly lower incidence of stent-related symptoms [RR 0.32 (95% CI 0.19 – 0.54), $p < 0.0001$, $I^2 = 24\%$] compared to the DJ-stent. There were no significant differences between EUC and DJ-stent in terms of postoperative fever ($p = 0.92$), urine leakage ($p = 0.21$), perinephric collection ($p = 0.85$), haemoglobin drop ($p = 0.06$), transfusion rate ($p = 0.27$), VAS score ($p = 0.67$), analgesic requirements ($p = 0.59$), stone-free rate ($p = 0.14$), duration of surgery ($p = 0.10$), and duration of hospitalization ($p = 0.50$).

Conclusion: The EUC demonstrated fewer stent-related symptoms than the DJ-stent in tubeless PCNL, while both methods showed comparable safety and efficacy. The choice between EUC and DJ-stent should consider patient preferences and surgeon expertise. Further randomized controlled trials (RCTs) with larger sample sizes are needed to affirm these results.

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INTRODUCTION

Urolithiasis is a common urological condition, with over 115 million cases globally and a prevalence ranging from 1% to 13% across different regions.(1) Percutaneous nephrolithotomy (PCNL) is a cutting-edge procedure for stone removal via percutaneous access and has become the preferred treatment for renal stones larger than two cm or those unresponsive to extracorporeal shock wave lithotripsy (2–4).

Traditionally, PCNL involves using a nephrostomy tube to maintain urinary drainage, control bleeding, and provide access for additional procedures if needed (5, 6). In 1997, Bellman introduced a modified technique using a double-J stent (DJ-stent), referred to as tubeless PCNL.(6, 7) This technique has been further modified by leaving an externalized ureteral catheter overnight. A meta-analysis of 14 randomized controlled trials (RCTs) demonstrated that tubeless PCNL reduces hospital stay duration, shortens recovery time, lowers postoperative pain scores, and decreases urine leakage compared to standard PCNL (8).

Despite these advantages, DJ-stents are associated with several adverse events and need to be removed after a few weeks, causing additional distress and costs for patients (9). Conversely, external ureteral catheters (EUCs) often result in fewer postoperative complaints, are easier to remove without additional distress, and do not incur extra costs (10, 11).

The literature comparing EUC and DJ-stent in tubeless PCNL shows conflicting results. An RCT by Telha KA et al. found lower postoperative complications with DJ-stent compared to EUC in tubeless PCNL.(10) In contrast, an RCT by Habib B et al. reported fewer stent-related symptoms in patients using EUC compared to those using DJ-stents.(11) Given these inconsistencies, a meta-analysis is necessary to clarify the comparative efficacy of EUC and DJ-stent as drainage methods in tubeless PCNL. This study aims to consolidate the latest evidence on this comparison.

MATERIALS AND METHODS

Eligibility Criteria

The study protocol was registered in the PROSPERO database, number CRD42023415836. This review follows the PRISMA statement and Cochrane Handbook guidelines (12,13). Included studies met these criteria: (1) adult patients with upper urinary tract (kidney and ureter) calculi treated with tubeless percutaneous nephrolithotomy (PCNL) (Population); (2) comparison between external ureteral drainage (EUC) and double-J stent (DJ-stent) in tubeless PCNL (Intervention and Control); (3) data on stent-related symptoms, postoperative fever, urine leakage, perinephric collection (urinoma, perinephric abscess, perirenal hematoma), haemoglobin drop, transfusion rate, postoperative visual analog scale (VAS) scores, analgesic requirements, stone-free rate, surgery duration, and hospitalization duration (Outcome); and (4) observational studies (cohort/case-control) or randomized clinical trials (RCTs) (Study Design). Excluded studies included: (1) on pediatric populations; (2) using standard (non-tubeless) PCNL; (3) presented as case reports, case series, or review articles; and (4) not available in full-text.

Literature Search and Study Selection

Two independent authors searched English literature in Europe PMC, Scopus, Medline, and ClinicalTrials.gov until July 15, 2023, using combined key words: "(ureteral catheter OR ureteric catheter OR external ureteral catheter OR EUC OR ureteral stent) AND (double J stent OR DJ-stent OR double pigtail stent) AND (percutaneous nephrolithotomy OR tubeless percutaneous nephrolithotomy OR PCNL)". After removing duplicates, titles and abstracts were screened, and full-text evaluations were performed on articles passing the initial screening to ensure they met inclusion criteria. Discrepancies were resolved by a third author.

Data Extraction and Quality Assessment

Data descriptions including author names, publication year, study design, sample size, baseline

characteristics (mean age, sex distribution, stone location, stone size/burden, affected side), and outcomes were collected. Two independent authors tabulated the data into Microsoft Excel 2019. Risk of bias was evaluated using the Cochrane Collaboration's Risk of Bias version 2 (RoB v2) instrument for RCTs, evaluating randomization, deviations from intended interventions, outcome measurement, and missing outcome data. Evaluations were categorized as "low risk," "high risk," or "some concerns" (14). For cohort/case-control studies, the Newcastle-Ottawa Scale (NOS) from the Ottawa Hospital Research Institute (OHRI) was used, assessing participant selection, comparability, and outcome ascertainment, with scores ≥7 indicating "good" quality (15).

Statistical Analysis

Common mean difference (MD) of 95% confidence intervals was used to pool continuous outcomes using the Inverse-Variance formula. For haemoglobin drop, we used standardized mean difference (SMD) due to data expression variations. Dichotomous outcomes were pooled into risk ratio (RR) with 95% CI by the Mantel-Haenszel formula. Random-effect models were used due to expected heterogeneity. Heterogeneity was assessed with the I-squared (I^2) statistic, with $I^2 > 50\%$ indicating significant heterogeneity. Data expressed as medians and interquartile ranges (IQR) or as medians with minimum and maximum values were converted to means and standard deviations (SD) using formulas from Wan X et al. and Luo D et al (16,17). Publication bias analysis was performed when more than 10 studies were available for an outcome. We used Review Manager 5.4 from the Cochrane Collaboration as the main software for statistical analysis of this study.

RESULTS

Study Selection and Characteristics

A search across four international databases identified 155 studies. After screening and eliminating duplicate studies, 131 studies were successfully excluded, leaving only 24 studies for further assessment in full-text. Of these, 15 studies were eventually ruled out for the following reasons: 10 used standard (non-tubeless) PCNL as the comparison, 4 lacked a control group, and 1 was only an abstract. Hence, there were only 9 studies included in the final analysis (Figure-1) (10, 11, 18–24). Of these, 6 were prospective RCTs and 3 were retrospective observational studies. Sample sizes ranged from 23 to 227 in the EUC group and 23 to 189 in the DJ-stent group. Stone locations included the renal pelvis, renal calyx, upper ureter, and staghorn calculi, with mean stone sizes from 1.6 to 9.1 cm. Both EUC and DJ-stent insertions were performed immediately after the procedure. Data on catheter or stent removal timing were not described. Baseline characteristics of the included studies are outlined in Table-1.

Quality of Study Assessment

The assessment for the bias risk using the RoB v2 instrument found that two of the six RCTs had a "low risk" of bias across all five domains (19, 21). The other four RCTs were rated as having "some concern" due to insufficient information on allocation concealment post-randomization (10, 11, 18, 20), despite appropriate randomization methods and balanced baseline characteristics. The NOS tool assessed all cohort studies as "good quality" with scores of 8. The risk of bias assessments is summarized in Table-2.

OUTCOMES OF INTEREST

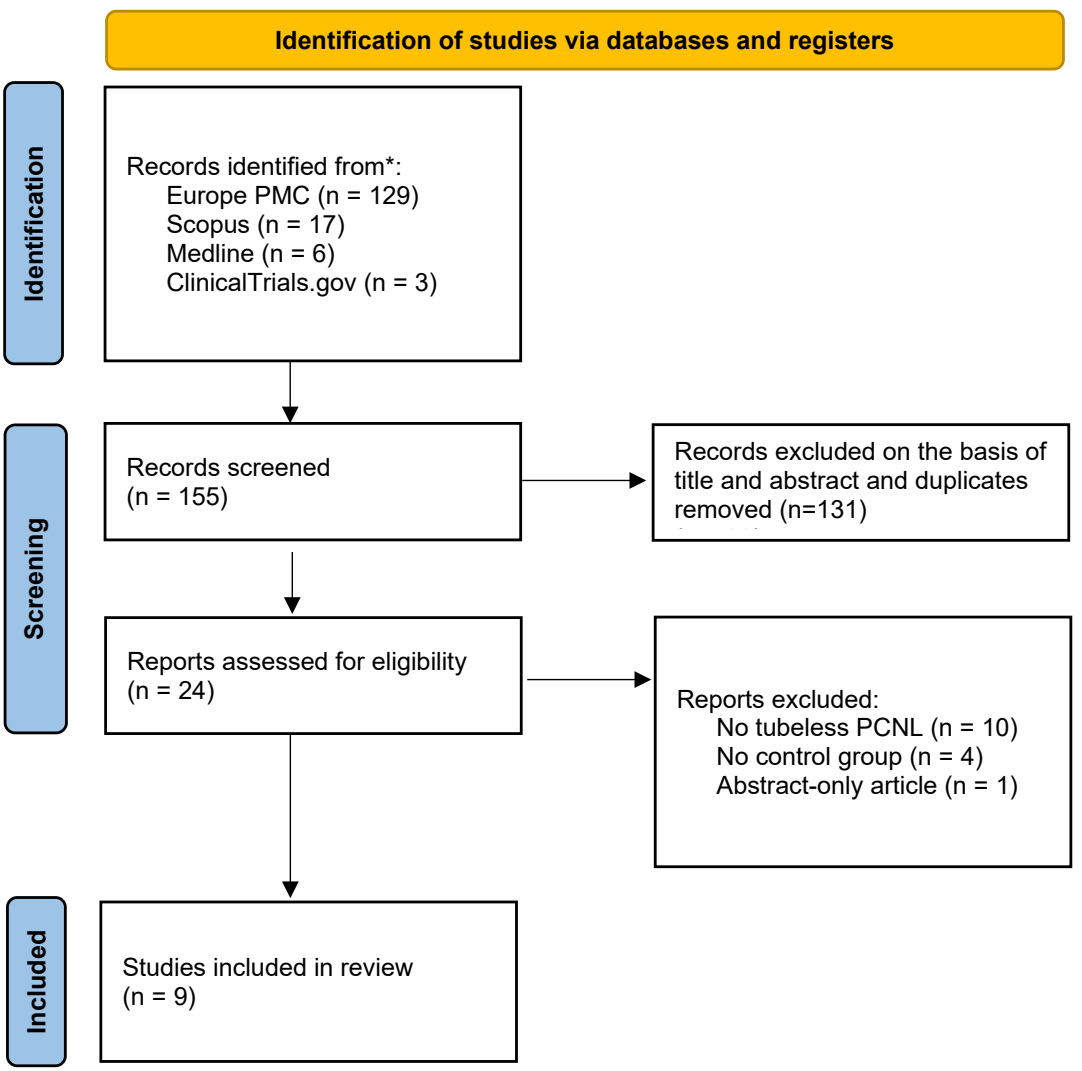
Stent-Related Symptoms

Pooled analysis from 3 RCTs (n = 235) showed that EUC was associated with a lower risk of stent-related symptoms compared to DJ-stent [RR 0.32 (95% CI 0.19 – 0.54), $p < 0.0001$, $I^2 = 24\%$] (Figure-2A).

Post-Operative Fever

Pooled analysis of 7 studies (n = 1,250) found no significant difference in post-operative fever rates between EUC and DJ-stent groups [RR 1.02 (95% CI 0.66 – 1.60), $p = 0.92$, $I^2 = 0\%$] (Figure-2B). Subgroup analysis by study design confirmed non-significant

Figure 1 - PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.



results for both RCTs (p = 0.98) and observational studies (p = 0.89).

Urine Leakage

Pooled analysis from 6 studies (n = 1,089) revealed no significant difference in urine leakage between EUC and DJ-stent methods [RR 1.53 (95% CI 0.79 – 2.98), p = 0.21, I^2 = 9%] (Figure-2C). Subgroup analysis by study design showed non-significant results for both RCTs (p = 0.16) and observational studies (p = 0.52).

Perinephric Collection

Pooled analysis from 4 studies (n = 900) found no significant difference in perinephric collection between EUC and DJ-stent methods [RR 0.82 (95% CI 0.12 – 5.87), p = 0.85, I^2 = 55%] (Figure-2D). Subgroup analysis showed non-significant re-

Table 1 - Characteristic of Included Study.

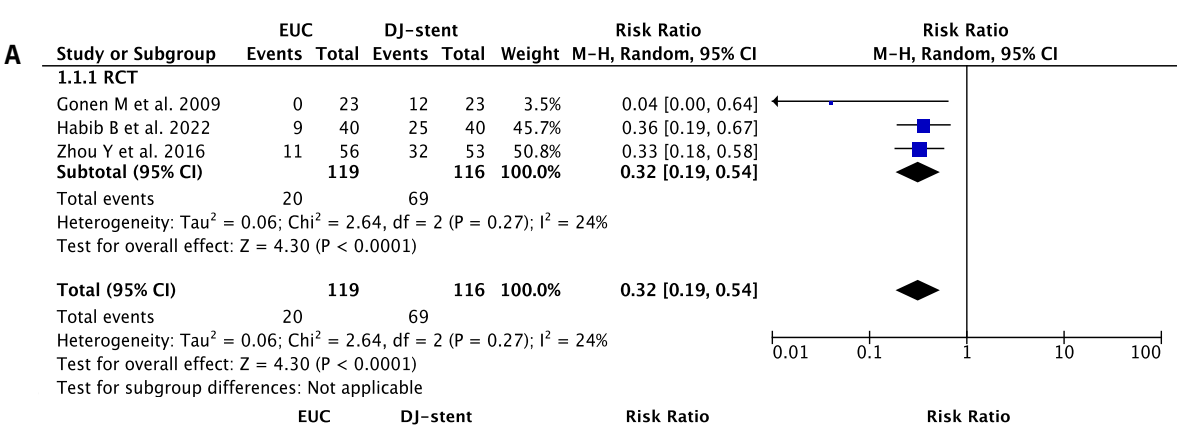
Authors	Study Design	Tubeless PCNL with EUC						Tubeless PCNL with DJ-stent					
		Sample size	Age (mean ± SD)	Male (%)	Stone location*	Stone measurement (mean ± SD)	Affected side	Sample size	Age (mean ± SD)	Male (%)	Stone location*	Stone measurement (mean ± SD)	Affected side
Randomized studies													
Gonen M et al.[18] 2009	Prospective RCT	23	44.5 ± 14.7	52.1%	P: 21.7% C: 34.7% P + C: 21.7% UU: 4.3% S: 17.3%	Burden: 909 ± 882 mm^2	R: 52.1% L: 47.9%	23	51.7 ± 13.9	47.9%	P: 30.4% C: 30.4% P + C: 8.7% UU: 17.4% S: 13%	Burden: 765.2 ± 610.7 mm^2	R: 47.9% L: 52.1%
Habib B et al.[11] 2022	Prospective RCT	40	41.5 ± 17.5	42.5%	NR	Size: 1.9 ± 0.4 cm	R: 45% L: 55%	40	39.7 ± 11.7	52.5%	NR	Size: 2.4 ± 0.6 cm	R: 42.5% L: 57.5%
Jiang H et al.[19] 2017	Prospective RCT	30	45.9 ± 11.4	46.7%	NR	Burden: 166 ± 78.7 mm^2	NR	30	49.4 ± 15.5	30%	NR	Burden: 169 ± 94.1 mm^2	NR
Mercado A et al.[20] 2013	Prospective RCT	35	48.9 ± 9	48.5%	NR	Burden: 4.9 ± 1.7 cm^2	NR	33	52.6 ± 11.9	51.5%	NR	Burden: 5.8 ± 2.8 cm^2	NR
Telha KA et al.[10] 2010	Prospective RCT	76	29 ± 8.9	73.6%	NR	Size: 4.3 ± 0.6 cm	R: 47.3% L: 52.7%	72	31 ± 9.2	75%	NR	Size: 4.9 ± 0.7 cm	R: 59.7% L: 40.3%

Zhou Y et al.[21] 2016	Prospective RCT	56	51.3 ± 12.6	55.4%	P: 42.9% C: 28.6% UU: 10.7% M: 17.8%	Size: 21.8 ± 9.19 mm^2	NR	53	48.6 ± 14.8	54.7%	P: 49.1% C: 32% UU: 7.5% M: 11.4%	Size: 22.5 ± 8.58 mm^2	NR
Observational studies													
Chung HS et al.[22] 2016	Retrospective cohort	61	56.6 ± 13.2	62.3%	P + C: 60.6% UU: 4.9% S: 23% M: 9.8%	Size: 4.2 ± 1.1 cm	R: 37.7% L: 62.3%	108	54.5 ± 12.6	58.3%	P + C: 54.6% UU: 3.7% S: 36.1% M: 6.4%	Size: 4.2 ± 1.4 cm	R: 41.6% L: 58.4%
Gonulalan U et al.[23] 2013	Retrospective cohort	148	46.8 ± 14.2	59.4%	P: 19.6% C: 43.9% P + C: 30.4% UU: 4.1% S: 2%	Burden: 33.8 ± 1.7 mm^2	NR	120	46.8 ± 14.2	59.4%	P: 19.6% C: 43.9% P + C: 30.4% UU: 4.1% S: 2%	Burden: 35.6 ± 1.5 mm^2	NR
Raharja PAR et al.[24] 2019	Retrospective cohort	227	50.7 ± 11.2	58.1%	P: 31.3% C: 27.8% P + C: 37.9% UU: 3.1%	Burden: 33.4 ± 17.2 mm^2	R: 49.3% L: 50.7%	189	50.3 ± 11.6	63.5%	P: 32.3% C: 28% P + C: 38.1% UU: 1.6%	Burden: 36.1 ± 22.1 mm^2	R: 46% L: 54%

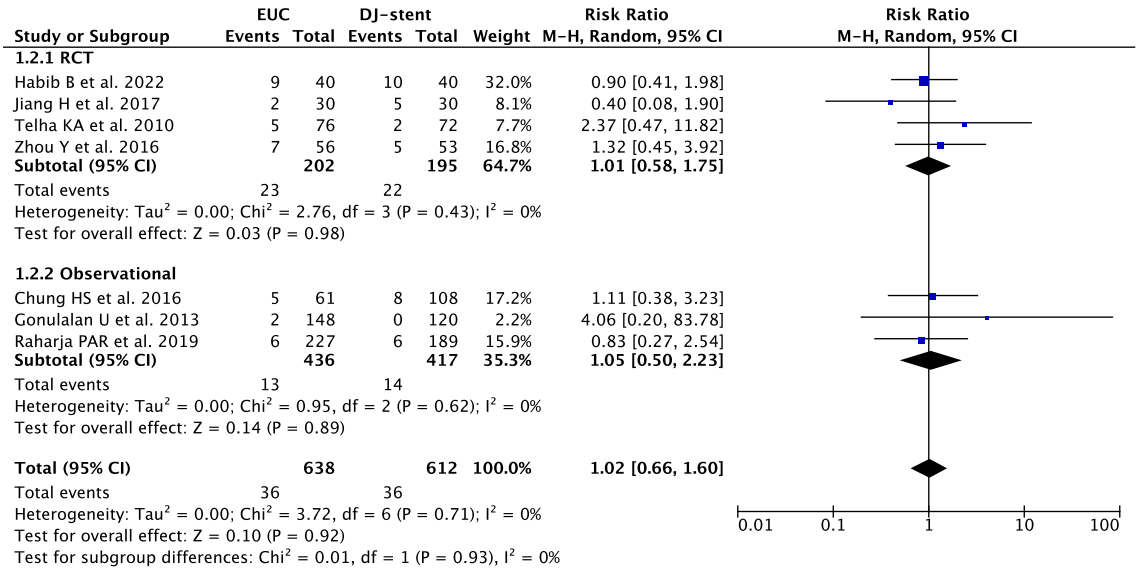
DJ-stent = double J stent; EUC = external ureteral catheter; NR = not reported; PCNL = percutaneous nephrolithotomy; RCT = randomized clinical trial; R/L = right/left; SD = standard deviation
*Stone location: P = pelvis; C = caliceal; P + C = pelvis and caliceal; UU = upper ureter; S = staghorn; M = multiple locations

Table 2 - Risk of Bias assessment of the included studies using RoB v2 tool.

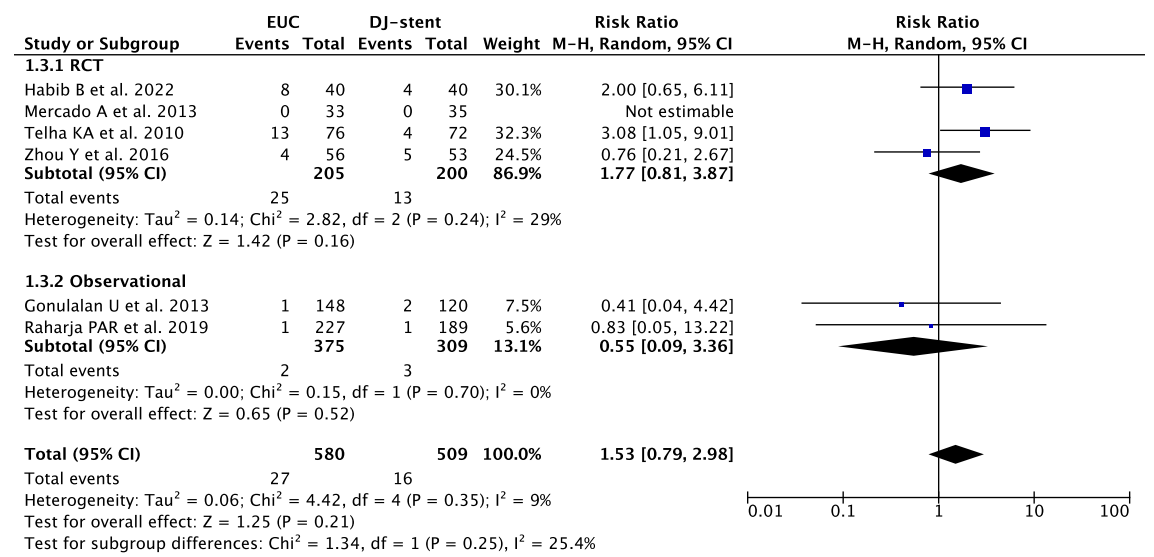
Figure 2 - Forest plot that demonstrates the comparison between EUC vs DJ-stent in tubeless PCNL in terms of: Stent-related symptoms (A), Postoperative fever (B), Urine leak (C), Perinephric collection (D), Haemoglobin drop (E), Transfusion Rate (F).



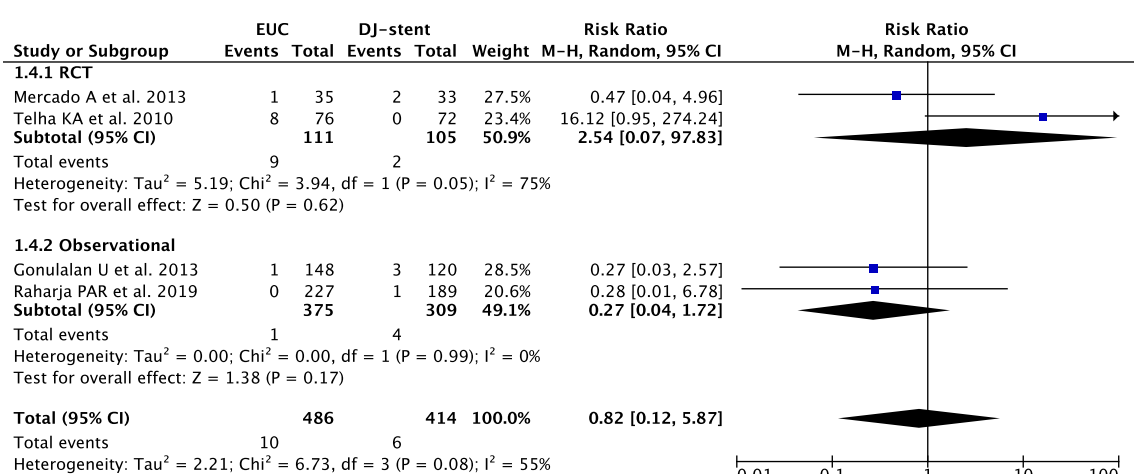
B

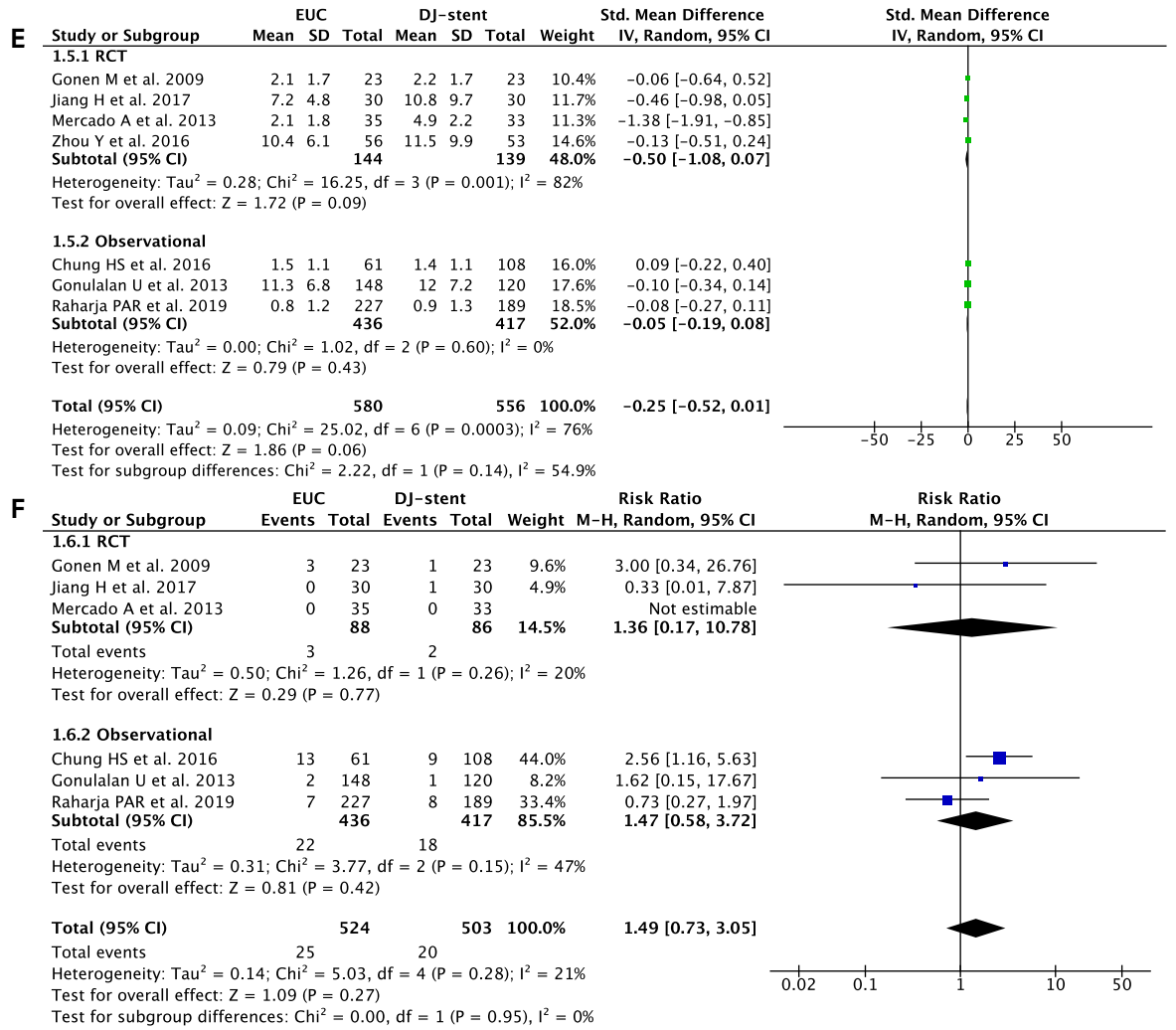

EUC
DJ-stent
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 RCT
Habib B et al. 2022 9 40 10 40 32.0% 0.90 [0.41, 1.98]
Jiang H et al. 2017 2 30 5 30 8.1% 0.40 [0.08, 1.90]
Telha KA et al. 2010 5 76 2 72 7.7% 2.37 [0.47, 11.82]
Zhou Y et al. 2016 7 56 5 53 16.8% 1.32 [0.45, 3.92]
Subtotal (95% CI) 202 195 64.7% 1.01 [0.58, 1.75]
Total events 23 22
Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
1.2.2 Observational
Chung HS et al. 2016 5 61 8 108 17.2% 1.11 [0.38, 3.23]
Gonulalan U et al. 2013 2 148 0 120 2.2% 4.06 [0.20, 83.78]
Raharja PAR et al. 2019 6 227 6 189 15.9% 0.83 [0.27, 2.54]
Subtotal (95% CI) 436 417 35.3% 1.05 [0.50, 2.23]
Total events 13 14
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Total (95% CI) 638 612 100.0% 1.02 [0.66, 1.60]
Total events 36 36
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 6 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%
0.01 0.1 1 10 100

C


EUC
DJ-stent
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.3.1 RCT
Habib B et al. 2022 8 40 4 40 30.1% 2.00 [0.65, 6.11]
Mercado A et al. 2013 0 33 0 35 Not estimable
Telha KA et al. 2010 13 76 4 72 32.3% 3.08 [1.05, 9.01]
Zhou Y et al. 2016 4 56 5 53 24.5% 0.76 [0.21, 2.67]
Subtotal (95% CI) 205 200 86.9% 1.77 [0.81, 3.87]
Total events 25 13
Heterogeneity: Tau² = 0.14; Chi² = 2.82, df = 2 (P = 0.24); I² = 29%
Test for overall effect: Z = 1.42 (P = 0.16)
1.3.2 Observational
Gonulalan U et al. 2013 1 148 2 120 7.5% 0.41 [0.04, 4.42]
Raharja PAR et al. 2019 1 227 1 189 5.6% 0.83 [0.05, 13.22]
Subtotal (95% CI) 375 309 13.1% 0.55 [0.09, 3.36]
Total events 2 3
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)
Total (95% CI) 580 509 100.0% 1.53 [0.79, 2.98]
Total events 27 16
Heterogeneity: Tau² = 0.06; Chi² = 4.42, df = 4 (P = 0.35); I² = 9%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.4%
0.01 0.1 1 10 100

D


EUC
DJ-stent
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 RCT
Mercado A et al. 2013 1 35 2 33 27.5% 0.47 [0.04, 4.96]
Telha KA et al. 2010 8 76 0 72 23.4% 16.12 [0.95, 274.24]
Subtotal (95% CI) 111 105 50.9% 2.54 [0.07, 97.83]
Total events 9 2
Heterogeneity: Tau² = 5.19; Chi² = 3.94, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 0.50 (P = 0.62)
1.4.2 Observational
Gonulalan U et al. 2013 1 148 3 120 28.5% 0.27 [0.03, 2.57]
Raharja PAR et al. 2019 0 227 1 189 20.6% 0.28 [0.01, 6.78]
Subtotal (95% CI) 375 309 49.1% 0.27 [0.04, 1.72]
Total events 1 4
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
Total (95% CI) 486 414 100.0% 0.82 [0.12, 5.87]
Total events 10 6
Heterogeneity: Tau² = 2.21; Chi² = 6.73, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.28), I² = 12.5%
0.01 0.1 1 10 100



sults for both RCTs (p = 0.62) and observational studies (p = 0.17).

Haemoglobin Drop

Pooled analysis from 7 studies (n = 853) showed no significant difference in haemoglobin drop between EUC and DJ-stent methods [SMD -0.25 (95% CI -0.52, 0.01), p = 0.06, I^2 = 76%] (Figure-2E). Subgroup analysis showed non-significant results for both RCTs (p = 0.09) and observational studies (p = 0.43).

Transfusion Rate

Pooled analysis from 6 studies (n = 1,027) found no significant difference in transfusion rates between EUC and DJ-stent methods [RR 1.49 (95% CI 0.73 – 3.05), p = 0.27, I^2 = 21%] (Figure-2F). Subgroup analysis showed non-significant results for both RCTs (p = 0.77) and observational studies (p = 0.42).

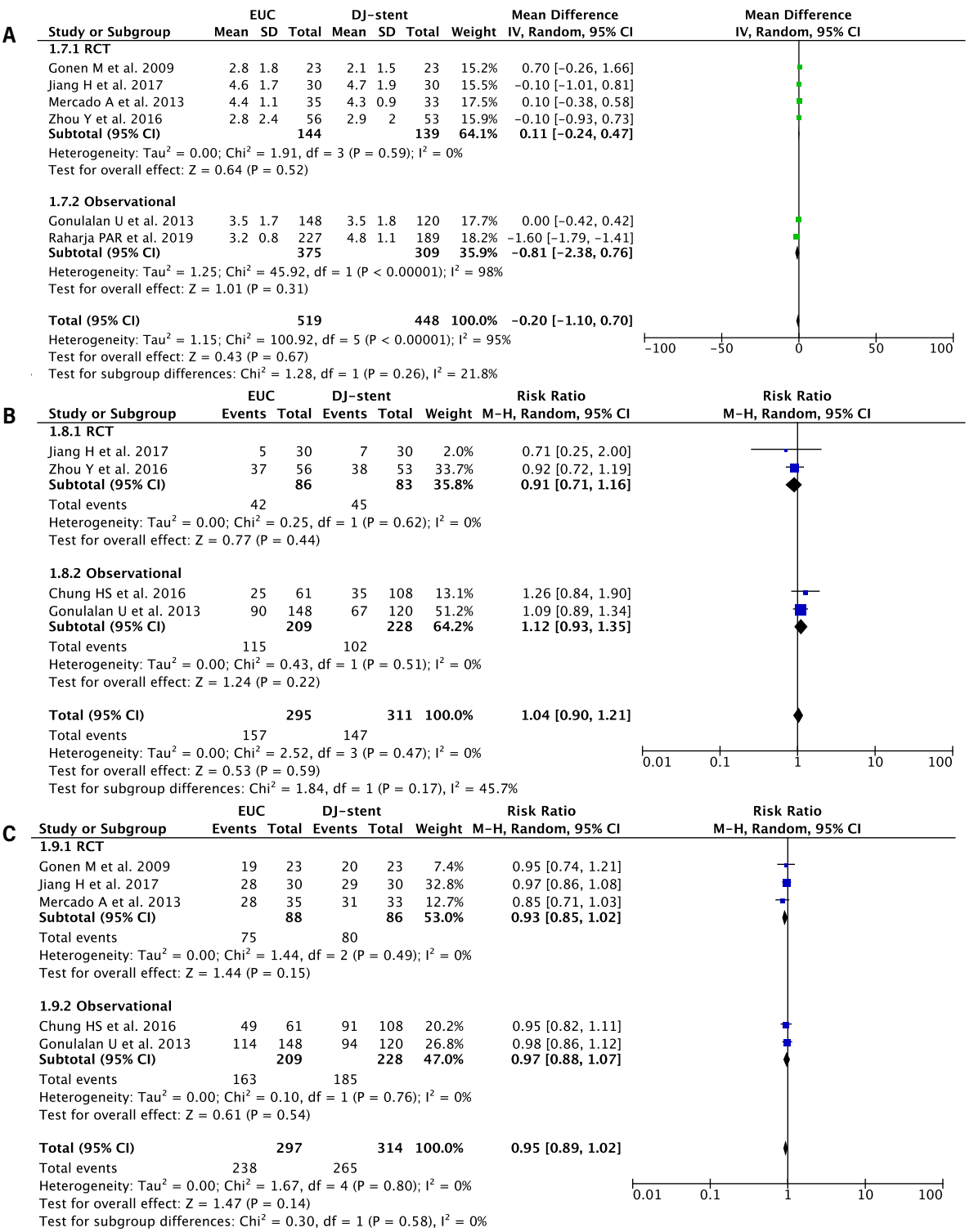
Visual Analog Scale (VAS)

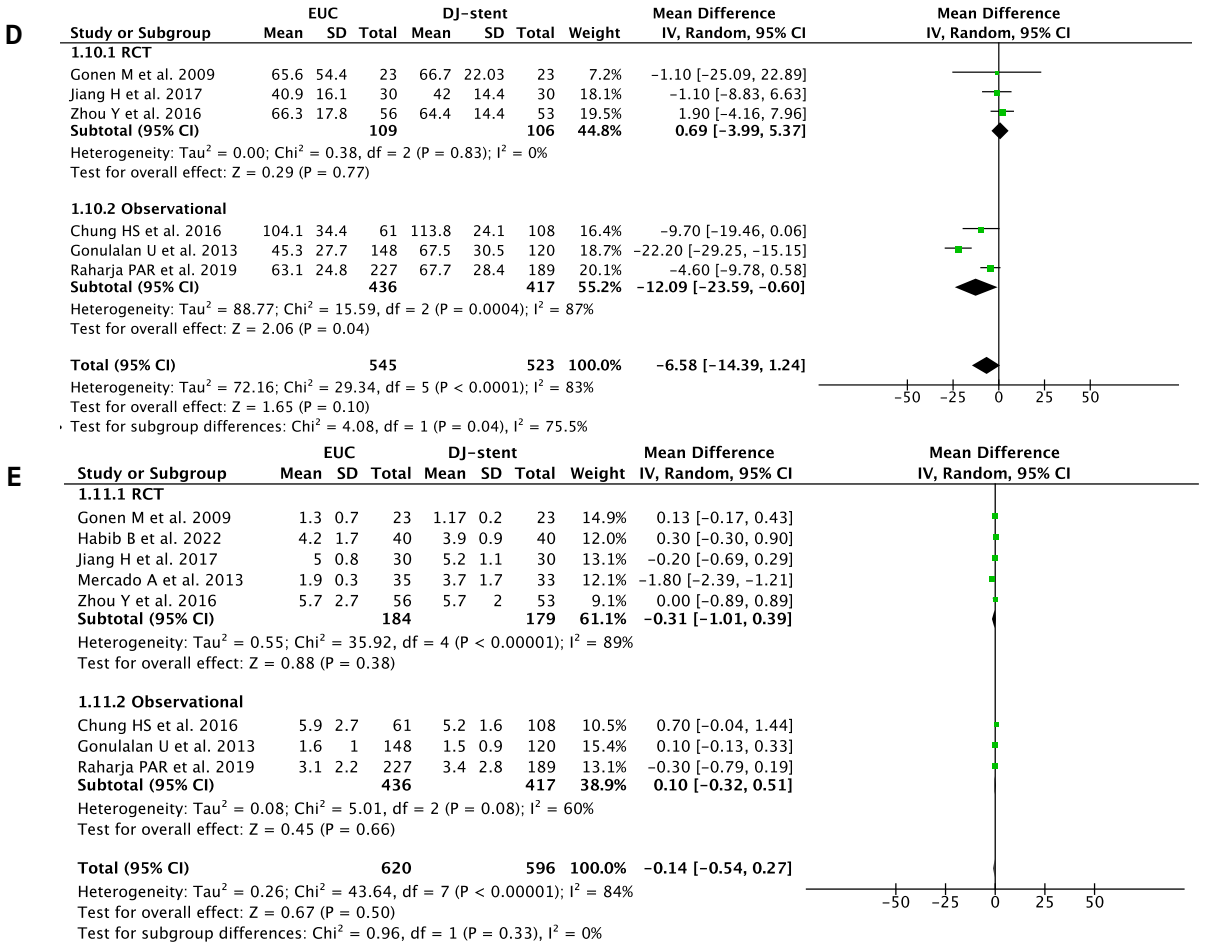
Pooled analysis from 5 studies (n = 611) showed no significant difference in post-operative VAS scores between EUC and DJ-stent methods [MD -0.20 (95% CI -1.10, 0.70), p = 0.67, I^2 = 95%] (Figure-3A). Subgroup analysis showed non-significant results for both RCTs (p = 0.52) and observational studies (p = 0.31).

Analgesic Requirements

Pooled analysis from 5 studies (n = 611) revealed no significant difference in analgesic requirements between EUC and DJ-stent methods [RR 1.04

Figure 3 - Forest plot that demonstrates the comparison between EUC vs DJ-stent in tubeless PCNL in terms of: VAS score (A), Analgesic requirement (B), Stone free rate (C), Duration of surgery (D), Duration of hospitalization (E).





(95% CI 0.90 – 1.21), p = 0.59, I^2 = 0%] (Figure-3B). Subgroup analysis showed non-significant results for both RCTs (p = 0.44) and observational studies (p = 0.22).

Stone-Free Rate

Pooled analysis from 5 studies (n = 611) demonstrated no significant difference in stone-free rates between EUC and DJ-stent methods [RR 0.95 (95% CI 0.89 – 1.02), p = 0.14, I^2 = 0%] (Figure-3C). Subgroup analysis showed non-significant results for both RCTs (p = 0.15) and observational studies (p = 0.54).

Duration of Surgery

Pooled analysis from 6 studies (n = 1,068) showed no significant difference in surgery duration between EUC and DJ-stent methods [MD -6.58 min (95% CI -14.39, 1.24), p = 0.10, I^2 = 83%] (Figure-3D). Subgroup analysis showed significant results for observational studies but with high heterogeneity [MD -12.09 min (95% CI -23.59, -0.60), p = 0.04, I^2 = 87%], while results for RCTs remained non-significant with low heterogeneity (p = 0.77, I^2 = 0%).

Duration of Hospitalization

Pooled analysis from 8 studies (n = 1,216) showed no significant difference in hospitalization duration between EUC and DJ-stent methods [MD -0.14 days (95% CI -0.54, 0.27), p = 0.50, I^2 = 84%] (Figure-3E). Subgroup analysis showed non-significant results for both RCTs (p = 0.38) and observational studies (p = 0.66).

Publication Bias

Bias analysis was not conducted because there were less than 10 studies available for each outcome. It makes both funnel plots and statistical tests to detect the publication bias to be less reliable.(25,26)

DISCUSSION

Our study demonstrates that using an external ureteral catheter (EUC) for drainage in tubeless percutaneous nephrolithotomy (PCNL) is associated with fewer stent-related symptoms compared to a double-J stent (DJ-stent) (25). However, no significant differences were found between EUC and DJ-stent regarding postoperative complications, visual analog scale (VAS) scores, analgesic requirements, stone-free rates, surgery duration, or hospitalization duration (25).

These findings are consistent with those of the previous meta-analysis by Chen Y et al., which also found that EUC had fewer stent-related symptoms than DJ-stent (25). Other outcomes, such as surgery duration and postoperative complications, showed no significant differences between the two methods. However, there are several important distinctions between our study and the meta-analysis conducted by Chen Y et al. (25).

First, our study included nine studies (six RCTs and three cohort studies), whereas Chen Y et al. included only seven studies (five RCTs and two non-RCTs) (25). By including more studies, our analysis provides a stronger evidence base and potentially more reliable conclusions.

Second, Chen Y et al. combined data from RCTs and non-RCTs in their analysis, which is not recommended by the Cochrane Handbook due to the potential biases inherent in observational studies (13, 25). Observational studies are susceptible to selection bias and information bias, which can impact the validity of the results.(13,26) Selection bias can lead to differences in baseline characteristics, and information bias can reduce data validity (26). RCTs minimize these biases through randomization and allocation concealment (27, 28). Our study adhered to Cochrane guidelines by separating the results of RCTs from those of observational studies, thereby ensuring more reliable findings (13).

Third, Chen Y et al. grouped postoperative complications into major and minor categories, potentially obscuring specific differences (25). Our study categorized complications into distinct types, such as postoperative fever, urine leakage, perinephric collection, haemoglobin drop, and transfusion rate, providing a clearer and more detailed comparison. Consequently, our study assessed 11 outcomes compared to Chen Y et al.'s nine (25).

The choice between EUC and DJ-stent for PCNL should consider their respective advantages and disadvantages. Our analysis highlights that EUC is associated with fewer stent-related symptoms and may be more cost-effective and practical, especially in resource-limited settings. EUC is easier to remove and more economical, which can be particularly beneficial for patients in developing countries or those with limited resources (29, 30). Despite fewer stent-related symptoms, the external ureteral catheter (EUC) does come with its own set of complications, notably spontaneous removal and displacement. These complications can lead to unexpected patient discomfort and the need for additional medical interventions. Given these potential issues, it is crucial for surgeons to carefully access clinical and physical condition of the patient.

DJ-stents offer specific benefits, such as maintaining ureteral patency, preventing obstruction, and facilitating the clearance of stone fragments. Despite their higher initial costs and potential discomfort, DJ-stents may be preferred in cases with complex stone burdens or challenging ureteral anatomy. (30) Ultimately, the decision should be based on individual patient characteristics, surgeon preference, and resource availability.

Endoscopic combined intrarenal surgery (ECIRS) is an emerging technique that combines retrograde and antegrade approaches for stone management (31). The increasing adoption of ECIRS has implications for the use of DJ-stents post-surgery, due to their ability to maintain ureteral patency and

prevent obstruction, which is particularly important when the ureter is manipulated extensively leading to local edema (32). Although our study focused on tubeless PCNL and did not evaluate ECIRS, it is crucial to acknowledge that the findings from our study may not be directly applicable to ECIRS. Future research should specifically address the outcomes and stent-related complications in the context of ECIRS to guide clinical practice accurately.

Our study has some limitations. The number of included studies, particularly the RCTs, are relatively small, with fewer than 100 participants in many cases. This may limit the generalizability of the results. Additionally, significant heterogeneity was observed in some outcomes, such as haemoglobin drop, VAS score, surgery duration, and hospitalization duration. This heterogeneity is likely influenced by variations in surgeon experience, surgical techniques, and outcome definitions. Differences in stone size and location across studies also contribute to this heterogeneity. Further well-designed larger RCTs are needed to affirm our findings. Moreover, data on long-term complications and readmission rates are lacking and should be addressed in future research.

CONCLUSION

Our study suggests that EUC results in fewer stent-related symptoms than DJ-stent in tubeless PCNL and is comparable in terms of postoperative complications, pain, surgery duration, and hospitalization. The choice between EUC and DJ-stent should be based on patient preference and surgeon judgment, considering individual risks and benefits. Future RCTs are recommended to validate our findings in this study.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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The Prevalence of Climacturia in Patients after Radical Prostatectomy: A Systematic Review

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ABSTRACT

Purpose: Prostate Cancer (PCa) is the most common non-cutaneous cancer in males, and Radical Prostatectomy (RP) is among the primary treatments for this condition. Our study aims to investigate the prevalence of climacturia (urine leakage at the moment of the climax), a potential post-RP change related to orgasm.

Material and Methods: A systematic review was conducted following PRISMA guidelines and registered on the PROSPERO platform. The search was performed using MEDLINE via PubMed.

Results: Thirteen studies met the inclusion criteria and were described separately. Within these studies, 5,208 patients were evaluated, among which 1,417 cases of climacturia were identified, with a prevalence of 27.2%. When we analyzed the robot-assisted radical prostatectomy (RARP) subgroup, the prevalence of climacturia was 5.7% vs 1.8% the open radical prostatectomy (ORP) subgroup.

Conclusion: Climacturia is a frequently underestimated complication by urologists. Given its significant impact on quality of life, it warrants greater attention from specialists following RP.

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INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer in males, with an approximate annual prevalence in 2024 of 299,010 cases in the U.S (1) In Brazil, PCa is also frequent, with an annual prevalence in 2023 of 71,730 cases, which represents 30% of all malignant neoplasms in males (2). In addition, PCa is the second most common cause of death in the male population, and it is expected that approximately 1 in 8 men will have this type of cancer diagnosed during their lives (3). Despite PCa having a high frequency among men, in most cases the cancer is localized at diagnosis and one of the most common treatments for these cases is radical prostatectomy (RP) (4).

In RP the entire prostate gland and the seminal vesicles are removed, and the surgery can be performed using three different approaches: the first and more traditional method is the open prostatectomy; the second is the laparoscopic prostatectomy; and the third is the robotic-assisted radical prostatectomy, in which the laparoscopic surgery is done assisted by robotic arms. Among the many possible complications of RP, erectile dysfunction, changes in orgasm and urinary incontinence are the most frequent (4). However, these complications seem to have neither a statistical difference when analyzing the techniques, the robotic platforms disposable in RARP or between ethnic groups (5–7). Nonetheless, minimally invasive surgery has best perioperative and complication outcomes (8).

Climacturia is one of the possible changes related to orgasm and pleasure that may occur after RP. It refers to a patient who notices various amounts of urine leakage at the moment of the climax (9). Research on this condition is relatively new: the first study to address orgasm-associated incontinence after RP was performed by Koeman et al. in 1996 (10); and the term climacturia was first coined by Lee et al. in 2006 (9). Prevalence of climacturia is still uncertain and variable. Several studies have reported rates ranging from 20% to 93% following RP (11, 12).

Climacturia is associated with a worse quality of life, as it can be bothersome and may lead to patient's avoiding sexual activity due to the embarrassment of urine leakage (11). While various series have evaluated the prevalence of climacturia, only two evaluated the prevalence of patient bother, with 44-48% of patients reporting significant bother and 21% perceiving a significant concern by their partners (12), but we know that the level of discomfort must be much greater but it simply has not yet been correctly assessed.

However, the pathophysiology of climacturia after RP is yet to be determined. Various mechanisms have been suggested, but none have been adequately tested (13). It is likely that anatomical alterations following RP, such as a decrease in functional urethral length, nerve damage and trauma to the bladder neck or urethral sphincter play a pivotal role (11, 14).

To the present moment, climacturia does not have a well-defined prevalence and probably has not been reported as adequately as it should, even though it is bothersome and impacts patients' quality of life. This study aims to understand the prevalence of this common complication of RP, increasing the awareness about this situation and pointing at possible solutions to this condition, through a systematic review of the literature.

MATERIALS AND METHODS

This systematic review was conducted according to PRISMA guidelines (15) and registered on the PROSPERO platform (PROSPERO no. CRD42021279827).

Search strategy

The research question was performed using the PICO method. We included patients who underwent RP, regardless of the surgical technique. Intervention was surgical treatment and the comparison was whether, or not, patients reported climacturia after RP. The main outcome variable was the prevalence of the climacturia in all patients analyzed.

We systematically searched for climacturia as a post-RP complication in the MEDLINE via PubMed database, from January 2016 until May 2024. The search terms used included the following: "radical prostatectomy" OR "post-radical prostatectomy" OR "post-prostatectomy"

[MeSH] AND "climactur*" OR "Orgasm-Associated Incontinence" OR "Orgasm-associated urinary incontinence" [MeSH] OR "sexual incontinence" OR "arousal incontinence" OR "coital incontinence" OR "complicat*" [MeSH]. The term "complication" was restricted to the title, as we sought to filter studies that aim to directly analyze the complications of RP. Inclusion criteria were journal articles published in the last eight years (2016-2024) in English, which presented the prevalence or incidence of the climacturia after RP.

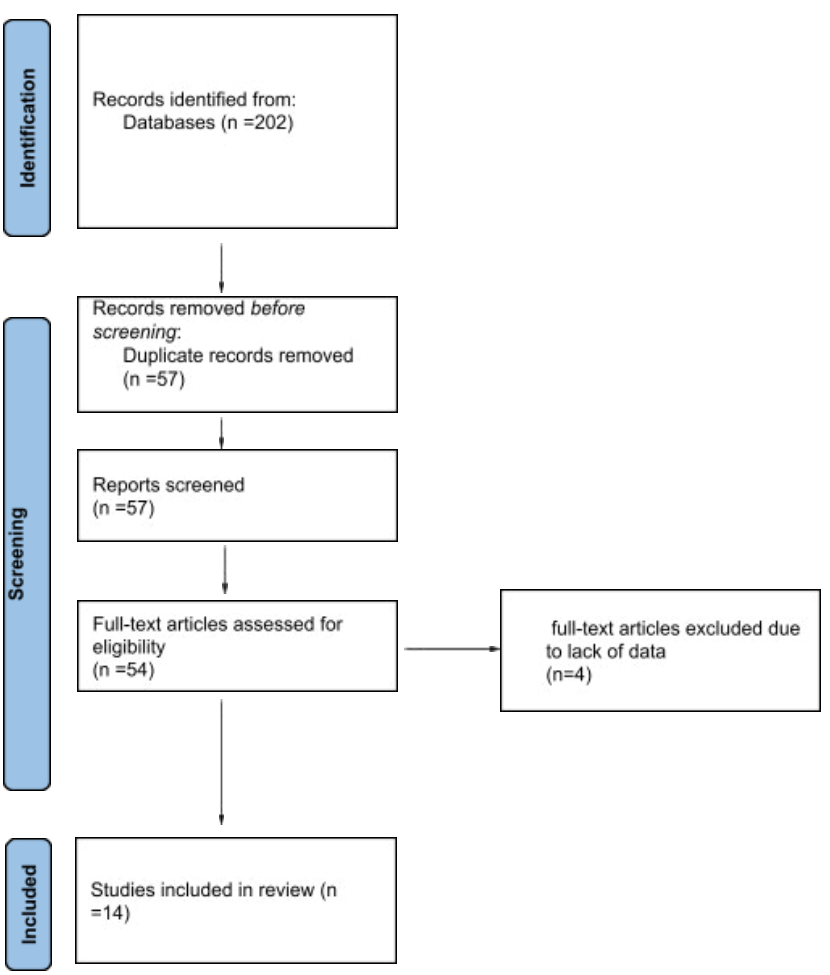
Studies were included in the Rayyan platform (16) for recording decisions. The search and selection process adhered to the requirements of PRISMA guidelines (15).

Prospective studies, retrospective studies, observational cohorts and case series reporting the prevalence of climacturia were included. We excluded case reports and articles that referred to the same series of patients. In these circumstances, we included the most recent series from the same group. Gray literature, such as congress presentations, meeting abstracts, posters, etc., was not included in the study. Figure-1 summarizes the flow diagram of study screening and selection.

Data extraction and quality assessment

Data collected from each manuscript included: author names, year of publication, country, study design, analytic sample size and prevalence of climacturia.

Figure 1 – Flow chart summarizing the studies selection process.



Two authors were responsible for selecting the articles. They dually and independently reviewed titles and abstracts, before conducting a full-text review of all potentially eligible studies. At each stage, decisions were compared and discrepancies resolved by consulting a third researcher. An Excel® spreadsheet was used for record decisions.

We analyzed the quality of the non-randomized studies using the Newcastle-Ottawa Quality Assessment Scale (NOS), more precisely the scale for Case Control Trials. In this method we evaluated studies with eight different items that were divided into three sections (Selection, Comparability and Exposure). The studies could range from 0-4 points in the Selection section, from 0-2 points in the Comparability section, and from 0-3 points in the Exposure section. NOS scale assigns scores range from one to nine, with research scoring less than four points are considered to be of low quality. Quality assessment of the included studies is presented in Table-1 (17).

RESULTS

The search strategy resulted in 202 articles. Of these, 144 were excluded after we analyzed their titles and abstracts. Of the remaining 57 articles, four did not have their full text found due to lack of data. After the full text analysis of the 54 remaining articles, 14 studies comprising 5,186 patients were included (Figure-1). Table-2 summarizes the data extracted from each manuscript.

From fourteen studies which met the criteria, twelve (12, 18–20, 22–29) were retrospective reviews, while one was a case series of two subjects (21) and one was a prospective pilot study (19). A total of 5,208 urological procedures were related to these studies, resulting in 1,417 cases of climacturia with different patterns which, in most cases, were not even discussed due to a different focus of the articles. The overall prevalence of 27.2% represents that over a quarter of the individuals have episodes of arousal incontinence at the climax after RP.

Regarding the prevalence of climacturia by procedure, only four studies distinguish whose patients were submitted to ORP or RARP. When we analyze the RARP subgroup, the prevalence of climacturia was 5.7% vs 1.8% the ORP subgroup.

DISCUSSION

Although the well-known complications of RP, such as erectile dysfunction and stress urinary incontinence, are actively investigated postoperatively and have a wide range of treatments available, other complaints, such as changes in orgasm and climacturia, have not received much attention. However, it has an important impact on quality of life. The literature, until now, does not bring a precise prevalence of climacturia among the studies. Our study aims to address this gap in the literature by presenting an overall prevalence of climacturia at 27.3% across the studies examined. In addition, when performing a subgroup analysis, we could demonstrate that patients submitted to ORP had 1.8% vs 5.7% of those who underwent RARP. Nonetheless, this data does not highlight the real subgroup prevalence, due to the lack of data between the studies selected.

The majority of studies that were found in the initial search, before the selection process, didn't include the prevalence of climacturia. Although, even with the low number of articles eligible to the review, two articles (12, 18) were important in defining the scenario of climacturia in recent years.

Even if some hypotheses are raised (25), there is no consensus about the pathophysiology of climacturia. Koeman et al. were the first to propose that climacturia is a direct side effect of damage to the internal sphincter during RP. This incontinence would probably be caused by the complete absence of the patient's internal sphincter, combined with the "normal" relaxation of the sphincter at the time of orgasm (10). This hypothesis was weakened as other studies suggested a possible correlation between external sphincter injury and internal sphincter dysregulation, eventually causing climacturia (31). On the other hand, O'Neil et al. reported climacturia in 5.2% of patients treated with radiation as radical therapy for PCa (32). This supports the hypothesis

Table 1 - Quality assessment of the studies using NOS scale.

Study	Newcastle-Ottawa Scale			Score
	Selection	Comparability	Exposure	
Capogrosso et al. (2016) (18)	★★	★★	★★★	7
Yafi et al. (2018) (19)	★★★	★★	★★★	8
Andrianne (2019) (20)	★★	★	★★	5
Salter et al. (2019) (12)	★★	★★	★★	5
Towe et al. (2019) (21)	★★	★	★	4
Valenzuela et al. (2019) (22)	★★	★	★★	5
Jimbo et al. (2020) (23)	★★	★★	★★	6
Nolan et al. (2020) (24)	★★	★	★★	5
Sullivan et al. (2020) (25)	★★	★★	★★★	7
Parra López et al. (2021) (26)	★★★	★★	★★★	8
Hammad et al. (2023) (28)	★★	★★	★	5
Honda et al. (2022)(27)	★★★★	★★	★★★	9
Huynh et al. (2023) (29)	★★★★	★★	★★★	9
Gamberini et al. (2024) (30)	★★★	★	★★	6

that radiation-induced nerve damage can lead to the development of climacturia. In addition, attached to the theory of nerve damage, during surgery the indirect stretching of the pudendal nerve can disrupt the physiological mechanism of ejaculation, thus leading to functional dyssynergia (33).

Capogrosso et al. collected answers of 749 patients from a non-validated 28-item questionnaire. Predominantly, 395 (52.7%) patients were treated with Open Radical Prostatectomy (ORP) and 354 (47.3%) with Robot Assisted Radical Prostatectomy. The groups didn't differ in postoperative outcomes. Furthermore, 221 patients (29.5%) reported postoperative climacturia. It was evoked as occurring at every orgasm by 42 patients (19%) and described as occurring more than half of the time by 31 patients (14.1%). Self-reported volume of orgasm-associated urine leakage was ≥ 5mL in 85.2% of the patients. Interestingly, robotic-assisted RP was correlated with faster climacturia recovery compared to open RP (18).

In a prospective, multicenter, pilot study of 38 patients that presented with climacturia and/or mild urinary incontinence (two or less pads per day) post-RP, the patients underwent inflatable penile prosthesis insertion with concomitant placement of a mini-jupette graft. Data were collected in the US, France, Belgium, Germany and Korea. Of the 38 patients who underwent the mini-jupette sling procedure, 30 had post-RP climacturia. Additionally, after the procedure, climacturia showed improvement in 22 of 28 (78.6%) patients with follow-up, of which 19 (67.9%) had complete resolution (19).

Andrianne, in a cohort study, described post-RP climacturia with significant psychological suffering in six of fifteen patients (incidence of 40.0%). between 2006 and 2015 (20).

Table 2 - Individual characteristics of studies included in the systematic review.

Author (year)	Country	Study design	Analytic sample size	Surgical approach	Overall climacturia	Climacturia by procedure
Capogrosso et al. (2016) (18)	Italy	Retrospective study	749	395 (ORP) 354 (RARP)	221	94 (ORP) 127 (RARP)
Yafi et al. (2018) (19)	USA	Prospective pilot study	38 (36/38 RP)	16 (ORP) 20 (RARP)	30	NA
Andrianne (2019) (20)	Belgium	Retrospective study	15	NA	6	NA
Salter et al. (2019) (12)	USA	Retrospective study	3207	1122 (ORP) 770 (LP) 1315 (RARP)	745	NA
Towe et al. (2019) (21)	USA	Case series	2	2 (RARP)	2	2 (RARP)
Valenzuela et al. (2019) (22)	USA	Retrospective chart review	36	NA	30	NA
Jimbo et al. (2020) (23)	USA	Retrospective study	RP alone (139), RT alone (22), RP + RT (31)	NA	73	54 (RP alone), 3 (RT alone), 16 (RP+RT)
Nolan et al. (2020) (24)	USA	Retrospective chart review	17	NA	11	NA
Sullivan et al. (2020) (25)	USA	Retrospective study	194	NA	56	NA
Parra López et al. (2021) (26)	Spain	Retrospective study	62	NA	11	NA
Honda et al. (2022)(27)	Japan	Retrospective study	259	259 (RARP)	44	44 (RARP)
Hammad et al. (2023) (28)	USA	Retrospective study	38	10 (ORP) 11 (LP or RARP)	21 (remaining cohort)	NA
Huynh et al. (2023) (29)	USA	Retrospective study	339	339 (RARP)	127	127 (RARP)
Gamberini et al. (2024) (30)	Brazil	Retrospective study	60	46 (ORP) 11 (LRP) 3 (RARP)	40	NA

RP = radical prostatectomy; RT = radiation therapy; RARP = robot-assisted radical prostatectomy; ORP = open radical prostatectomy; NA = not available

Salter et al. performed a retrospective analysis at a single center of patients who presented for the management of postoperative sexual dysfunction between 2006 and 2018, who had previously undergone RP. A total of 3,207 patients post-RP were included in the analysis. The mean age was 61±7 years. Most (97%) were heterosexual and 82% were Caucasian. The median time between the procedure and survey was 203 days. Forty-one percent of men had a RARP, 35% had an ORP and 24% underwent a laparoscopic prostatectomy. Men with climacturia were slightly younger (60.3 years old) than men without climacturia (61.6 years old). Forty-five percent of the men with climacturia admitted to being bothered by their symptom, 62% reported mild bother, 29% moderate and 9% severe bother. Of them, 745 (23%) experienced climacturia post-RP: 70% reported a small volume of urine leakage (drops) whereas 24% reported moderate volume (<30mL) and only 6% had large volume (>= 30mL). Thirty-one percent of men categorized climacturia as rare, 47% as occasional, and 22% as frequent (12).

Towe et al. reported a case series that documented two patients who presented with concomitant erectile dysfunction and climacturia following RP, and who subsequently underwent IPP surgery with placement of an autologous fascial mini jupette sling (21).

Valenzuela et al. aimed to describe a technique modified by Yafi et al of the Mini-Jupette sling with placement of an inflatable penile prosthesis (IPP) (19). They followed 36 patients during postoperative clinic visits and with telephone calls. From those, 30 patients (83%) reported climacturia (22).

Jimbo et al. developed an 89-item questionnaire for all patients who presented to their Men's Health Clinic between 2014 and 2017. A total of 1,359 patients fulfilled the intake questionnaire. Of these, 1,117 (82%) reported that they were able to achieve orgasm and 192 (17%) patients had a prior history of definitive therapy for PCa: 139 (72%) underwent RP alone, 22 (11%) had a history radiotherapy (RT) alone and 31 (16%) underwent RP and RT. Among the 139 patients with a history of RP, 54 (39%) reported climacturia and among the 31 patients who underwent RP and RT, 16 (52%) reported the same problem. Overall, 60/170 patients (35%) undergoing RP or RT+RP reported climacturia. Additionally, 26 (15.2%) of those who performed RP or RP+RT felt some level of discomfort. Finally, among the 925 patients with no prior history of prostate cancer or RP, 22 (2.4%) reported climacturia, of which ten (45%) said it was uncomfortable for them (23).

Nolan et al. sent 42 patients a questionnaire that was revised from Lee et al (9). They aimed to assess patients' changes in climacturia complaints after implantation of a urethral sling as a treatment for stress incontinence after RP. From those patients, 17 were returned for analysis. The median age of the sample at RP was 64 years. At the time of the study, 11 (64.7%) reported continued urinary loss during sexual arousal (24).

Sullivan et al. analyzed retrospectively a database of their sexual medicine database. A total of 194 patients were included in the analysis, 138 patients without and 56 (28.8%) with climacturia. The mean age of patients that reported climacturia were 59±7 years. Applying a multivariate model of logistic regression, urethral width was associated with climacturia (OR 1.34, 95% CI 1.05-1.71, p=0.02) (25).

Parra Lopez et al. conducted a retrospective study of 100 patients that underwent RARP. After excluding patients who didn't meet the eligibility, they were left with 62 patients who were investigated about presence and intensity of climacturia, orgasm quality, incontinence and erectile dysfunction. The mean age of patients with climacturia was 56 years. Eleven patients (17,9%) reported climacturia. Of those, 82% reported slight leaks and 18% reported severe leaks. In 37% of these patients, climacturia occurred in all orgasms (26).

Honda et al. found 417 eligible patients from 523 patients who underwent RARP. They excluded patients who underwent neoadjuvant therapy, adjuvant therapy, or died of other causes. They collected answers of 259 patients with a median age of 67 years old. Overall, 145 (56%) patients were sexually active after surgery; of those, 44 patients (30.3%) reported

climacturia, with 39 (88.6%) losing a small amount of urine, four (9.1%) losing a moderate amount, and one (2.3%) losing a large amount. Furthermore, they performed a multivariate logistic regression analysis to identify predictors and found urinary incontinence (OR 3.13, 95% CI 1.20-8.15) as a significantly predictive factor of climacturia (27).

Huynh et al. aimed to primarily measure the incidence and risk factors for climacturia and penile length shortening following RARP. Eight-hundred patients were retrospectively surveyed, with 339 (42%) and 369 (46%) responding about climacturia and penile length shortening. Among these patients, 127 (37.5%) reported climacturia. And this complaint was related to the absence of bilateral nerve sparing (29).

A recent study published by Gamberini et al. retrospectively surveyed sixty patients and actively investigated the occurrence of orgasmic disorders. The authors reported climacturia as the most common orgasmic disorder in 40 (66.6%) patients. However, only 14 patients (35%) reported that it frequently occurs more than half of the time. Among the patients who reported climacturia, 72.5% classified it as mild losses (30).

Moreover, several conservative and invasive treatments have been proposed for climacturia. For instance, behavioral treatment (such as emptying the bladder before sexual arousal and using a condom), pelvic floor muscle training, and the use of external occlusion loops (28, 34, 35). For patients with persistent bothersome climacturia, surgical interventions are sometimes required. The Mini-Jupette procedure (an inflatable penile prosthesis and a sling) has shown that it makes the climacturia disappear in 82% of patients who presented with erectile dysfunction and climacturia (20). The ideal material used as graft still needs to be determined. Valenzuela et al. published an approach called "Male Urethral Mini-Sling". Their modification to the Andrianne's "Mini-Jupette" was based on the proximal placement of a modified sling (Virtue™ mesh from Coloplast), leading to the complete resolution of climacturia and of stress urinary incontinence in 93% of patients (22).

Our systematic review has some limitations - we have accessed only one database (Pubmed), and included only literature in English language, which may have left out of our review other relevant publications. Our data is based on the validity and analysis of our selected published studies. In addition, the majority of the studies found are of low methodological quality. Most of them are retrospective and only two are of reliable quality. Finally, further studies about climacturia should be conducted. The creation of some sort of questionnaire that could be used by all patients of RP describing the frequency, duration and other characteristics of the climacturia would be a useful tool to evaluate, prevent and treat this common manifestation that may occur after radical prostatectomy.

CONCLUSION

Our review demonstrated an average prevalence of 27.3% of climacturia in patients undergoing different surgical techniques to treat PCa. Climacturia is underestimated by urologists, due to the lack of medical knowledge and the lack of a more targeted assessment through validated questionnaires, for example. This is a very relevant complication, as quality of life and sexuality are greatly compromised. Prospective studies are needed to determine the most appropriate approaches to managing this relatively common complication after radical prostatectomy.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Surgical Management of Ischemic Priapism: what are the New Options?

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ABSTRACT

Ischemic priapism is a true urologic emergency. Prompt intervention is required to alleviate the compartment syndrome and restore perfusion to the corporal bodies; failure to do so results in irreversible damage, fibrosis, and profound erectile dysfunction. This paper's objective is to review current literature surrounding the management options for ischemic priapism, focusing on newer surgical techniques. A PubMed database search was performed in June 2024, encompassing the terms "priapism," and "surgical management." Articles were reviewed by two authors independently and included if they were deemed to pertain specifically to management of ischemic priapism. In the acute setting (certainly for priapism lasting <24 hours), management is often successful using bedside maneuvers such as aspiration, irrigation, and injection of sympathomimetic agents. For more prolonged priapism, more aggressive intervention is often warranted. Newer tunneling techniques—including penoscrotal decompression and the corporal snake maneuver—have shown promising preliminary results, not just in terms of priapism resolution but also perhaps sexual function recovery.

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INTRODUCTION

Ischemic priapism is a urologic emergency defined as a painful erection lasting >4 hours; it presents with a rigid penis with tissue hypoxia as confirmed by corporal blood gas (1). The natural sequelae of ischemic priapism are corporal ischemia, necrosis, and fibrosis, eventually culminating in erectile dysfunction (2). The longer the duration, the more challenging it becomes to treat (1). As such, prompt treatment of priapism is imperative to preserve erectile function.

At 24-36 hours after priapism onset, the rate of erectile dysfunction is around 50% (3). Medical management at this point usually fails, and surgical approaches are required (4). Currently, there is no consensus definition of "prolonged" ischemic priapism by the American Urological Society or the Sexual Medicine Society of North America (5). However, given the difference in management for long-standing priapism we herein define acute ischemic priapism as that lasting <24 hours in duration and prolonged ischemic priapism lasting ≥24 hours.

Management methods for ischemic priapism range from simple corporal aspiration and irrigation to operative intervention via shunt or penile prosthesis placement. The choice of approach depends on the priapism duration, failure of other modalities, patient's baseline erectile function, and surgeon comfort with procedures (6). In this review, we describe classic ischemic priapism management strategies and then consider more recently described surgical techniques.

MATERIALS AND METHODS

A narrative review was carried out on the management options for ischemic priapism, with analysis of papers published over the past 50 years. A comprehensive PubMed search was performed in June 2024 using the Medical Subject Heading (MeSH) term: "priapism." Additional free-text searches were performed using the following terms: "ischemic priapism," "management," "tunneling." Articles were reviewed individually by two authors (RB and SR) for inclusion. Articles were excluded if upon review the focus was non-ischemic priapism, malignant priapism, or pediatric priapism. Non-English articles and case reports were also excluded.

MANAGEMENT OF ACUTE ISCHEMIC PRIAPISM

Acute ischemic priapism is typically managed with a combination of corporal irrigation/aspiration and injection of sympathomimetic agents (7). After ensuring adequate local anesthesia via local block, an arterial blood gas needle is inserted into one corpus cavernosum, taking care to avoid urethral injury. Blood gas analysis showing low pO2, high pCO2, and acidic pH confirms ischemic priapism. If blood gas shows high pO2, low pCO2, and normal to slightly basic pH, this suggests nonischemic priapism, which does not routinely require intervention (8). Treatment may be offered in select cases; however, these management strategies are beyond the scope of this review.

After confirmation of ischemic priapism, a 16- or 18-gauge needle is placed into the lateral corpora. A combination of irrigation and aspiration with normal saline disrupts and evacuates the ischemic coagulum from the corporal bodies. Manual pressure on the phallus shaft may also help to decompress the clotted blood. This process typically resolves the penile compartment syndrome and allows the return of oxygenated blood, facilitating recovery (9).

Injecting a sympathomimetic agent along with aspiration and irrigation can improve chances of successful detumescence and is recommended in AUA guidelines (5). Phenylephrine, an alpha-1 agonist, is the preferred agent for priapism takedown given its lower risk for cardiotoxicity versus similar medications like epinephrine, norepinephrine, and ephedrine. Telemetry monitoring is mandated given the risk of hypertension and reflex bradycardia. These agents should be avoided in those patients with uncontrolled hypertension and monoamine oxidase inhibitor use (10). Success rate for priapism resolution is ~30% with aspiration alone, whereas the combination of aspiration, injection of sympathomimetic, and irrigation have a reported efficacy of 43-81% (11, 12).

While these approaches are fairly effective in the acute setting, they are typically not effective for prolonged ischemic priapism (13). Given their less invasive nature, it is generally recommended to attempt aspiration/irrigation initially. Should this fail, however, surgical intervention should be considered promptly.

MANAGEMENT OF PROLONGED ISCHEMIC PRIAPISM

Prolonged ischemic priapism, recurrent ischemic priapism, or priapism refractory to medical management pose a more challenging task for management. For these patients, failure of non-surgical management should prompt consideration of operative intervention in order to relieving the compression syndrome (5). Surgical approaches vary widely and include distal shunts, proximal shunts, tunneling procedures, or immediate penile prosthesis implant. Each carries its own risks, benefits, and varying likelihood of resolving prolonged ischemic priapism.

Distal Shunts

When non-surgical intervention fails, AUA guidelines recommend the use of distal shunts with or without tunneling procedures (5). The principle of these procedures is to create a connection from the corpora cavernosum to drain the stagnant deoxygenated blood and introduce fresh, oxygenated blood. Various distal corpora-glanular shunts have been described and may be categorized as either percutaneous or open shunts. Percutaneous shunts include the Winter shunt, Ebbehoj shunt, and T-shunt, while open distal shunts consist of the Al-Ghorab shunt (14-16). No studies have compared these shunts head-to-head.

A Winter's shunt involves the use of a large bore biopsy needle to create a connection between the corpora cavernosum and the glans penis (16). This can be performed multiple times in each corpora or bilaterally to maximize drainage of ischemic blood. While relatively simple and quick, there may be limited drainage due to small shunt size. The Ebbehoj shunt uses an 11-blade scalpel rather than a needle to generate larger connections from the glans to the corpora cavernosum (15). Given the larger degree of shunting, this method tends to be more effective than the Winter's shunt at achieving detumescence (8). A T-shunt involves using a 10 blade to make a 'T'-shaped incision on the glans (17). Typically, there is quick return of abundant ischemic blood and detumescence once this shunt is created. Though quite effective, this method has associated risks of urethral injury and glans necrosis (18).

If the above attempts at percutaneous distal shunting are insufficient, open distal shunts can be considered. The Al-Ghorab shunt involves excising 1 cm of tunica albuginea from the distal portion of the corpora cavernosa (14). This tends to be the most effective distal corpora-glanular shunt, but it is also more invasive, has a higher rate of erectile dysfunction, risk of urethral injury, glans necrosis, glans numbness, and damage to dorsal arteries or dorsal nerves (8, 18).

From a physiologic standpoint, their arterial inflow increases into the corpora cavernosa after a corpora-glanular shunt is created. This "post-ischemic hyperemia" presents similarly with decreased rigidity and pain but persistence of woody fibrosis of penile on exam (5, 18). The increased cavernosal pressure can cause a small shunt—such as Winter's or Ebbehoj—to close, causing recurrent priapism (18).Signs of recurrent or increased penile rigidity and pain should raise concern, and cavernosal blood gas should be repeated; if confirmed, more invasive management is required (5). Larger T-shunts face a lower risk of post-ischemic hyperemia from shunt closure. However, collagen exposure and tunica albuginea injury-mediated activation of the clotting cascade can cause shunt thrombosis (18). The use of antiplatelet agents in the perioperative period may decrease this risk.

Success rates for distal shunts range from 65-75% in retrospective studies, while rates of *de novo* erectile dysfunction range from 14-25% (12, 19, 20). Given the real risk of developing erectile dysfunction, it bears noting that these distal shunts necessarily violate the glans penis and the distal cap of the corporal bodies. Since refractory erectile dysfunction may require penile prosthesis placement, this glans violation has the theoretic potential of increasing the risk of cylinder extrusion through the glans.

Proximal Shunts

Proximal shunts, such as the Quackel's and Grayhack shunts, were previously considered for cases of persistent acute ischemic priapism after a failed distal shunting procedure. However, there is limited high-quality data supporting their efficacy, with only 62 documented cases from 1960 to 2020. Of these, there was significant heterogeneity with respect to patient characteristics, duration of priapism, prior aspiration/irrigation attempts, and prior attempts at distal shunting. While aggregate data from these patients revealed a successful priapism resolution rate of 77%, reported complications included urethral injury, urethrocutaneous fistulas, cavernositis, and even pulmonary embolism.18 Given the limited supporting data after over six decades, the most recent American Urological Society/Sexual Medicine Society of North America guidelines committee deems proximal shunts a historical procedure (5).

Tunneling Procedures – The New Frontier

In cases of prolonged ischemic priapism, distal shunting may be ineffective due to the sustained hypoxia that has caused significant edema and tissue necrosis, especially at the distal portion of the corpora cavernosa (8). More recently, tunneling techniques have been described in an effort to improve outcomes in refractory cases and avoid the need for upfront penile prosthesis placement (21). This was first popularized by Dr. Arthur "Bud" Burnett who modified the Al-Ghorab shunt; once the distal corporal window has been achieved through a 2cm glans incision, a 7/8 Hegar dilator is passed several inches proximally within the corpora (10). This so-called "snake" maneuver allowed improved disruption of the ischemic coagulum, which could then be evacuated via manual compression. In the initial description, 8 of 10 patients treated for ischemic priapism using this technique achieved successful resolution of priapism with no recurrence (22). The group recently published their long-term experience with this technique and found that 92% of patients treated with distal shunt with tunneling achieved priapism resolution (24/26) despite mean priapism duration of 58.7 hours versus only 54% of those undergoing distal shunt alone (30/56, p<.001) (23). Of those with documented sexual function at follow-up, 43% (6/14) reported erections firm enough for penetration with or without the use of phosphodiesterase 5 inhibitors. Tom Lue similarly described tunneling using urethral sounds passed retrograde via a T-shunt for refractory cases where the shunt alone does not provide adequate decompression (24).

As an alternative, penoscrotal decompression was described by Morey in 2018 (25). He noted that during penile prosthesis placement for refractory ischemic priapism, detumescence was achieved during the process of corporal dilation before the device was even placed. While achieving similar disruption of the ischemic coagulum, this method avoids violation of the distal glans, which has both cosmetic and functional implications. Penoscrotal decompression is performed via a transverse penoscrotal incision similar to that used for penoscrotal penile prosthesis placement. Dissection is carried out to the corporal tunica albuginea which are then incised down to the layer of the spongy erectile tissue. Disruption of the ischemic blood is achieved by passing a metal pediatric Yankauer (or alternative dilator such as Brooks or Hegar if the former is not available) both distally and proximally in the corpora. Decompression is then achieved via manual compression of the penile shaft. In the initial description, this process was carried out unilaterally, with the expectation that deoxygenated blood could be evacuated via the septal communication between the corpora. However, there was a higher rate of early priapism recurrence (2/10) in those undergoing unilateral decompression versus 0/15 in those in whom the procedure was performed bilaterally (26). Early reports also suggest that many patients regain some degree of erectile function even after prolonged priapism (26). For those that do develop refractory erectile dysfunction, a penile prosthesis may be placed in a delayed fashion with less concern for distal erosion.

Reflecting their enhanced efficacy at resolving cases of refractory ischemic priapism, tunneling procedures are now included in the newest American Urological Society/Sexual Medicine Society of North America guidelines. Currently, the guidelines state that clinicians should consider the addition of corporal tunneling in those patients with persistent priapism after distal shunt. However, given more recent data supporting the efficacy

and potential benefits of penoscrotal decompression, it is likely to be addressed in future iterations of the guidelines as suggested by thought leaders in the field (27).

No studies have been conducted comparing the efficacy of tunneling performed via a distal glans-violating approach versus a penoscrotal glans-sparing approach. Among surgeons who had performed both procedures, a recent survey suggests that penoscrotal decompression was perceived as more effective than distal tunneling procedures (6). However, this was a survey of surgeon impression and thus subject to significant potential recall bias. The likelihood of sexual function recovery was seen as similar between the two approaches. While multi-institutional comparative studies are required, these are unlikely to be performed given the relative rarity of ischemic priapism (28). For this reason, the decision on which tunneling procedure to perform should be made at the discretion of the surgeon in the absence of more definitive data (22, 24, 26).

Early vs Delayed Penile Prosthesis Implantation

Early penile prosthesis has been widely accepted in the management of refractory or recurrent ischemic priapism (13, 29). In such cases, the vascular smooth muscle is affected by hypoxia and acidosis as soon as 6 hours following the onset of priapism (30). Left unchecked, replacement of the vascular smooth muscle with dense corporal fibrosis is inevitable. This fibrosis leads to tissue contraction and penile shortening, and also complicates placement of penile prosthesis cylinders in the delayed setting (31).

Placement of a penile prosthesis in the acute setting thus offers the opportunity to restore sexual function in a less hostile surgical environment before the corporal fibrosis develops. This also facilitates placement of full-sized cylinders, preserving penile length and bolstering patient satisfaction (32). By contrast, with delayed placement, intra-operative complications such as cross-over events and urethral injury are more frequent, and narrow cylinders may be required (33-35). Nearly 90% of subspecialty urologists perceive prosthesis placement to be more difficult after priapism, especially when performed in the delayed setting (6). The risk of device infection may also be as high as 10% for delayed placement versus 6% for acute placement (36).

Early prosthesis placement may be performed using malleable or inflatable devices, with neither clearly showing superiority (33). Malleable devices are technically easier to place, afford a lower cost to the patient, and obviate the concern for mechanical breakdown. However, the risk of distal perforation may be higher when the glans has been violated by distal shunts (36, 37). Should a malleable be placed initially, this may be revised to an inflatable device in the future (33). Others have reported excellent outcomes when inflatable devices are placed primarily (31). Inflatable options have improved concealability when deflated and higher patient satisfaction (31). Current opinions suggest that 75% of subspecialty urologists prefer using a malleable device in the acute setting, while 84% prefer inflatable devices in the delayed setting (6). Decision of which implant to use should be made jointly between surgeon and patient after thorough discussion of risks and benefits.

The data for tunneling procedures—both penoscrotal decompression and the "snake" maneuver—suggests that some patients do recover some degree of sexual function (23, 26). In these patients, placement of a penile prosthesis may represent overtreatment. In this vein, 70% of subspecialty urologists now prefer tunneling procedures for cases of prolonged ischemic priapism (duration >24 hours) while only 10% would choose up front penile prosthesis placement (6). One ongoing research question is whether MRI may determine which patients should receive upfront IPP placement versus tunneling procedures. Smooth muscle necrosis seen on MRI correlates with the development of erectile dysfunction and may be a useful tool to decide if a patient should undergo immediate IPP placement to avoid this sequela (38).

For those patients who do require delayed penile prosthesis placement, multiple techniques have been described to mitigate the associated risks. The use of vacuum erection devices pre-operatively improves blood flow to the corpora and suppresses pro-fibrotic factors, which may reduce the technical challenge of corporal dilation (39). Cavernotomes may facilitate corporal dilation, while extended corporotomies and distal

counter-incisions facilitate formal corporal excavation. Both the AMS 700™ (Boston Scientific, Marlborough, MA) and the Titan (Coloplast Corporation, Minneapolis, MN) now come in narrow cylinder options which have greatly improved the ability to successfully place cylinders in hostile corpora. As with malleable device placement, these patients may be offered revision to full-sized cylinders if desired (40).

CONCLUDING THOUGHTS

Prolonged cases of ischemic priapism are associated with increasing difficulty in achieving detumescence and significantly increased risk of erectile dysfunction. Non-surgical management may be effective in the acute setting, but in cases of refractory or prolonged priapism, distal shunts may be required. Newer tunneling procedures appear to more effectively evacuate deoxygenated blood and potentially facilitate recovery of erectile function.

While upfront penile prosthesis placement was previously considered the procedure-of-choice for cases of severe refractory priapism, there has more recently been a paradigm shift towards the utilization of tunneling procedures in the acute setting. The high efficacy of these maneuvers and the potential for sexual function recovery, potentially allow penile prostheses to be avoided in some patients; further studies are needed to investigate this hypothesis. For those ultimately requiring delayed penile prosthesis placement, the increased complication rates should be acknowledged, although multiple techniques exist to facilitate device placement. Ultimately, there is no proven algorithmic approach to the management of this challenging condition; interventional approach remains a nuanced one that depends on both patient and surgeon factors.

COMPLIANCE WITH ETHICAL STANDARDS

This study was exempt from IRB review given its nature as a narrative review

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CONFLICT OF INTEREST

None declared.

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Comparison of Morphological and Functional MRI Assessments of Periprostatic Fat for Predicting Prostate Cancer Aggressiveness

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ABSTRACT

Purpose: The objective of this study was to evaluate whether morphological (linear measurements) and functional (ADC value) assessments of periprostatic fat can predict the aggressiveness of prostate cancer (PCa) over a 5-year follow-up period.

Material and Methods: This retrospective study included patients with histologically proven PCa who underwent 3.0T MRI between July 2016 and June 2018. Clinical and demographic data collected included PSA, PSA density (dPSA), ISUP grade, clinical and pathological staging, and treatment details. MRI-derived parameters were assessed by an experienced radiologist, who measured subcutaneous and periprostatic fat thickness, and calculated ADC values from ROI plots in periprostatic fat. Clinical and MRI parameters were analyzed for associations with biochemical recurrence, systemic metastasis, and PCa-related mortality.

Results: After applying exclusion criteria, 109 patients were included. Using the Cox model, dPSA ($p<0.01$), systemic disease at diagnosis ($p<0.01$), and mean ADC ($p<0.02$) were independent predictors of overall survival (OS). For progression-free survival (PFS), only dPSA ($p<0.01$) and systemic disease at diagnosis ($p<0.01$) were significant predictors. In the Poisson Model for systemic recurrence risk, dPSA had a relative risk (RR) of 1.04 (95%CI 1.0-1.07, $p=0.03$), systemic disease at diagnosis had an RR of 63.3 (95%CI 3.7-86.4, $p<0.01$), and average ADC had an RR of 3.42 (95%CI 1.52-7.69, $p<0.01$).

Conclusions: The ADC value of periprostatic fat may serve as an additional tool for PCa risk stratification, correlating with poorer outcomes such as systemic recurrence and overall survival. If validated by external, prospective, multicenter studies, these findings could impact future therapeutic decisions.

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INTRODUCTION

Prostate cancer (PCa) is the most common non-cutaneous cancer in men and the fourth leading cause of cancer mortality in men worldwide. In 2020, over 1.4 million new cases of prostate cancer were reported globally (1).

A wide variety of external and environmental factors are associated with the risk of developing PCa (2, 3). Specifically, different eating habits and genetic susceptibilities have been shown to influence the risk of PCa (4). Family history, BRCA gene mutations, and metabolic syndrome (especially hypertension and obesity) are associated with a higher risk of developing PCa (5). Dietary factors, such as alcohol intake, have also been linked to a higher risk of PCa and PCa-related mortality (6). Therefore, preventive interventions at all levels of care may influence adherence to disease treatment and prevention of its progression.

Currently, the diagnosis of PCa is based on prostate biopsy, preferably after a Prostate MRI has identified a lesion (7-10). The fusion-guided US/MRI biopsy has become the modality of choice, significantly enhancing the detection of clinically significant PCa, while reducing the detection of clinically insignificant cases (11). In addition to the development of new software, artificial intelligence models have increased the positive predictive value of fusion biopsies compared to those using MRI alone (12). Also, over the past decade, liquid biopsy has been extensively studied as a non-invasive alternative for detecting and predicting prostate neoplasia, primarily through the quantification of serum biomarkers (13).

Multiparametric magnetic resonance imaging (mpMRI) is used beyond diagnosis to identify the extent of extra prostatic involvement, invasion of neurovascular structures, and for stratification of clinically significant lesions, with high accuracy (14).

The apparent diffusion coefficient (ADC) is an MRI quantitative parameter that calculates the extent of diffusion of water molecules within tissues using automatic software applied to MRI with diffusion-weighted imaging (DWI) (15). ADC measurement can be performed on a single slice by selecting a specific region of interest (ROI) in the relevant finding displayed on the map or can be volumetric when the entire lesion is evaluated (16). Low ADC values can indicate regions of high cellularity. Previous studies have shown that the ADC of periprostatic tissue is lower in patients with prostate cancer than in those without cancer and that there is an inverse correlation between ADC of the PCa and the Gleason score, which is an indicator of tumor aggressiveness (14).

The relationship between obesity and more aggressive cancers has been reported in many studies across various primary sites (17). The increase in serum growth factors and levels of pro-inflammatory cytokines resulting from obesity may explain this association (18). García-Martínez et al. also identified a relationship between the telomere ratio of subcutaneous and visceral fat as a possible biomarker in colorectal carcinoma (19). Furthermore, obesity has been linked to an increase in periprostatic adipose tissue, playing a specific role in the induction and progression of prostate neoplasia (20). The thickness of periprostatic and subcutaneous fat has been reported as a potential predictor of unfavorable outcomes in patients with prostate cancer, as it indirectly indicates a higher body mass index and greater risk of recurrence and mortality (21).

While the prognosis of prostate cancer can rely on several factors, the stage of the disease at diagnosis is a primary predictor (22). Most patients have low-risk, non-life-threatening tumors, but some have extremely aggressive disease, compromising their quality of life and leading to high rates of morbidity and mortality (23).

Current therapeutic options depend on the severity and extent of the disease and range from minimal or non-invasive methods, such as active surveillance (AS), to more aggressive treatments like radical prostatectomy, external radiotherapy/brachytherapy, chemical or surgical castration, and chemotherapy (24, 25). Identifying tumors with an unfavorable prognosis that present as localized disease at diagnosis could benefit patients through more aggressive therapeutic approaches (26).

Since functional changes usually precede morphological alterations, the objective of this study was to evaluate whether functional assessment (ADC

value) of periprostatic fat is a better predictor of the aggressiveness of PCa than morphological assessment (linear measurements) over a 5-year follow-up.

MATERIAL AND METHODS

Patient Selection

This retrospective study was conducted at a single center with a waiver for informed consent due to its retrospective nature (IRB number 69251723.3.0000.5440). Using electronic data from the Radiology and Pathology records, we searched for "prostate cancer" and "prostate neoplasia" in both data sets, retrospectively identifying all patients with these diagnoses, confirmed by biopsy and/or surgery, who had undergone 3.0T multiparametric MRI between July 2016 and June 2018. This approach allows the study to evaluate each patient's outcomes over the 5-year oncological follow-up, including overall survival, disease-free period, biochemical recurrence, emergence of metastases, lymph node disease, and disease-related deaths. We also reviewed the electronic medical records of all patients, verifying their age, race, PSA levels, multiparametric MRI results, pathology (biopsy or surgical specimen), and treatments used.

The exclusion criteria were: a) absence/unsatisfactory MRI images; b) absence of PSA at diagnosis or follow-up; c) patients who had already undergone some PCa treatment; d) patients with 1.5T MRI examination; e) loss of follow-up; f) interval between MRI and anatomopathological study greater than 6 months (Figure-1).

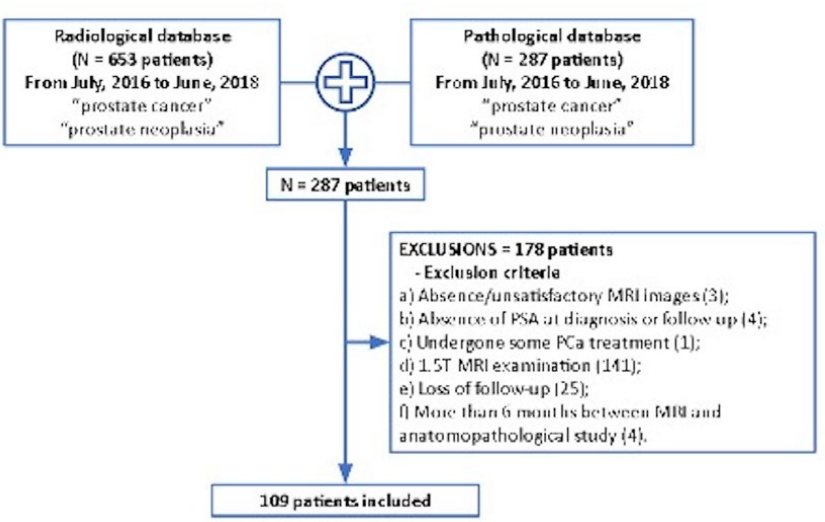
MRI Protocol

All MRI exams were performed using a 3 Tesla MRI machine, Achieva, manufactured by Philips (The Best- Netherlands), with a 16-channel Pelvic Phased Array coil. A protocol following PI-RADS v2.1 guidelines was employed (14), including high-resolution T2 acquisition in three planes, diffusion-weighted imaging (DWI) with b values of 0, 250, 500, and 1000 mm/s^2, and another acquisition with a b value of 1400 mm/s^2. Dynamic contrast enhancement (DCE) sequence was obtained with the injection of 0.1 mmol/kg gadolinium-based contrast agent, capturing images every 6 seconds for 10 minutes.

MRI Analysis

The PI-RADS classification was obtained from the original report and was based on a double reading

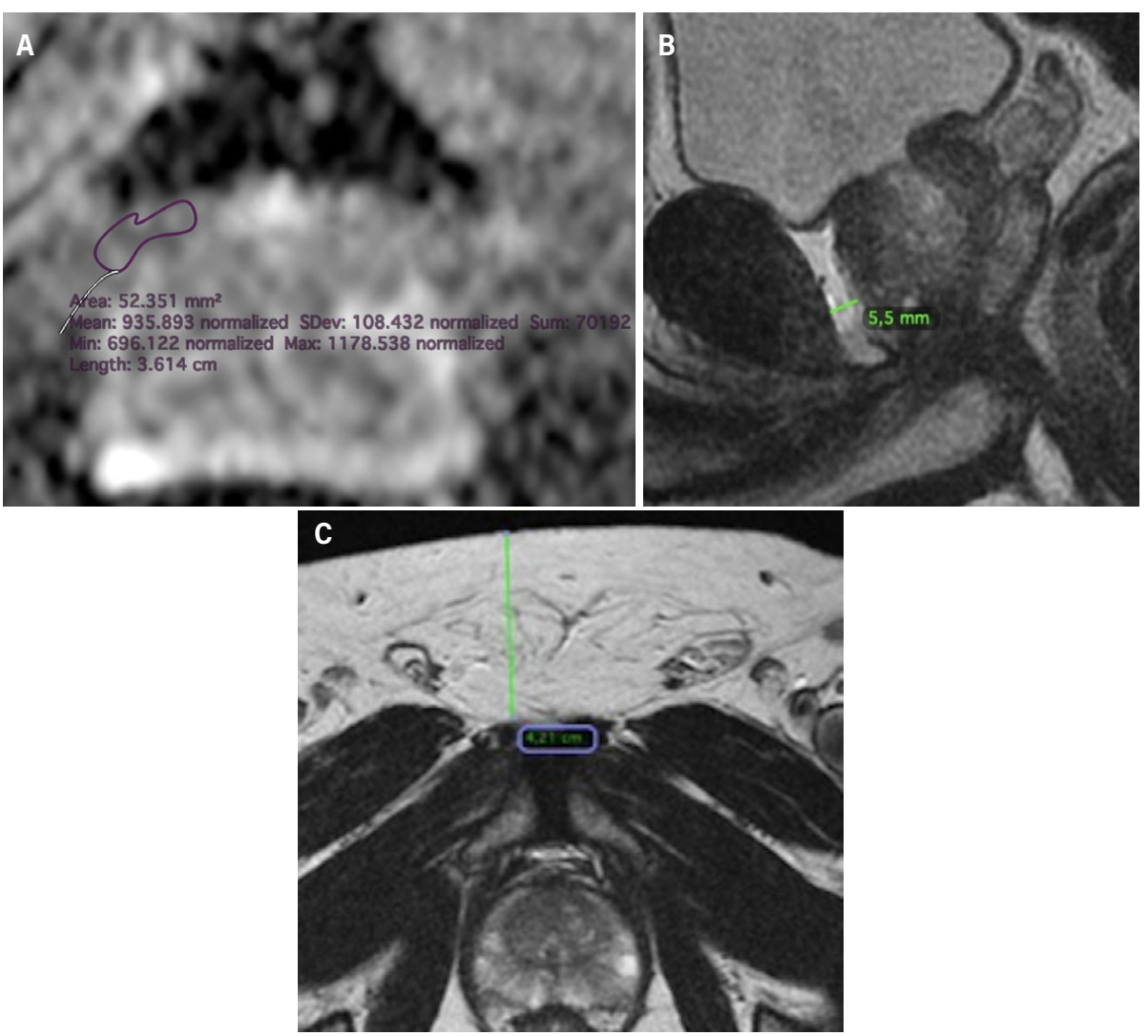
Figure 1 - Flowchart showing database, the exclusions and final number of patients enrolled in this cohort.



by an experienced reader (15 years of prostate imaging) and one of four fellows in abdominal imaging. All images were reviewed by a radiologist with 5 years of experience for the quantitative analysis. The mean ADC value was calculated in the axial plane, with a circular ROI with an average diameter of 0.5 cm in the periprostatic fat between the prostatic base and the pubis (Figure-2A). Linear measurements of subcutaneous and periprostatic fat were performed in the axial and sagittal T2 plane using the same anatomical parameters as the ADC (Figures 2B and C).

The gold standard was histopathological analysis, either by biopsy (n=38 patients) or radical prostatectomy specimen (n=71 patients). Prostate biopsies were performed by attending physicians using cognitive or automated fusion, given the patients had prior MRI, using transrectal approach. For patients with both biopsy and prostatectomy, the analysis prioritized the surgical specimen for higher accuracy in locating index lesions. The correlation between tumor location in the surgical specimen/biopsy and MRI images was

Figure 2 – A) Measurement of the mean ADC value of periprostatic fat, using a ROI placed in the anterior periprostatic fat. B) Linear measurement of periprostatic fat thickness in the T2WI sagittal plane, and C) Linear measurement of subcutaneous fat thickness in the T2WI axial plane.



performed by the senior researcher with around 20 years of abdominal imaging experience.

Electronic medical records were analyzed by four radiologists with 4 years of experience, collecting the following information: race, age at diagnosis, PSA and dPSA at diagnosis, treatment performed, clinical and surgical staging, biochemical recurrence, disease progression within 60 months (metastasis or lymph node disease), and survival in 60 months.

Statistical Analysis

Initially, the data were described using absolute frequencies and percentages (qualitative variables) and through measures such as mean, standard deviation, minimum, median, and maximum (quantitative variables). To investigate the potential association between periprostatic and subcutaneous fat and worse prognosis (death or recurrence), the Cox proportional hazards model was proposed (27). This model calculates the Hazard Ratio (HR), which indicates the risk of death/relapse in one category compared to another. To estimate the crude and adjusted Relative Risk, the Poisson regression model with robust variance (28), simple and multiple, was used.

All data analysis was performed using R software, version 4.1.3, or SAS 9.4. A significance level of 5% was adopted for all analyses.

RESULTS

Initially, 287 patients were identified as having undergone mpMRI of the prostate and had a histopathological diagnosis of prostate cancer from July 2016 to June 2018. After applying the exclusion criteria, only 109 patients remained.

The mean age of patients was 65.3 ± 8.4 years. PSA levels ranged from 0.7 to 1346 ng/dL, with a median of 8.0. The PSA density (dPSA) varied from 0.04 to 72.8, with a median of 0.25 and a mean of 1.87 ± 8.8 (Table-1).

Of the 109 PCa cases, 33 (30.3%) were non-significant cancers (GG6 / ISUP1), and 76 (69.7%) were clinically significant cancers with the following distribution: 34 (31.2%) had ISUP 2; 25 (22.9%) had ISUP3, and 17 (15.6%) had ISUP 4 or 5 PCa.

At the time of diagnosis, 78 (71.6%) had localized disease (T1 and T2), and 31 (28.4%) had extra prostatic disease, with 26 patients classified as T3 and 5 as T4. Regarding lymph node status, 98 were negative (89.9%) and 11 (10.1%) were involved. Eight patients (7.4%) had systemic disease at diagnosis (Table-1).

The MRI analysis indicated a high predominance of PI-RADS 4 (n=44, 40.4%) and 5 (n=47, 43.1%). Only 2 (1.8%) patients were scored as PI-RADS 3, and 18 (16.5%) had a score of 2. The quantitative analysis showed a mean thickness of periprostatic fat of 5.21 ± 2.96 mm (range 1.0 - 17.1 mm), while for subcutaneous fat, the values were 33.8 ± 13.5 mm (range 8 to 88 mm). The mean ADC of periprostatic fat was 0.913 ± 0.319 x 10^-3 mm/s^2. The mean size of cancerous visible lesions on mpMRI was 15.7 ± 8.1 mm, measured on the most conspicuous sequence (T2 or DWI) (Table-1).

When assessing patients' outcomes, the overall survival was independently predicted by ISUP 2 or greater (at the limit, p=0.05), nodal (p<0.01), or systemic (p<0.01) involvement at the time of diagnosis. Notably, there was only one death among the 33 patients with ISUP 1 lesions (3.0%), while there were 14 deaths among the 76 patients (18.4%) with clinically significant cancers (ISUP 2 or greater).

For the assessment of the risk of recurrence using the Poisson Model, the independent predictors were nodal (p<0.01) or systemic (p<0.01) involvement and the mean ADC value of the periprostatic fat (p<0.01). In contrast, the thickness of periprostatic (p=0.29) or subcutaneous fat (p=0.11) were not predictors of recurrence (Table-2).

The main outcome, overall survival, analyzed using the Cox model, showed statistical relevance for the ADC value of periprostatic fat (p<0.02) with a Hazard Ratio of 2.74 (1.15-6.51). There was no statistically significant value for periprostatic (p=0.60) and subcutaneous fat (p=0.09). These findings may indicate that patients who present functional and inflammatory changes in periprostatic fat may have a worse outcome than those without such changes (Table-2).

Table 1 - Demographic, clinical and pathological data and MRI-derived parameters of the entire cohort.

PARAMETER			
Age (years			65.3 ± 8.4 (39-86)
PSA (ng/dL)			median - 8.04 (0.7-1346)
PSA density			median 0.25 (0.04-44.9)
ISUP		1	33 (30.3%)
		2	34 (31.2%)
		3	25 (22.9%)
		4	7 (6.4%)
		5	10 (9.2%)
Nodal Staging		Negative	98 (89.9%)
		Positive	11 (10.1%)
Systemic Metastases		Negative	101 (92.7%)
		Positive	8 (7.3%)
Clinical Staging	I		8 (7.3%)
	II	A	21 (19.3%)
		B	39 (35.8%)
		C	2 (1.8%)
	III	A	5 (4.6%)
		B	18 (16.5%)
		C	3 (2.7%)
	IV	A	5 (4.6%)
		B	8 (7.3%)

Risk Stratification	Very Low	9 (8.2%)
	Low	5 (4.6%)
	Favorable Intermediate	32 (29.4%)
	Non-Favorable Intermediate	23 (21.1%)
	High	40 (36.7%)
Therapeutics	Only Prostatectomy	58 (53.2%0
	Prostatectomy and combination*	16 (14.7%)
	Radiation Therapy and combination*	22 (20.2%)
	ADT - Androgen deprivation therapy	5 (4.6%)
	Active Surveillance	7 (6.4%)
	Orchiectomy and combination*	1 (0.9%)
PARAMETER		
Lesion size (mm)	15.7 ± 8.1 (5-42)	
Prostate Volume (cc)	median - 32.8 (12-307)	
Periprostatic fat (mm)	5.21 ± 2.96 (1.0 - 17.1)	
Subcutaneous fat (mm)	33.8 ± 13.5 (8-88)	
mean ADC (x10-3 mm/s2)	0.913 ± 0.319 (0.352-1.659)	
PI-RADS	2	16 (14.7%)
	3	2 (1.8%)
	4	44 (40.4%)
	5	47 (43.1%)

* and combination means association with chemotherapy and/or ADT.

Table 2: Risk of systemic recurrence - Poisson Model and Overall survival - Cox model.

Risk of Systemic Recurrence: Poisson Model				
Characteristic	Relative Risk	CI 95%		p-value
PSA density (ng/ml/cm^3)	01.04	1.00	01.07	**0.03**
PI-RADS: 4 and 5 vs 2 and 3	0.99	0.12	7.97	0.99
Staging: III/IV vs I/II	8.97	01.09	74.10	**0.04**
T3/T4 vs T1/T2	12.58	1.53	103.39	**0.02**
N1 vs N0	17.82	3.67	86.40	**<0.01**
M1 vs M0	63.13	8.35	477.17	**<0.01**
Periprostatic fat thickness (mm)	01.08	0.94	1.24	0.29
Subcutaneous fat thickness (mm)	0.92	0.84	01.02	0.11
Periprostatic adipose tissue ADC X 10-6	3.42	1.52	7.69	**<0.01**
Overall Survival Rates: Cox Model				
Characteristic	Hazard Ratio	CI 95%		p-value
ISUP grade group: 1 or >1	06.07	0.80	46.13	0.08
PSA density (ng/ml/cm^3)	01.08	01.05	1.12	**<0.01**
PI-RADS: 4 and 5 vs 2 and 3	1.54	0.35	6.81	0.57
Staging: III/IV vs I/II	3.21	1.14	09.01	**0.03**
T3/T4 vs T1/T2	2.58	0.94	7.14	0.07
N1 vs N0	5.27	1.65	16.83	**0.01**
M1 vs M0	31.20	8.96	108.70	**<0.01**
Periprostatic fat thickness (mm)	01.05	0.88	1.25	0.60
Subcutaneous fat thickness (mm)	0.96	0.92	01.01	0.09
Periprostatic fat ADC X 10-6	2.74	1.15	6.51	0.02

p-values in bold are indicative of statistical significance (<0.05). Abbreviations: OR = Odds Ratio. CI = Confidence Interval; PSA. prostate-specific antigen; PIRADS. prostate imaging reporting & data system; ISUP. International Society of Urological Pathology.

DISCUSSION

Our results showed that dPSA, systemic disease at diagnosis, and mean ADC were independent predictors of overall survival (OS). For progression-free survival (PFS), only dPSA and systemic disease at diagnosis were significant predictors. These results are aligned with a recent study by Tafuri et al. (15), which reported higher positivity in biopsies and a higher ISUP grade in prostate neoplasms for patients with lower ADC values of periprostatic fat, indicating more aggressive tumors. Similarly, Gulcap et al. found that fat inflammation in periprostatic white adipose tissue, collected from 169 men undergoing prostatectomy, was associated with higher ISUP groups IV/V tumors (29). Despite some methodological and technical differences (1.5 T vs. our 3.0T scanner), we evaluated a similar number of patients (109 vs. 132), monitored clinical outcomes for a longer period (60 months vs. 30 months), and obtained comparable results.

Periprostatic fat has also been used in different contexts for patients with prostate cancer. Zhai et al. indicated that periprostatic fat measurement, combined with PI-RADS v2 scores, could predict pathologic upgrading among patients who had biopsy Gleason 6 (3+3) PCa after radical prostatectomy (30). A similar finding was reported by Uzun et al., who included all patients, not just those with non-clinically significant cancer (31). Gregg et al. suggested another interesting approach by assessing the periprostatic fat volume normalized by the prostate volume in patients under Active Surveillance. In their study, this parameter (normalized periprostatic fat volume) predicted which patients would have shorter progression-free survival (32).

Several mechanisms have been proposed for the association between obesity and prostate cancer (PCa). The role of periprostatic white adipose tissue as an important source of local factors that stimulate PCa progression, and it is a hot topic in research (3, 18). The adipocytes, and their progenitor stromal adipose cells (ASCs), which proliferate to accommodate the expansion of white adipose tissue in obesity, are being implicated as inductive factors of cancer progression. In preclinical studies, ASCs promote tumor growth by remodeling the extracellular matrix and supporting neovascularization (2).

However, the association between periprostatic fat and PCa aggressiveness has also been questioned in the literature. For instance, Laine-Caroff et al. did not find such an association in a cohort of 121 patients (33). In our study, linear measurement was not associated with aggressive tumors, similar as in the Laine-Caroff cohort. A potential interpretation is that morphological changes typically occur later in the disease course, and depending on the timing of MRI morphological measurements, they may not be fully developed, failing to demonstrate an association. Conversely, functional changes are usually more dynamic and occur earlier in any disease condition, allowing a functional parameter (like ADC) to demonstrate such associations almost from the early development of PCa and related periprostatic adipose tissue changes.

All these studies used morphological parameters, including periprostatic fat linear measurement, volume of periprostatic fat, subcutaneous fat, and/or variations such as normalized periprostatic fat volume. Despite being preliminary data and the need for further studies and validations, these promising results could form the basis for new studies evaluating the functional alteration of fat in patients with intermediate tumors, such as Gleason 3+4, to determine if they could benefit from more aggressive treatments.

There are some limitations to this study. It is a retrospective study from a single center with inherent problems, especially selection bias. We used strict inclusion and exclusion criteria to minimize these methodological limitations. We also had a limited number of patients and did not assess the reproducibility of results using a second reader, which also limits the generalizability of our results. However, our approach, using linear measurement of periprostatic fat and ROI placement for obtaining ADC values, are techniques extensively tested in the literature with consistent reproducibility (34, 35). Additionally, only one ADC value measurement was obtained, not a volumetric assessment. Contrary to tumors where a volumetric approach is more adequate for capturing heterogeneity and potential areas of undifferentiated tumors, adipose tissue without any medical intervention tends to be fairly homogeneous, making the ADC values difference between different levels of measurement negligible (16, 36). Lastly, our institution is a quaternary healthcare center with a high volume of oncological cases, which generates a selection bias in the studied population by pre-selecting more aggressive lesions.

In conclusion, our results indicate that the ADC value of periprostatic fat can be an additional tool for risk stratification in prostate cancer, as it was associated with worse outcomes (systemic recurrence and overall survival). If validated by external, prospective, and multi-institutional studies, these results could influence decisions regarding the therapeutic approach to these patients in the future.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Long-term Follow-up of Patients Undergoing Nephrectomy for Urolithiasis

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ABSTRACT

Purpose: This prospective study aimed to identify risk factors associated with progression to stage 3 chronic kidney disease (CKD) and the occurrence of kidney stone formation or growth following nephrectomy for urolithiasis.

Materials and methods: From January 2006 to May 2013, patients undergoing nephrectomy for urolithiasis were enrolled. Renal function was assessed using estimated glomerular filtration rate (eGFR) via the Chronic Kidney Disease Epidemiology Collaboration equation, while kidney stone events were detected using computed tomography.

Results: Among 107 patients followed for an average of 83.5 months, type 2 diabetes mellitus (T2DM) significantly increased the risk of progression to stage 3 CKD by 34.79-fold (p=0.004). Age was associated with a 15% increase in the odds of developing stage 3 CKD per year (p=0.01), while higher preoperative eGFR was protective (OR=0.84, p<0.01). DMSA-99mTc values below 15% were less likely to lead to renal function deterioration. New kidney stone formation occurred in 15.9% of patients and stone growth observed in 12.1%. Contralateral kidney stones (p<0.01) and hypercalciuria (p=0.03) were identified as risk factors for kidney stone events.

Conclusions: T2DM and age were predictors of CKD progression, while higher preoperative eGFR was protective. Hypercalciuria and contralateral kidney stones increased the risk of kidney stone formation and/or growth post-nephrectomy for urolithiasis.

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INTRODUCTION

Urolithiasis is a common and recurring disease that can impair patient's quality of life (1). Several studies have demonstrated an increased risk of chronic kidney disease (CKD) in patients with urinary calculi (2-4). The causes are probably multifactorial and include the cumulative effects of transient renal obstruction during the stone passage, secondary infection, renal injury due to urolithiasis treatments, and the deposition of intratubular crystals causing interstitial inflammation and tubular cell damage (5-7). Despite advances in minimally invasive procedures, nephrectomy is still used for the treatment of kidney stones in case of irreversible loss of renal function associated with pain or severe life-threatening urinary infections (8-10).

It is crucial to predict renal function progression and the likelihood of kidney stone recurrence after nephrectomy to make informed treatment decisions and closely monitor high-risk patients (11). Our hypothesis is that these patients already affected by urolithiasis have specific risk factors for deterioration of renal function and recurrence of kidney stones. We aimed to identify the risk factors for progression to stage 3 CKD and new stone formation or growth of preexisting kidney stones in the contralateral kidneys of patients undergoing nephrectomy for urolithiasis.

MATERIALS AND METHODS

We prospectively observed a cohort that included patients who underwent nephrectomy for urolithiasis between January 2006 and May 2013. The exclusion criteria were: [1] follow-up period <6 months, [2] recurrent tract infections after nephrectomy, [3] spinal cord injuries that compromised mobility, or [4] refused participation in the study. Total nephrectomy for urolithiasis was indicated for patients who experienced the loss of renal function accompanied by pain or recurrent urinary tract infection as well as for those who presented with severe infections associated with urinary focus sepsis (12, 13). After being instructed by the researchers about all stages of this study, all patients signed a Free and Informed Consent Form. This study was approved by the Ethics Committee (no. 63637416.6.0000.0068) and was conducted in accordance with the ethical principles and the Helsinki Declaration guidelines.

Preoperative assessment

We evaluated the comorbidities of the patients using the age-adjusted Charlson Comorbidity Index, and the surgical risk was stratified according to the American Society of Anesthesiologists (ASA) classification. In order to assess stone status and the relative function of each kidney, all patients underwent preoperative abdominal and pelvic computed tomography (CT) and static renal scintigraphy with dimercaptosuccinic acid (DMSA-99mTc).

Follow-up

The patients were followed up to November 2019 through periodic medical appointments, occurring quarterly in the first 6 months after surgery and annually for the remainder of the follow-up period. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. At least one valid 24-hour (h) urine sample was obtained 6 months after nephrectomy to measure calcium, oxalate, citrate, and uric acid levels in all patients. A sample was considered valid in the absence of urinary tract infection, with no diuretics, potassium citrate, or allopurinol use, no hormone replacement, and the presence of adequate values of creatinine (1,040–2,350 mg/24 h for men and 740–1,570 mg/24 h for women). The abnormal values of the 24-h urinary parameters according to the reference values of the enzymatic assays used in our institution were as follows: hypercalciuria, >300 mg/24 h of calcium excretion for men and >250 mg/24 h for women; hypocitraturia, <320 mg/24 h citrate excretion; hypernatriuria, >220 mEq/24 h sodium excretion; hyperoxaluria, >31 mg/24 h of oxalate excretion; and hyperuricosuria >800 mg/24 h of uric acid excretion for men and > 750 mg/24 h for women.

Metabolic abnormalities were managed according to the institutional protocol during follow-up, with hydrochlorothiazide titrated up to 50 mg/day for patients with idiopathic hypercalciuria and potassium citrate at variable doses from 20-60 mEq/day for pa-

tients with hypocitraturia (14). Chemical analyses were performed on the urinary stones to determine their composition.

Kidney and urinary tract ultrasonography was performed once a year for all patients. In cases where the growth or formation of a new urinary stone was observed, a non-contrast-enhanced CT scan was performed for confirmation (15-17). A new event related to urolithiasis in the postoperative follow-up was defined as the formation or growth of renal calculi in the remaining kidney, as confirmed by CT (18).

Statistical analysis

Statistical analysis was conducted using R statistical software (19). In the descriptive analysis of demographic data, numeric variables are reported as mean values and standard deviations, while categorical variables are presented as absolute numbers and percentages. To identify predictors of kidney function and new urolithiasis events after nephrectomy, a logistic regression model was developed using the purposeful selection method proposed by Hosmer and Lemeshow for selecting variables (20). McFadden's pseudo coefficient of determination (pseudo-R^2) was used to assess the accuracy of the model (21). The significance level used for the final model was 5%, and a 25% significance level was used for the preliminary univariate analysis. We employed the Kaplan–Meier estimator to analyze censored curves by progression to CKD stage 3 and new urolithiasis events, and the log-rank test was used to compare related variable curves (22, 23). To predict the final GFR and CKD-EPI values, we developed a mathematical model using multivariate linear regression, employing the backward variable selection method and calculating the Akaike Information Criterion (AIC) value (20). The quality of the model was ensured through residual analysis and the determination coefficient R^2.

RESULTS

During the study period, 150 patients underwent nephrectomy for urolithiasis. We excluded three patients with spinal cord injuries. After nephrectomy, 40 patients did not meet the necessary follow-up criteria due to discontinuation of outpatient follow-up before 6 months or failure to return for the requested complementary tests. Therefore, these patients were excluded from the study.

Preoperative demographic and clinical characteristics

Of 107 patients, 78.5% (84/107) were women. The average BMI was 26.9 kg/m2. Type 2 diabetes mellitus (T2DM) and systemic arterial hypertension (SAH) were detected in 15% and 50.9% of patients, respectively. Furthermore, 51.4% and 36.4% of patients were classified with ASA 2 score and Charlson comorbidity index ≥ 1, respectively. Forty-nine patients (45.8%) patients had stage 2 CKD, with an overall mean eGFR of 73.48 (±29.41) mL/min/1.73m^2. The DMSA-99Tc value of the affected kidneys was < 15% in 83 patients. Table-1 provides additional information on recruited patients.

Nephrectomy

Nephrectomy was performed laparoscopically in 62 patients (57.9 %). Staghorn stones accounted for 67.3% of the kidney stones removed, while ureteral and pelvic stones were responsible for nephrectomy in 19 (17.8%) cases. An anatomopathological report of the removed kidneys revealed chronic pyelonephritis, xanthogranulomatous pyelonephritis, pyonephrosis, and renal atrophy in 36 (33.6%), 26 (24.3%), 22 (20.6%), and 15 (14.0%) patients, respectively. Stone composition analysis showed that 67 (62.6%) of the removed stones were composed of calcium, of which 83.5% were exclusively composed of calcium oxalate and 16.5% were composed of calcium phosphate. Struvite was observed in 56 (52.3%) cases (alone or in combination), while two (1.9%) cystine stones were evident.

Follow-up

The average follow-up period was 83.5 (±35.5) months. During this period, 32 (29.9%) patients experienced a decline in the CKD stage, 53 (49.5%) had albuminuria levels exceeding 30 mg/g, and six (5.6%) progressed to dialysis. Additionally, 30 patients (28.0%) reported new occurrences of urolithiasis. Of the total patients, 78 (72.9%) had at least one urinary metabolic alteration that increased the risk of urolithiasis. Hypoci-

Table 1 - Preoperative and follow-up data after nephrectomy for urolithiasis.

Variable	Value
Patients, N	107
Female, N (%)	84 (78.5%)
Age, years (mean ± SD)	49 (±13)
Black race, N (%)	54 (50.5%)
BMI (Kg/m^2), (mean ± SD)	26.9 (±5.2)
SAH, N (%)	54 (50.9%)
Diabetes Mellitus, N (%)	16 (15%)
Affected kidney side, left, N (%)	53 (49.5%)
Preoperative infecction, N (%)	70 (65.4%)
Charlson ≥1, N (%)	39 (36.4%)
ASA, N (%)	
1	27 (25.2%)
2	55 (51.4%)
3	22 (20.6%)
4	3 (2.8%)
Affected kidney DMSA-99Tc, (mean ± SD)	8.8 (±9.7)
Affected kidney DMSA-99Tc < 15%, N (%)	83 (77.6%)
CKD stage N (%)	
1	31 (29%)
2	49 (45.8%)
3	16 (15%)
4	2 (1.9%)
5	9 (8.4%)
eGFR (mL/min/1.73m^2), (mean ± SD)	73.4 (±29.4)
Contralateral kidney stone, N (%)	35 (32.7%)
Follow up time, months (mean ± SD)	83.5 (±35.5)
Final eGFR (mL/min/1.73m^2), (mean ± SD)	67.3 (±27.4)
Outcome	
Stage improvement, N (%)	15 (14%)
Stage worsens, N (%)	32 (29.9%)
Stage maintenance, N (%)	60 (56.1%)
Albuminuria >30 mg/g, N (%)	53 (49.5%)
Dialysis, N (%)	6 (5.6%)
New urolithiasis event, N (%)	30 (28%)
Urinary metabolic disorder, N (%)	78 (72.9%)
Hypocitraturia, N (%)	71 (66.4%)
Hypercalciuria, N (%)	17 (15.9%)
Hyperoxaluria, N (%)	5 (4.7%)
Hypernatriuria, N (%)	6 (5.6%)
Hyperuricosuria, N (%)	6 (5.6%)
Cystinuria, N (%)	2 (1.9%)
Urinary pH, (mean ± SD)	6.5 (±0.7)
Urinary volume, mL/24h (mean ± SD)	1,874.3 (±529.3)

N, number; ST, standard deviation; BMI, body mass index; SAH, systemic arterial hypertension; ASA, *American Society of Anesthesiologist*; DMSA-99mTc, dimercaptosuccinic acid; CKD, chronic kidney; eGFR, estimated glomerular filtration rate;

traturia was the most common alteration, accounting for 66.4% of the cases (Table-1).

Analysis of predictors for progression to stage 3 CKD

Univariate analysis was conducted using preoperative variables of patients with stage 1 or 2 CKD before nephrectomy.

Following the initial univariate analysis, only the variables that yielded a likelihood test p-value of < 0.25 were considered for the model. A purposeful selection of variables was conducted, leading to the final model, as presented in Table-2. T2DM was identified as a significant risk factor, resulting in a 34.79-fold increase in the likelihood of progression to stage

Table 2 - Univariate and multivariate analysis of stage 3 CKD progression predictors - preoperative variables.

Univariate				Multivariate			
Variable	Progression to stage 3 of CKD. n 80		p1	Coefficient	Odds ratio (OD)	95%CI	P value
	Yes (N = 12)	No (N = 68)					
Female	8 (66.6%)	56 (82.3%)	0.2	-1,9	0.14	0.01 – 1.18	0.09
Age, years (mean ± SD)	59.5 (±13.6)	45.4 (±10.9)	0.004	0.14	1.15	1.04 – 1.31	0.01
BMI (Kg/m2), (mean ± SD)	27.9 (±6.9)	26.8 (±4.7)	0.6				
Black race, N (%)	6 (50%)	33 (48.5%)	0.9				
Diabetes Mellitus, N (%)	6 (50%)	6 (8.8%)	0.001	3.55	34.79	4.15 – 606.26	0.004
SAH, N (%)	8 (66.6%)	28 (41.8%)	0.1				
ASA 1, N (%)	1 (8.3%)	25 (36.7%)	0.06				
ASA 2, N (%)	8 (66.6%)	37 (54.4%)					
ASA >3, N (%)	3 (25%)	6 (8.8%)					
Charlson >1, N (%)	6 (50.00%)	11 (16.1%)	0.01				
Preoperative infection, N (%)	6 (50%)	46 (67.6%)	0.2				
eGFR (mL/min/1.73m^2) (mean ± SD)	68.4 (±10.5)	88.8 (±19.7)	<0.001	-0.17	0.84	0.72 – 0.94	0.007
Stage 1 of CKD, N (%)	1 (8.3%)	30 (44.1%)	0.01				
Stage 2 of CKD, N (%)	11 (91.6%)	38 (55.8%)					
Affected kidney DMSA-99Tc (mean ± SD)	11.75 (±9.3)	7.7 (±7.4)	0.1				
Contralateral kidney stone, N (%)	4 (33.3%)	18 (26.4%)	0.6				

[1] Likelihood ratio test for categorical variables and t-test for numerical variables.Hosmer-lemeshow test, p=0.575; pseudo-R^2 = 0.57.
SD = Standard deviation; BMI = body mass index; N = number; SAH = systemic arterial hypertension; ASA = *American Society of Anesthesiologist;* CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; DMSA-99mTc = dimercaptosuccinic acid.
95%CI, 95% confidence interval.

3 CKD. Furthermore, for every additional preoperative eGFR unit, the risk of progression to stage 3 CKD decreased by 0.84 folds. Finally, the odds ratio for developing stage 3 CKD increased by 15% every year.

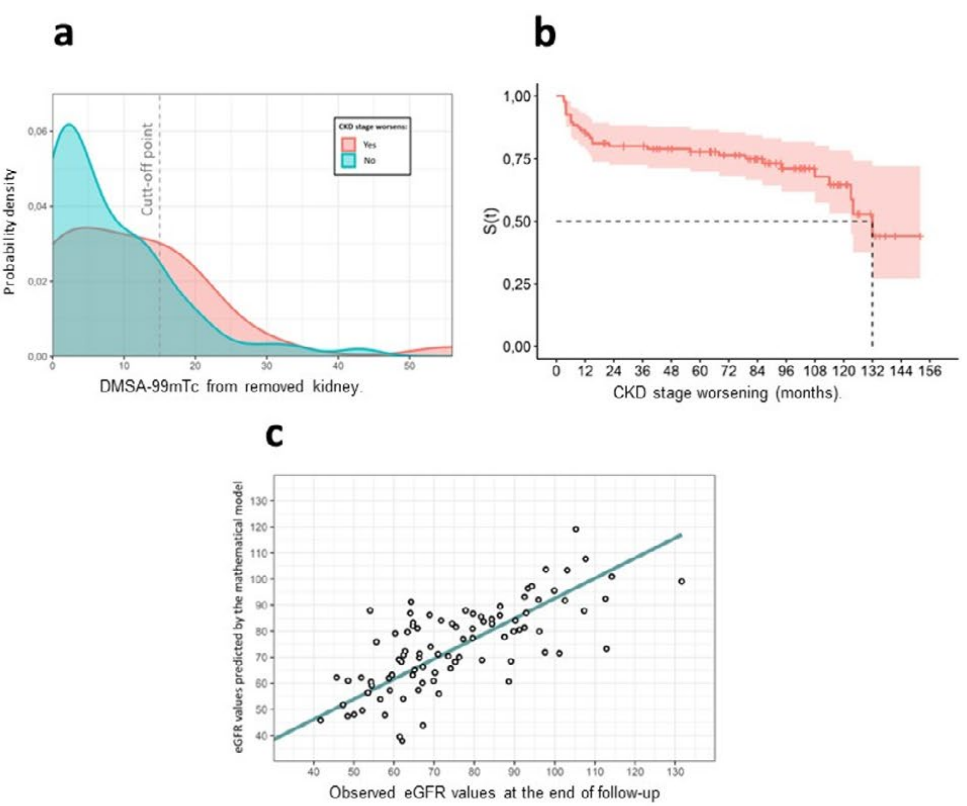
DMSA-99mTc cut-off point

We proposed a DMSA-99mTc cut-off point to aid in decision-making regarding patient management and to assess the impact of removal on long-term renal function. We performed logistic regression of the preoperative variables using a worsening CKD stage as an outcome. To evaluate the linearity of the numerical variable DMSA-99mTc, we transformed it into a categorical variable and established a cutoff point by separating it into quartiles. The suggested cutoff point was 15%, owing to the lower p-value. This value was found to illustrate the most significant difference in behavior through the probability density function, with DMSA-99mTc values lower than 15% being less likely to cause long-term worsening of renal function – Figure-1a.

Kaplan Meier curve for CKD stage worsening

Figure-1b depicts the Kaplan–Meier curve estimate of the time taken in months for the CKD stage to worsen. The median curve function was 132 months, indicating a 50% probability of a patient experiencing a worsening stage of CKD after 132 months.

Figure 1: a) Probability density of worsening kidney function as a function of the DMSA value of the removed kidney. Kaplan Meier curve for CKD stage worsening. DMSA-99mTc values lower than 15% being less likely to cause long-term worsening of renal function; b) Kaplan Meier curve for CKD stage worsening. The shaded area in salmon represents the 95% confidence interval; c) Distribution of observed values by predicted estimated glomerular filtration rate (eGFR) values at the end of follow-up – mean time. The blue line represents the identity function.



Mathematical model for the eGFR value at the end of follow-up.

Table-3 displays the results of both univariate and multivariate analyses of the final model. In this regression, the p-value from the univariate analysis may not necessarily determine the significant variables because of the influence of multicollinearity with other variables in the multivariate model and the presence of confounding effects. The final model obtained is given by the following equation:

Final eGFR = +8.7+0.77*preoperative eGFR+0.33*BMI-1.2*SAH-10.61*Charlson>1-0.2*DMSA

Figure-1c shows the scatter plot comparing the predicted and observed eGFR values. Pearson's correlation coefficient obtained was 0.78 with $p \leq 0.001$.

New urolithiasis events

We developed a logistic regression model using the purposeful selection of variables method to determine the final model of risk factors for the occurrence of new urolithiasis-related events during patient follow-up. Among the patients, 30 had a new event, with 13 (43.3%) having preexisting calculus enlargement and 17 (56.7%) forming new calculi.

Table-4 presents the univariate analysis and final model for the occurrence of a new urolithiasis-related event during patient follow-up. The variables included the presence of contralateral kidney stones and hypercalciuria. The presence of a contralateral stone increased the chance of a patient experiencing a new event by 3.24 folds.

DISCUSSION

Currently, this is the first prospective study in literature with a long-term follow-up of patients who underwent nephrectomy for urolithiasis. We evaluated 107 adult patients who underwent nephrectomy for urolithiasis in a prospective observational cohort with a mean follow-up period of > 83 months. We found that

Table 3 - Multivariate linear regression analysis for final eGFR value - preoperative variables.

	Univariate			Multivariate		
Variable	Coefficient	95%CI	p	Coefficient	95%CI	p
Female	6.5	-6.2 ;19.41	0.3			
Age	-0.6	-1.06 ; -0.29	<0.001			
Black race	4.3	-6.20; 14.91	0.4			
BMI (Kg/m^2)	-0.04	-1.05 ; 0.98	0.9	0.3	-0.18 ; 0.84	0.2
Diabetes Mellitus	-8.7	-23.47 ; 6.04	0.2			
SAH	-14.8	-25.17 ; -4.59	0.005	-1.2	-6.74 ; 4.33	0.6
ASA, 2	-13.3	-24.03 ; -2.74	0.01			
ASA, 3 e 4	-43.3	-55.90 ; -30.75	<0.001			
Charlson>1	-32.8	-41.86 ; -23.91	<0.001	-10.6	-16.91 ; -4.31	0.001
Preoperative infection	1.3	-9.74 ; 12.52	0.8			
eGFR (mL/min/1.73m^2)	0.7	0.68 ; 0.88	<0.001	0.7	0.65 ; 0.88	<0.001
Affected kidney DMSA-99mTc	-0.2	-0.81 ; 0.28	0.3	-0.2	-0.47 ; 0.07	0.1
Contralateral Kidney stone	-7.12	-18.33 ; 4.08	0.2			

R^2 = 0.77.95%CI, 95% confidence interval; BMI, body mass index; ASA, *American Society of Anesthesiologist*;; SAH, systemic arterial hypertension; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; DMSA-99mTc, dimercaptosuccinic acid.

Table 4 - Univariate and multivariate analysis of risk factors for the occurrence of new urolithiasis event.

Univariate				Multivariate[2]			
				Coefficient	Odds ratio	95%CI	p
Variable	Ocurrence of new urolithiasis event		p[1]				
	Yes (N = 30)	No (N = 77)					
Female, N (%)	22 (73.3%)	62 (80.5%)	0.4				
Age (mean ± SD)	47.1 (±14.5)	49.7 (±12.4)	0.4				
BMI (Kg/m^2), (mean ± SD)	26.5 (±6)	27 (±4.9)	0.6				
Black race, N (%)	17 (56.6%)	37 (48%)	0.4				
Diabetes Mellitus, N (%)	4 (13.3%)	12 (15.5%)	0.7				
Preoperative infection, N (%)	20 (66.6%)	50 (64.9%)	0.8				
eGFR (mL/min/1.73m^2), (mean ± SD)	71.1 (±31.2)	74.3 (±28.8)	0.6				
Transfusion, N (%)	4 (13.3%)	5 (6.4%)	0.2				
Preoperative contralateral Kidney stone, N (%)	16 (53.3%)	19 (24.6%)	0.005	1.17	3.24	1.31 – 8.15	0.01
Unrinary metabolic disorder, N (%)	25 (83.3%)	52 (67.5%)	0.09				
Hypercalcuria, N (%)	9 (30%)	8 (10.3%)	0.01	1.19	3.3	1.08 – 10.28	0.03
Hypocitraturia, N (%)	23 (76.6%)	48 (62.3%)	0.1				
Hyperuricosuria, N (%)	1 (3.3%)	5 (6.4%)	0.5				
Urinary pH (mean ± SD)	6.6 (±0.7)	6.4 (±0.8)	0.6				
Urinary volume (mL), (mean ± SD)	1,854.3 (±482.1)	1,882.1(±549.3)	0.7				

[1] Likelihood ratio test for categorical variables and T test for numerical variables. [2] Hosmer-Lemeshow test, p=0.530; pseudo-R^2 = 0.10.
N, number; %; SD, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate; DMSA-99mTc, dimercaptosuccinic acid.95%CI, 95% confidence interval.

T2DM and advanced age increased the risk of developing stage 3 CKD, whereas higher initial eGFR provided a protective effect. We also showed that patients with contralateral kidney stones and hypercalciuria had an increased risk of developing new urolithiasis events after nephrectomy. In addition, we developed a mathematical model to predict long-term eGFR in patients who underwent nephrectomy for urolithiasis.

Although urinary lithiasis is more prevalent in males, when evaluating cases of more complex urinary stones that require hospitalization and surgical interventions, we observe a higher prevalence among female patients (24). When assessing the formation of staghorn calculi, loss of renal function, and nephrectomy due to urolithiasis, women exhibit twice the prevalence compared to men (8). A study evaluating 101 nephrectomies for urolithiasis showed that women more frequently progress to renal function loss due to lithiasis than men (10). The indications for nephrectomy occur more often in patients with complex stones associated with recurrent urinary tract infections, which may have contributed to the predominance of female patients in our study.

Previous research by Lee et al. retrospectively analyzed the recurrence of urinary calculi and renal function in 50 patients who underwent nephrectomy for urolithiasis; however, they excluded patients with contralateral kidney stones and only had a mean follow-up of 70 months (25). Our study found that 32.7% of the patients who underwent nephrectomy also had bilateral stones. Therefore, Lee et al. excluded a significant portion of the patient population analyzed in our study.

Renal function can be directly influenced by several clinical factors, with SAH and T2DM being the main causes of CKD worldwide (26). Recognition of CKD in its early stages and early medical follow-up are fundamental for controlling the evolution of the disease and reducing the need for renal replacement therapy (27-29). Ellis et al. retrospectively evaluated a cohort of 709 nephrectomies for renal cell carcinoma and reported a 59% incidence of CKD up to 12 months after surgery, in addition to an increased risk of CKD in patients of advanced age (odds ratio 1.5 [95% confidence interval 1.4–1.6]) (30). In our cohort, we observed that the presence of T2DM before nephrectomy increased the chances of patients progressing to stage 3 CKD by 34.7 times. Advanced age is another predictor of CKD progression. Assessment of these risk factors led to the creation of a mathematical equation to predict long-term eGFR after nephrectomy with great potential for use in clinical practice, allowing the selection of patients at a greater risk of loss of renal function.

Relative renal uptake on DMSA-99mTc scintigraphy has an excellent correlation with eGFR (31, 32) and has been used in clinical practice to assess the viability of the renal unit, which often supports the decision to perform nephrectomy when associated with a severe infectious process or recurrent pain. There is no consensus on an exact DMSA-99mTc cutoff point that could predict the impact of removing the renal unit on eGFR in the long term in patients with urolithiasis. In our study, we defined a cutoff point for DMSA-99mTc values by adapting the variables to assess the worsening stage of CKD. Evaluating the point where the behavior change presented the greatest statistical difference, a value of 15% was reached, and patients whose kidney was removed had DMSA-99mTc values > 15% and had a greater chance of progressing to a worsening stage of CKD.

Metabolic acidosis resulting from nephron loss increases the risk of kidney stone formation due to its effects on calcium metabolism, leading to hypercalciuria, parathyroid hormone dysregulation, and increased levels of 1,25-$(OH)_2$ vitamin D (33). This highlights the importance of identifying risk factors for urolithiasis in patients undergoing nephrectomy. Bagrodia et al. compared radical nephrectomies with nephron-sparing surgeries for renal tumors, demonstrating a significant association between a history of urolithiasis and the development of postoperative kidney stones (34).In our study, the presence of a contralateral stone and hypercalciuria increased the risk of the new urinary stone-related event 3.2 times and 3.3 times, respectively. Lee et al. reported a higher frequency of urinary calculi recurrence in patients with metabolic calculi than in those with infectious (25). These data are demonstrated in our study, with a significant influence of hypercalciuria on the risk of a new event related to urinary calculi.

A predictive model of postoperative renal function can influence the planning and decision to perform

a nephrectomy (35-37). To date, our study is the first to propose a predictive model of renal function after nephrectomy for urolithiasis. Multivariate linear regression analysis showed that the variables included in the model were preoperative eGFR, BMI, SAH, Charlson score >1, and the DMSA score of the affected kidney.

This study had several limitations. There were significant losses of patients in the postoperative period due to the long follow-up period, and the sample was heterogeneous, with a greater representation of women, perhaps explained by the trend towards a higher frequency of complex cases of urolithiasis in this population.

CONCLUSIONS

The findings of our study underscore the importance of early detection, management, and intervention to mitigate the risk of CKD progression, particularly in high-risk populations. Additionally, provides valuable insights for clinicians to identify high-risk patients and plan careful follow-ups and treatments to prevent further kidney damage and urolithiasis recurrence.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are not publicly available due to non-authorization of the institution where the study was carried out but are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None declared.

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The Management of Children and Adolescents with Overactive Bladder Refractory to Treatment with Parasacral Transcutaneous Electrical Nerve Stimulation

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ABSTRACT

Background: Although parasacral TENS (pTENS) has been employed in various centers, there is a lack of studies on how children with overactive bladder (OAB) respond after failing to complete pTENS sessions. This study aimed to describe and assess treatments for OAB in children who did not respond to pTENS.

Material and Methods: This retrospective case series examined patients aged 4-17 years. Patients were given subsequent treatment options, including: behavioral therapies; oxybutynin; imipramine; a combination of oxybutynin and imipramine; parasacral percutaneous electrical nerve stimulation (PENS); or a repeat course of pTENS. Outcomes were evaluated using the Dysfunctional Voiding Scoring System (DVSS) and the Visual Analogue Scale (VAS).

Results: Thirty children were included, with a median age of 7 years. Patients received one or more treatments. Of these, 70% underwent monotherapy. Among them, 57% experienced complete resolution of symptoms, 28% had partial resolution and were satisfied with the results, and 14% discontinued treatment. 30% out of the whole sample continued to experience bothersome symptoms. Complete response, according to initial subsequent, was achieved in: 54% with intensified behavioral therapies, 33% with oxybutynin, and 50% with imipramine alone. The median DVSS score decreased from 7.0 to 2.0 (p=0.025), while the median VAS score increased from 80 to 100 (p<0.001). Conclusion: Children with OAB refractory to pTENS who received structured subsequent treatments showed partial response in all cases, with complete symptom resolution in half of the patients. More intensive urotherapy, medications, or repeat pTENS in combination with oxybutinin can be effective for managing this challenging condition.

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INTRODUCTION

Lower urinary tract dysfunction (LUTD) is a disorder resulting from abnormalities in the filling or voiding phases of the bladder in individuals with no associated neurological abnormality. Overactive bladder (OAB) is the most prevalent form of LUTD, and, from a clinical point of view, it manifests as the presence of urgency to void, associated or not with incontinence, nocturia or pollakiuria (1). Due to the impact of urinary symptoms in the patient´s quality of life and its association with vesicoureteral reflux and recurrent urinary tract infections, the timely management of OAB is essential (2, 3). According to ICCS, voiding diary is one of the three diagnosis tests included in the non-invasive urodynamic (1). Franck HHM et al. (2023) have shown that only one voiding diary is enough to assess these children (3).

Behavioral therapies involving lifestyle changes have been used as first-line therapy for OAB. However, a certain proportion of patients requires further assistance (4). The pharmacological treatment using oxybutynin represents an efficient treatment option, with an improvement rate of 60% and a complete resolution rate of 30%. Despite benefits, oxybutynin can trigger undesired side effects, such as dry mouth, constipation, and other symptoms that lead to a drop rate of 10% (5). Bladder wall thickness measurements and nerve growth factor (NGF) / creatinine values could predict the outcomes in this population (6). Furthermore, vitamin D deficiency is more common in children with urinary incontinence and OAB than in healthy children. Vitamin D supplementation may improve urinary symptoms and quality of life in patients with OAB (7).

In this respect, parasacral transcutaneous electrical nerve stimulation (parasacral TENS) has been used as an option for the treatment of OAB. This treatment modality consists of a non-invasive technique with no significant side effects that also has an additional beneficial effect on constipation (5). The rate of complete resolution of urinary symptoms with TENS is similar to that achieved with pharmacological treatment (3). However, in around 40% of patients who undergo treatment with TENS, symptoms will not resolve completely (8).

Although various studies have dealt with the treatment of this dysfunction, to the best of our knowledge, up to the moment no studies in the literature have described and analyzed the therapeutic management of patients who fail to respond to parasacral TENS. Such studies are necessary to support decision-making in the case of patients with OAB refractory to parasacral TENS. We hypothesize that children and adolescents with OAB who failed to respond to parasacral TENS can still achieve complete resolution of symptoms after further assistance. Therefore, the objective of the present study was to describe and evaluate the treatments given to patients with OAB who failed to respond to parasacral TENS.

MATERIAL AND METHODS

Study design

This is a descriptive, longitudinal, analytical case series conducted by evaluating the records of patients undergoing treatment at a specialist center. The institution's internal review board approved the study protocol under reference number / CAAE: 13212419.3.0000.5544.

Sample selection

The inclusion criteria were patients of 4-17 years of age with non-complicated OAB refractory to two or three 20- minute sessions a week of parasacral TENS, for a total of 20 sessions. Patients no longer being followed up at the center were contacted by telephone to obtain the relevant data.

All patients included in the present study have failed standard urotherapy for the period of one month before being submitted to parasacral TENS. No patients included had any upper tract involvement or major complications.

Children and adolescents whose records were incomplete in relation to the principal endpoint and with neurodevelopment or psychiatric issues were excluded from the study.

Electrical nerve stimulation was performed using a Dualpex Quark 961 device (Quark Medical, Piracicaba, Brazil) at a frequency of 10HZ, pulse width

of 700 microseconds, over two or three 20-minute sessions a week for a total of 20 sessions.

Evaluation instruments

The data collected included: Age; Gender; The different types of treatments and associations instituted during follow-up; Scores obtained using the Dysfunctional Voiding Scoring System (DVSS) and the visual analogue scale (VAS), applied to evaluate symptoms prior to and following treatment. The version of the DVSS validated for use in the Portuguese language was used to determine the severity of symptoms, with scores ≥ 6 for girls and 9 for boys being indicative of severe LUTD and a post-treatment score of 0 being considered complete resolution of symptoms [6]. The VAS is used to evaluate clinical improvement, with scores ranging from 0 to 10 in which 0 reflects no improvement at all and 10 is indicative of complete resolution [7]. These VAS scores were then multiplied by a factor of 10 to calculate the percentage of improvement. The center routinely collects these data for all patient visits.

Patients who failed to respond to TENS were given a subsequent treatment by using one of the following treatment options: Behavioral therapies; Oxybutynin; Imipramine; Oxybutynin in combination with imipramine; Parasacral percutaneous electrical nerve stimulation (PENS) or a repeat course of parasacral TENS.

The following criteria were used to select treatment after parasacral TENS has failed.

Patients with few symptoms, particularly those in whom urinary urgency was associated with voiding postponement, were instructed to continue with and intensify behavioral therapy.

For more symptomatic patients, oxybutynin was prescribed, and the dose of the drug was increased until adequate therapeutic response was obtained or adverse events developed. If side effects occurred or the patient failed to respond to oxybutynin, imipramine was used.

When the patient failed to respond to oxybutynin or imipramine alone, the two drugs were then given in combination.

When parents chose not to have their child undergo pharmacological treatment since the drug would have had to be used over a period of some months, preferring to repeat parasacral TENS or try a new type of treatment, parasacral PENS [8].

All patients with psychological issues were managed by our team of psychologists.

All constipated patients had the bowel dysfunction treated by our proctologist.

Due to our patients' inability to afford mirabegron, we did not test the use of this medication. Patients were reassessed every 3 months to analyze treatment outcomes, regardless of the treatment modality.

Statistical analysis

The data collected were stored and analyzed using the SPSS software program, version 14.0. The results are presented as graphs. The dependent variables were the treatments given after TENS had failed, while the independent variables were: Sex; Age; DVSS score and VAS score. The numerical data from the DVSS and VAS were expressed as medians and interquartile ranges (IQR). The categorical variables (the treatments instituted and the number of patients who went on to achieve complete resolution of symptoms) were expressed as frequencies (%). To compare the median DVSS and VAS scores prior to and following each type of treatment, the Wilcoxon test was used after the normality of distribution had been determined. P-values <0.05 were considered statistically significant.

RESULTS

Thirty children, 20 of whom were girls, with a median age of 7.0 years (IQR: 5-10 years) who have failed to respond to parasacral TENS were included in the study. Failure to respond to TENS consisted of the persistence of symptoms in 29 cases (97%) and symptom recurrence after an initial period of complete resolution in one case (3%). Median follow-up time was 9 months (IQR: 3.25- 26 months).

Daytime symptoms before the subsequent treatment

All the patients continued to have daytime symptoms. Some patients had more than one symptom, with 6 (20%) having three associated symptoms and 11 (36%) having only two associated symptoms. Table-1 shows demographic information of the sample, frequency of symptoms before the subsequent treatments and median VAS score before and after the subsequent treatments, according to the gender.

The median VAS score was 80 (IQR: 50-90). In one case, in which symptoms recurred after having been completely resolved, the VAS score was 100%, indicating complete resolution at that moment.

Outcome after subsequent treatments

During the follow-up period, after the patients failed to parasacral TENS, they were then submitted to one or more types of treatment. A total of 21 patients (70%) underwent monotherapy (Figure-1). Of them, 12 patients (57%) had complete resolution of the symptom, 6 (28%) had partial resolution and were satisfied with the results and 3 (14%) abandoned treatment. Nine patients out of the whole sample (30%) maintained bothersome symptoms and required further assistance after the first subsequent treatment has failed. For these patients, we offered different or adjuvant therapies (Figure-2).

The median DVSS score decreased from 7.0 (IQR: 3-9) prior to the first treatment instituted post-TENS to 2.0 (IQR: 0.2-6.5) after treatment (p=0.025). The median VAS score increased from 80 (IQR: 50-90) to 100 (IQR: 80-100), respectively (p<0.001). According to the DVSS score, complete resolution of symptoms was achieved in 11 patients (36%), 9 of whom were girls. , symptoms were completely resolved in 16 patients (53%) (Table-2).

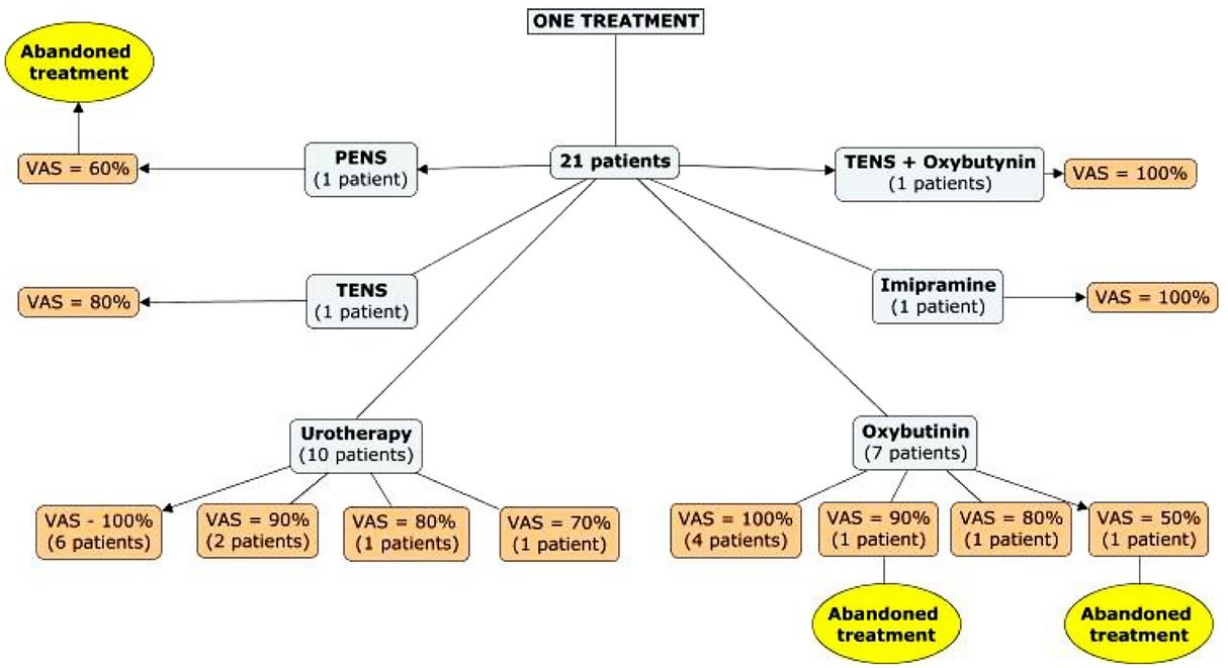
According to the success rate of initial subsequent treatment modality, complete response to symptoms was achieved in 6/11 patients (54%) who underwent intensified behavioral therapies, in 4/12 (33%) who used oxybutynin, in 1/2 (50%) who used imipramine alone and in the only patient submitted to further sessions of parasacral TENS associated with oxybutynin. The only patient submitted to anoth-

Table 1 - Demographic data, symptom frequency before the subsequent treatments and median VAS scores before and after the subsequent treatments, according to the gender.

Variables	Male (N=10)	Female (N=20)	Total (N=30)
Median Age (IQR)	5 (4.75-7.25)	7.5 (6-10)	7 (5-10)
Symptoms (%)			
Urinary urgency	8 (80%)	11 (55%)	19 (63%)
Urge-incontinece	6 (60%)	13 (65%)	19 (63%)
Nocturnal enuresis	8 (80%)	10 (50%)	18 (60%)
Incontinence without urgency	3 (30%)	5 (25%)	8 (26%)
Holding maneuvers	3 (30%)	4 (20%)	7 (23%)
Pollakiura	0 (0%)	2 (10%)	2 (6%)
Median VAS scores (IQR)			
Before subsequent treatments	65 (50-90)	80 (50-87,5)	80 (50-90)
After subsequent treatments	100 (67,50-100)	90 (82,50-100)	100 (80-100)

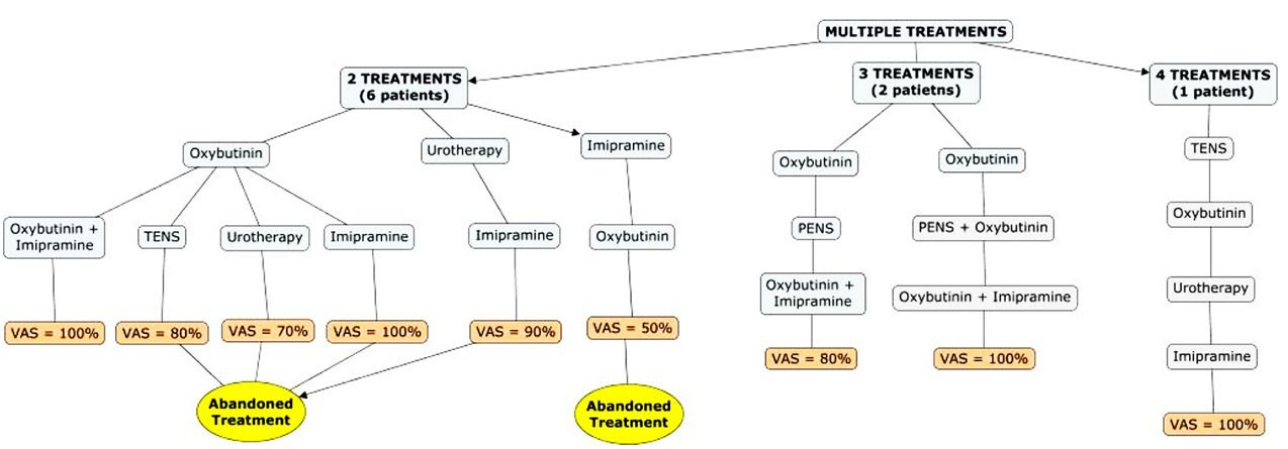
IQR: Interquantil Range; VAS: Visual Analogue Scale

Figure 1 – Treatment given, its efficacy according to VAS score and the cases of abandonment treatment for patients who underwent only one treatment.



VAS: Visual analogue scale
PENS: Percutaneous eletrical nerve stimulation
TENS: Transcutaneous eletrical nerve stimulation

Figure 2 – Sequence in which treatments were given, efficacy of the treatment according to the VAS score, and the cases of abandonment treatment for patients who underwent multiple treatments.



VAS: Visual analogue scale
PENS: Percutaneous eletrical nerve stimulation
TENS: Transcutaneous eletrical nerve stimulation

Table 2 - The VAS scores before subsequent treatments (immediately following parasacral TENS) and the VAS scores after the other treatments provided.

VAS scores	Before subsequent treatments (N=30)	After subsequent treatments (N=30)
0	2 (6%)	0 (0%)
40	2 (6%)	0 (0%)
50	6 (20%)	0 (0%)
60	5 (16%)	2 (6%)
70	4 (13%)	0 (0%)
80	4 (13%)	4 (13%)
90	2 (6%)	6 (20%)
100	5 (16%)	18 (60%)

VAS: Visual analogue scale

er series of TENS alone as initial subsequent treatment modality did not achieve complete response to symptoms.

For the patients who failed to respond to the initial subsequent treatment modality, different therapies were given. Complete resolution of symptoms was achieved in 1 out of the 2 patients (50%) who continued treatment with oxybutynin, in 1/2 patient (50%) who were submitted to continued urotherapy, in 2/3 (66%) patients who used oxybutynin associated with imipramine and in 2/3 (66%) patient who used imipramine alone.

DISCUSSION

Our study demonstrated that after TENS failure, 53% patients with LUTD had complete response to subsequent treatment and all achieved at least partial response of the symptoms. Our data shows that 30% need further treatment, demonstrating a multimodal and multiprofessional approach is needed for treatment of the LUTD. This is the first study that describes the outcome of patients who underwent further treatment after parasacral TENS fails for this condition.

Behavioral therapies (urotherapy) are the first-line treatment for children with OAB who have never been treated before (3). In this study, symptoms were completely resolved in 6 of the 11 patients who continued with the urotherapy as the first treatment following parasacral TENS. It is important to underline that standard urotherapy was maintained and reinforced in cases of children with holding maneuvers who had failed to follow the instructions correctly. These data highlight the difficulty that parents and their children go through to maintain this treatment over the long- term, but reinforce the importance of persisting with standard urotherapy. In this respect, the work of a multidisciplinary team may help in assuring the compliance of the children and their families with the treatment.

Oxybutynin is widely used as second-line therapy for children with OAB, with an efficacy rate of 30-40% (3, 11). In the present study, oxybutynin was the most used option, particularly for patients with persistency of overactive bladder symptoms. When oxybutynin was used alone as first line treatment after parasacral TENS failure, 50% of the patients had their symptoms completely resolved. It is surprisingly that we did not find in the literature any study of oxybutynin for refractory patients.

In a randomized clinical trial, investigators from Aarhus, Denmark, showed that the combination of oxybutynin with parasacral TENS was more effective than either treatment alone (12). If this association had been used more frequently in the present

study, it is possible that the results could have been better. However, the associations of oxybutynin with electrical nerve stimulation (PENS + oxybutynin and TENS + oxybutynin) were used in too few patients. In short, one patient underwent treatment with TENS + oxybutynin, resulting in complete resolution of symptoms, and one patient was treated with PENS + oxybutynin, resulting in a reduction in the DVSS score but no improvement in the VAS score.

We evaluated 2 patients who underwent another series of electrical nerve stimulation. One patient, refractory to TENS was treated with PENS, a more invasive type of stimulation, had a final VAS score of 60 and did not come back to the clinic for follow-up. Other patient who had recurrency of the urinary symptoms after an initial complete resolution of them, underwent a new series of parasacral TENS, achieving a VAS score of 80 and showing that, for these cases, redo TENS can be a good option.

Imipramine has been shown beneficial for some children with OAB who have failed to respond to other forms of treatment (11); however, it is still not considered a standard treatment due to the lack of data from randomized clinical trials. In the study conducted by Franco et al. (12), symptoms were resolved in 42.7% of the patients with refractory LUTD who went on to use imipramine, while 22.3% had a partial improvement, 15.5% obtained no response to treatment and 19.5% were lost to follow-up. In the present series, complete resolution of symptoms was achieved in 1 out of 2 patients treated with imipramine as the first subsequent treatment after parasacral TENS failure and in 2 out of 3 patients who used it as alternative for further treatment, suggesting that this is a viable option for cases refractory to TENS.

The combination of oxybutynin with imipramine tends to be used in more severe cases; however, no studies have yet been conducted to evaluate the efficacy of this combined treatment on OAB. The few studies that have been published refer to children with monosymptomatic enuresis, with 66.6% of patients obtaining complete resolution of symptoms (13). In the present study, this treatment option was used primarily for patients who had failed to respond to other forms of treatment. Complete resolution of symptoms was achieved in 2 out of 3 patients who used this strategy as an alternative therapy to other treatments, suggesting that this could be a good option for more refractory cases.

There are some limitations associated with the present study, including the small number of patients and its retrospective nature and the fact that some patients were lost prior to completing treatment. Treatment abandonment may have occurred due to one of two reasons: 1) Patients were sufficiently satisfied with the results achieved even before symptoms had completely disappeared; or 2) Patients became demotivated due to the slowness of progress in extremely refractory cases. Therefore, since many patients abandoned treatment, it was impossible to evaluate the progress made in the whole sample until complete resolution of symptoms.

CONCLUSIONS

For children with OAB refractory to TENS who underwent a structure subsequent treatment, partial response was achieved in all patients and the symptoms completely resolved in half the patients undergoing further treatment. A more intense urotherapy, medications or redo TENS in combination with oxybutynin can be successful used for this difficult situation. For case of recurrence of symptoms after a period of complete resolution of them, redo TENS alone can be useful. It is important to remember that all patient with LUTD who fail to treatment need reevaluation of the bowel function and psychological status.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Effects of Chronic Stress and Comfort Food in Testicular Morphology in Adult Wistar Rats

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ABSTRACT

Purpose: To investigate the effect of chronic stress on testicular morphology in adult Wistar rats, as well as the impact of comfort food consumption on these parameters.

Material and methods: 32 Wistar rats (10 weeks old) were divided into four groups: control (C), stressed (S), control + comfort food (C+CF), and stressed + comfort food (S+CF). Chronic stress was induced by the restraint method during 8 weeks in groups S and S+CF, while groups C and C+CF were maintained under normal conditions. Groups C and S received a standard rat chow diet, while groups C+CF and S+CF received both the standard chow and comfort food (Froot Loops®). After 8 weeks of experiment, all animals were euthanized and the testes were collected for histomorphometric, immunohistochemical and gene expression analysis.

Results: Comfort food was preferred over standard chow in groups C+CF and S+CF, but this preference was more preeminent in stressed animals (S+CF). The consumption of comfort food resulted in testicular weight reduction. The seminipherous epithelium was reduced in group S in comparison to controls. While comfort food also reduced the epithelium in C+CF in comparison to controls, for group S+CF the comfort food ameliorated the stress-induced damage. The cell proliferation rate and the relative expression of StAR and BLC2 genes were similar between the groups.

Conclusion: Both chronic stress and comfort food consumption resulted in morphological alterations of the testes but the consumption of comfort foods during chronic stress partially prevented the stress-induced detrimental effects on testes.

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INTRODUCTION

Stress is an imbalance disorder of the body, caused by external and internal factors (1). The exposure to those factors (stressors) directly and rapidly affects homeostasis, and when prolonged has a destructive effect on tissues, negatively influencing cell proliferation and differentiation, and prejudicing various body activities (2).

Chronic stress is associated with metabolic disorders and changes in energy homeostasis (1). Further, the high glucocorticoids levels contribute to the loss of control between appetite and satiety. This is related to an increased consumption of highly palatable foods (3-5). In turn, dietary change influences the response to chronic stress as, compensatory, it acts to inhibit some of the effects regulated by glucocorticoids (6, 7).

The consumption of comfort foods in society is closely linked to negative emotions and actions. That is, stressful factors (in a person's day or life) can trigger the search for comfort in food. This information is extremely relevant for stress studies since the consumption of comfort foods during stressful situations can act as a compensation for the situation itself, modulating the organic effects of stress (8).

It has been demonstrated that chronic stress promotes negative (morphological and functional) modifications in the testicles. Rats subjected to chronic stress stimuli showed impairment in sperm production and a reduction in serum testosterone levels, as well as a decrease in testicular weight (9). The apoptotic increase in testicular germ cells was seen after 7 days of (2-hour daily) immobilization stress (10). As testicles are androgen-dependent organs, the influence of stress on testosterone levels leads to several histological changes, which justifies the harm caused on sperm parameters (11, 12).

The resultant impact on the reproductive process is important. There is a clear association of stress, both acute and chronic, with male fertility. Further, the harmful effects of stressful stimuli can generate a vicious cycle of changes in reproduction; as the diagnosis of reproductive damage (caused by chronic stress), is per se a stressful event that increases the levels of stress, it compounds the reproductive condition (13).

The objective of this study is to investigate the effect of chronic stress on testicular morphology in adult Wistar rats, as well as the impact of comfort food consumption on these parameters. The present study raises three hypotheses to be answered: the first is that chronically stressed animals (more than non-stressed ones) increase the consumption of comfort foods; the second hypothesis is that chronic stress, despite the consumed diet, promotes deleterious effects on the testicle; finally, it is also hypothesized that the consumption of comfort foods can ameliorate the harmful effects of stress on the testicles.

MATERIALS AND METHODS

Animals

Thirty-two male Wistar rats were used in the experiments. All animals were bred in the Urogenital Research Unit animal facilities and were kept in a room with a controlled temperature (21°C ± 2°C) and artificial dark-light cycles (lights on from 7:00 am to 7:00 pm) and had free access to standard rat chow and water. This project was formally approved by the local ethics committee for the care and use of experimental animals (CEUA) under protocol number 004/2019 and followed national and international regulations on the experimental use of animals.

Experimental design

When animals completed ten weeks of age they were randomly allocated into 4 groups as follows: Control group (C, n=8); Stressed group (S, n=8); Control + comfort food group (C+CF, n=8); and Stressed + comfort food group (S+CF, n=8).

For all animals, 50g of standard chow (Nuvilab CR-1, Quimtia, Colombo, Brazil) were offered daily. While animals of groups C and S received only standard rat chow, groups C+CF and S+CF received 30g of comfort food (Froot Loops, Kellogg Brazil, São Paulo, Brazil) in addition to the standard rat chow. Froot Loops was used as a comfort food due to its palatability, interesting aspect, and nutritional components.

Animals of groups S and S+CF were submitted to a chronic stress protocol by the immobilization

method (14). Each animal was maintained in a rigid opaque plastic tube to restrain its movements, two hours daily, during eight weeks. Tubes with different diameters and lengths were adjusted weekly depending on the animal's size. All tubes had small holes to allow adequate ventilation. Meanwhile, the control groups (C and C+CF) were kept under normal conditions and not submitted to any stress procedure, though food was removed during the same period as that of stressed groups (2 hours daily) to avoid any bias in food intake measurements. All animals were killed the day after the last stress stimuli, when the animals were 18 weeks old.

Dietetic, Biometric and glycemic analyses

For all groups, the standard chow present in each cage was weighted daily and completed for 50g per animal. For groups C+CF and S+CF, in addition to the standard chow, 30g of Froot Loops per rat was offered, and its consumption was also weighted daily. Food consumption (in grams and Kilocalories per body mass) as well as food preference (in percentage of consumption in grams; for groups C+CF and S+CF) was calculated and compared among groups. The food consumption was measured per cage (with 2 or 3 rats of the same group in each cage) and calculated individually (as a mean of the cage). Body mass was measured individually once a week.

Capillary blood glucose was measured (after a 12-hour fast) at the beginning (10 weeks of age) and at the end of the experiment (18 weeks of age) with a portable glucose monitor (Accu-Chek, Roche, São Paulo, Brazil).

Morphometrical analyses

After eight weeks of experiments, the animals were submitted to euthanasia by isoflurane (Isofluorano, BioChimico, Itatiaia, Brazil). Both testes were dissected from their appendages, and their masses and volumes were measured by Scherle's method (15).

For morphometrical analyses, testes were fixed in Bouin solution by immersion for 24 hours, after which they were transversally sliced and immersed in buffered formaldehyde 3.7%. Furthermore, the samples were processed for paraffin embedding to obtain 5-µm-thick histological sections. Morphometrical analyses were performed in hematoxylin and eosin (H&E) stained sections using a microscope (BX51, Olympus, Tokyo, Japan) coupled with a digital camera (DP70, Olympus). All images were obtained and saved at a resolution of 2040 × 1536 pixels (16).

For each rat, the diameters of 125 cross-sections of seminiferous tubules were measured on images obtained at x100 magnification. The straight-line tool of the ImageJ software (National Institutes of Health, Bethesda, USA) was used to measure the tubule diameter. Only round-section tubules were considered, and the straight line always crossed through the center of the tubules. The seminiferous epithelium height was also measured in 125 tubules per rat by using images obtained at x200 magnification. For this analysis, 3 equidistant lines were drawn from the tunica propria of the seminiferous tubules to the last germinative cell, thus excluding the spermatozoa. The mean of these three lines was considered as the height of that seminiferous tubule (16).

The volumetric density (Vv) of each testicular structure was assessed using the point counting method (16). For each rat, 25 fields randomly captured were evaluated. Briefly, using the ImageJ software, a 99-point grid was superimposed over images at x400 magnification. However, to overlay the grid, the area of the image was previously measured using the "measure" tool of the ImageJ software. Each structure touched by the grid point was counted using the "cell counter" tool of ImageJ. The density was determined as a percentage of the analyzed field. In this way, we quantified the Vv of the tunica propria, seminiferous epithelium, tubular lumen, and intertubular compartment. The sum of the Vv[tunica propria], Vv[seminiferous epithelium], and Vv[tubular lumen] was considered the Vv[tubular compartment]. The points on the interstitial space were considered the Vv[intertubular compartment]. For each parameter, the result was expressed as a percentage and calculated from the average of the results of each analyzed image.

The cell proliferation rate was determined through PCNA (cell proliferation nuclear antigen) immunolabeled sections. Routine protocol for immunolabeling was performed, including the use of anti-PCNA primary antibody (clone PC10, cat. no. 13-3900, Life Technolo-

gies, Carlsbad, CA, USA), secondary antibody (MP-7452, Vector Laboratories, Newark, USA), diaminobenzidine revelation (SK-4105, Vector Laboratories, Newark, USA) and counterstaining with hematoxylin. The antigen retrieval was carried out in a water bath at 100ºC for 15 minutes, using citrate buffer at pH 6.0, and incubation with the primary antibody was carried out overnight at 4ºC. For each animal, 30 immunolabeled fields were captured at x400 magnification. The "cell counter" tool of ImageJ was used to count the labeled cells while the "free-hand selection" tool was used to determine the tubular area on each filed. The results were expressed as number of labeled cells per tubular squared millimeters.

Gene expression analysis by reverse transcription quantitative real-time PCR (RT-qPCR)

Testis samples were collected from each animal for gene expression analyses by RT-qPCR. The samples were minced into small fragments, snap-frozen in liquid nitrogen and stored at -80ºC. Total RNA isolation was performed using the ReliaPrep™ RNA Tissue Miniprep System extraction kit (Promega, Wisconsin, USA), according to the manufacturer's protocol. Tissue RNA extraction was carried out using 2.8 mm diameter ceramic beads (CK28, Bertin Technologies, Montigny-le-Bretonneux, FRA) and the Precellys tissue homogenizer (Bertin Technologies), 2 cycles of 20 seconds at 5000 RPM. RNA purity and concentration were determined using the NanoDrop spectrophotometer (ND-1000 Spectrophotometer, Thermo Fisher Scientific, Massachusetts, USA).

Reverse transcription for the synthesis of complementary DNA (cDNA) and quantitative real-time PCR (qPCR) were performed with the GoTaq® Probe 1-Step RT-qPCR System kit (Promega), according to the manufacturer's instructions. The AriaMx Real-Time PCR equipment (Agilent Technologies, Santa Clara, USA) was used to carry out the experiment, and the resulting data were analyzed and quantified with the AriaMx Software. Each gene was evaluated in technical triplicate in all samples and normalized by the reference gene (GAPDH) using the formula: $^{\Delta}Ct$ = Ct (gene of interest) - Ct (reference gene). The $^{\Delta}Ct$ values of each group were used for statistical analysis (two-way ANOVA test). The relative fold change of gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method (17). The qPCR primers were purchased from Thermo Fisher Scientific, with the following sequences (5'-3'): GAPDH Foward (GGT TAA AGT GGA AGG CGA TGT); GAPDH Reverse (CTC GCA TGC TGA TCA CAA TC); StAR Foward (CAC CAC CTT ACT TAG CAC TTC A); StAR Reverse (CAA GGA GAG GAA GCT ATG CAA); BCL2 Foward (CCA GGA GAA ATC AAA CAG AGG T); BCL2 Reverse (GAT GAC TGA GTA CCT GAA CCG).

Statistical analysis

All parameter values were analyzed using the Kolmogorov-Smirnov normality test. Parametric data was compared by two-way ANOVA, with Tukey's post-test. Student's t-test was used to analyze food preference. All analyses were performed with the GraphPad Prism 9.0 software (GraphPad Software, San Diego, USA). Mean differences were considered significant when their p values were <0.05. All results are presented as mean ± standard deviation.

RESULTS

Dietetic, Biometric and glycemic analyses

Chronic stress did not alter the food consumption (measured in grams) among the groups. However, animals receiving comfort foods reduced the weight of food consumed by 9.5% (p=0.0004). Among the groups, S+CF had the lowest food consumption, 14.3% (p=0.0011) lower than group C, 10.2% (p=0.0324) lower than group C+CF, and 14.4% (p=0.0009) lower than group S. Also, two-way ANOVA showed that there is a significant interaction (p=0.0449) between the factors (stress and access to comfort food) regarding food consumption.

Also, chronic stress did not affect the food consumption measured by Kilocalories per body mass, but the access to comfort food did (p=0.0495). In this analysis, it was found that groups receiving comfort foods consumed 7.7% more calories than groups receiving only standard chow.

Animals that received standard chow and comfort food showed a significant preference for the latter, both in the C+CF and S+CF groups. The consumption of comfort food in the C+CF group was 73.3% higher than

the consumption of standard chow (p<0.0001). For the S+CF group, this difference was in effect drastic: comfort food was consumed 123.5% more than standard chow (p<0.0001).

The initial body mass, the final body mass, the initial capillary blood glucose levels, and the final capillary blood glucose levels were similar among the groups, with no detected effect of stress, comfort food or the interaction among these parameters. The dietetic, biometric and glycemic data are presented in Table-1.

Morphometrical analyses

The access to comfort food resulted in a reduction of 9.6% in the testicular mass (p=0.0309). Even so, there were no changes in testicular volume between animals receiving standard chow and those receiving comfort food. Also, the stress factor did not cause changes in testicular weight and volume.

The seminiferous tubule diameter and epithelium height were not affected either by stress or access to comfort food. Even so, two-way ANOVA showed that there was a significant interaction between these two factors (stress and comfort food). Tukey's post-test pointed out that group S had its epithelium height reduced by 16.7% (p=0.0332) in comparison to group C. Further, when comparing non stressed rats with (C+CF) or without access to comfort food (C), it was observed that comfort food promoted a reduction of 8.4% (p=0.0332) in epithelium height. On the other hand, comfort food had a different (and positive) effect in stressed animals: Group S+CF showed increased epithelium height by 18.2% (p=0.0471), in comparison to group S. Group S+CF also showed 7.5% higher values (p=0.0471) than those in group C+CF These results are illustrated in Figure-1.

Stressed groups showed a 29.5% (p=0.0074) increase in tubular lumen Vv volumetric density in comparison to non-stressed animals. Post-test showed that groups S and S+CF had 60.3% (p=0.0122) and 56.4% (p=0.0201) higher tubular lumen Vv in comparison to group C. For the other volumetric densities studied, no differences were observed among the groups, as presented in Table-2. The analyses of the cell proliferation rate also showed a similarity between the experimental groups, without statistical differences among them.

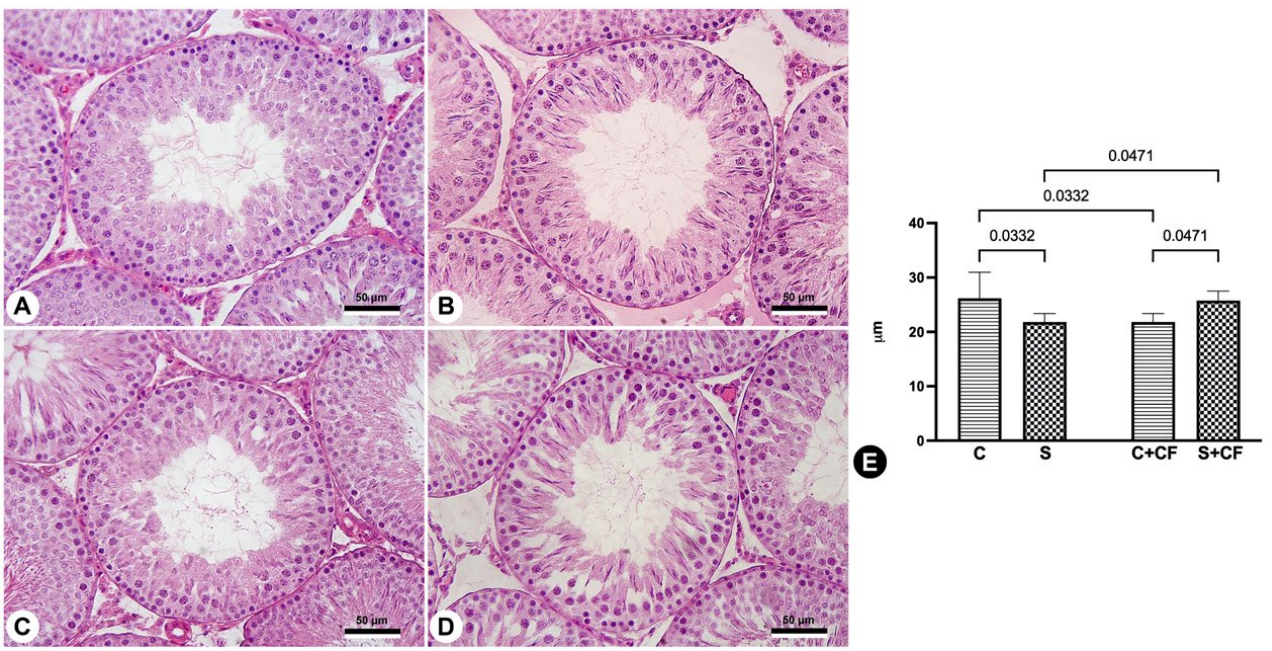
Table 1 - Biometrical data of rats submitted to stress conditions with or without access to comfort foods.

	C	S	C+CF		S+CF		p value[1]	p value[2]	p value[3]
Initial blood glucose (mg/dL)	89.25 ± 9.19	98.63 ± 13.21	95.38 ± 14.69		89.29 ± 11.88		0.7162	0.7221	0.0952
Final blood glucose (mg/dL)	89.19 ± 7.95	96.13 ± 13.67	99.71 ± 13.41		90.57 ± 8.88		0.7914	0.5520	0.0622
Initial body mass (g)	319.10 ± 57.85	348.00 ± 29.63	373.00 ± 41.24		313.40 ± 24.90		0.3125	0.6175	0.0618
Final body mass (g)	388.10 ± 70.45	378.60 ± 43.53	423.70 ± 38.93		364.90 ± 34.29		0.0648	0.5443	0.1759
Food intake (g)	27.77 ± 1.69	27.81 ± 1.95	26.51 ± 2.04		23.81 ± 1.67		0.0515	**0.0004**	0.0449
Food intake (kcal/kg BM)	0.24 ± 0.02	0.24 ± 0.02	0.27 ± 0.03		0.25 ± 0.03		0.1819	**0.0495**	0.1819
Food preference (g)			**SF**	**CF**	**SF**	**CF**	**p value[4]**	**p value[5]**	
			9.70 ± 0.95	16.81 ± 1.51	7.36 ± 1.69	16.45 ± 1.89	<0.0001	<0.0001	

C = Control group; S = Stress group; C+CF = Control + Comfort Food group; S+CF = Stress + Comfort Food group; SF = Standard Food; CF: Comfort Food; *p* value[1] indicates stress effects; *p* value[2] indicates comfort food effects; *p* value[3] indicates interaction between the two factors; *p* value[4] indicates the comparison of food preference of the C+CF group; *p* value[5] indicates the comparison of food preference of the S+CF group.

Data expressed as mean ± standard deviation.

Figure 1 - Photomicrographs representing the testicular seminiferous tubules of different groups.



(A) Control group (B) Stressed group (C) Control + comfort food group (D) Stressed + comfort food group (E) Graphical representation revealing significant differences of the testicular seminiferous epithelim height of different groups. Sections were stained using hematoxilin and eosin and captured under 400× magnification. Scale bar represents 50µm.

Table 2 – Testicular morphometric data of rats submitted to stress conditions with or without access to comfort foods.

	C	S	C+CF	S+CF	p value[1]	p value[2]	p value[3]
Testicular mass (g)	1.72 ± 0.12	1.75 ± 0.11	1.63 ± 0.19	1.51 ± 0.27	0.5314	**0.0309**	0.3054
Testicular volume (mL)	1.66 ± 0.18	1.64 ± 0.23	1.58 ± 0.07	1.48 ± 0.24	0.4755	0.1628	0.6476
Seminiferous tubule diameter (µm)	245.46 ± 8.81	237.04 ± 11.59	232.61 ± 10.37	238.51 ± 9.58	0.7714	0.1538	0.0862
Seminiferous epithelium height (µm)	26.17 ± 4.77	21.80 ± 1.58	23.97 ± 1.34	25.77 ± 1.74	0.2153	0.3896	**0.0005**
Seminiferous epithelium Vv (%)	53.47 ± 2.17	52.10 ± 4.88	49.84 ± 3.70	52.21 ± 5.30	0.7627	0.2969	0.2673
Tunica propria Vv (%)	3.68 ± 0.50	3.56 ± 1.00	3.73 ± 0.69	2.96 ± 0.44	0.1099	0.3147	0.2441
Tubular lumen Vv (%)	10.32 ± 2.34	16.54 ± 3.81	14.91 ± 1.74	16.14 ± 4.40	**0.0074**	0.1117	0.0611
Tubular compartment Vv (%)	69.17 ± 4.42	64.60 ± 19.39	68.50 ± 5.11	71.33 ± 9.39	0.8464	0.5012	0.4130
Intertubular compartment Vv (%)	30.45 ± 4.32	27.71 ± 7.17	30.91 ± 5.12	28.21 ± 9.22	0.3123	0.8562	0.9946
Nuclear proliferation rate (cells/mm^2)	1268 ± 116.4	1278 ± 110.4	1255 ± 102.8	1311 ± 107.5	0.4404	0.8110	0.5974

C = Control group; S = Stress group; C+CF = Control + Comfort Food group; S+CF = Stress + Comfort Food group.
p value1 indicates stress effects; p value2 indicates comfort food effects; p value3 indicates interaction between the two factors.
data expressed as mean ± standard deviation.

StAR and BCL2 gene expression analysis

The expression of the StAR gene was decreased by 26.45% in the stressed groups compared to the non-stressed animals, with fold change value of 0.54 of group S in relation to C, although the p-value did not reach statistical significance (p=0.0589). Furthermore, the post-test showed no differences among the four groups studied. The fold change of group C in relation to C+CF was 0.84. The fold change of group S in relation to S+CF was 1.07. The fold change of group C+CF in relation to S+CF was 0.68. Regarding the BCL2 gene, the relative expression levels were similar among the groups. The fold change of group C in relation to S was 0.97. The fold change of group C in relation to C+CF was 0.94. The fold change of group S in relation to S+CF was 0.91. The fold change of group C+CF in relation to S+CF was 0.95.

DISCUSSION

This study sought to understand the effects caused by chronic stress on the testicles of adult Wistar rats, in addition to studying the relationship between stress and the eating behavior in this animal model. The activation of the hypothalamus-pituitary-adrenal axis by the stressor stimulus leads to endocrine dysregulation and elevation of glucocorticoids, which impacts many physiological pathways (1). The restraint stress methodology used in this study is associated with an increase in corticosterone levels and important impacts on the organism of rodents (6, 18).

Among the stress-induced physiological modifications, one explored in this study is the search for foods that stimulate comfort and could be a mitigating agent. In some cases, these mitigating agents can stop the progression or promote a recovery from the damages caused by stress (19). The selection of comfort food in this study was based on the sensory characteristics of rodents, as Froot Loops generates both visual, gustative, and tactile appeals. Comfort food was not chosen to study metabolic changes, but rather to analyze eating behavior during the chronic stress condition.

When comparing the numerical results regarding the food intake of all groups, the animals with access to comfort food reduced their food intake (measured in grams) but augmented the calories consumed, certainly due to the higher energetic density of the comfort food used. The effects of stress over food intake were not observed by our statistical methods, but the stress condition induced a marked modification of food preference on groups with access to comfort food. Both stressed and non-stressed groups preferred to eat comfort food than standard chow, as expected. However, this preference was more drastic for stressed animals: while non-stressed animals consumed 73.3% more comfort food than standard chow, stressed animals consumed 123.5%.

It is well known that changes arising from stress directly affect eating behavior, since satiety and appetite control are regulated by the hypothalamus, which is activated during chronic stress by raising the glucocorticoids bloodstream levels, impacting all hormonal regulation (3-5).

The preference for consuming comfort foods in non-stressed animals is explained by its palatability, but its higher preference by stressed animals can be associated with the search for pleasurable sensations as an amelioration of the stressful situations (4). Previous studies have pointed to the greater search for compensation in people and animals that have had negative mood stimuli. For these situations, the search for comforting sensations (including comfort food), is clearly a compensation for the mechanisms of the action of stress (8, 19).

The impact of chronic stress is not limited to physiological modifications. It also exerts great impact on the morphology of the organs, which is probably a consequence of the physiological modifications. The induced chronic stress in this experimental model was previously associated with morphological modifications in the urogenital system organs. Impacts on kidneys, bladder, prostate and penis were documented by this research group (12, 20, 21). The impacts of stress on testicular morphology and function were also explored before. In some studies, the impact of chronic stress over the testes was such that it caused a significant atrophy of the organ (12, 18). In the present study, such drastic changes were not observed. Testicular volume and weight were similar among the groups, suggesting that

the chronic stress in this experiment was not as high as in previous studies. On the other hand, the access to comfort food reduced the testicular weight of the rats, which can only be explained by some alteration promoted by the altered diet, with higher levels of sugars (22).

Also, a decrease in the diameter of the seminiferous tubules in stressed animals was previously reported (9, 12), which was not observed in the present study, coinciding with no atrophy of the testicles. While the tubule diameter remained similar among groups, the seminiferous epithelium height was impacted by the interaction of stress and comfort food. The results of this analysis were very interesting; while both stress (group S) and comfort food (group C+CF) individually promoted a reduction in epithelium height, the stressed animals eating comfort food (group S+CF), showed better results. At first, this indicates that both stress and comfort food, alone, causes detrimental effects.

This alteration of seminiferous epithelium height may be associated with altered testicular function. As a result, from the germinative epithelium alterations, the production of spermatozoa will be affected. Such morphological changes may find an explanation in the decrease in steroidogenic activity. As spermatogenesis occurs in the seminiferous epithelium under appropriate hormonal conditions, dysregulations in testosterone levels can lead to alterations of this germinal epithelium (23). As is known, testosterone levels are commonly reduced during chronic stress by the interference of the hypothalamus-pituitary-adrenal axis on the hypothalamus-pituitary-gonadal axis (11, 12). The testicle is a highly proliferative and sensitive organ and depends on a very delicate microenvironment to properly produce hormones and masculine gametes, and any imbalance in homeostasis induces deleterious effects on its physiology (24). It is presumable that the impact of stress and comfort food consumption on the germinal epithelium may lead to altered sperm production, affecting the reproductive function.

Interestingly, when comparing the stressed animals (with and without access to comfort foods), a higher epithelium height of those with access to comfort food was observed. This suggests that comfort food acted as an ameliorating or preventing agent for the deleterious effects of chronic stress. This was actually so effective that the epithelium height of S+CF animals was similar to those of the control group. This reinforces the thesis that comfort food shows it is very beneficial during chronic exposure to stress, attenuating some detrimental effects normally caused by the stress condition.

While the analyses of seminiferous epithelium confirmed the hypothesis that comfort food may act as a stress mitigating agent, the data of tubular lumen does not. Tubular lumen was affected by stress similarly, whether in the groups receiving comfort food or those which did not. For this parameter, the access to comfort food neither prevented nor prejudicated the effects caused by stress.

The process of spermatogenesis depends on a delicate balance of apoptotic and proliferative factors. Previous work showed that chronic stress is capable of altering germ cells, impairing spermatogenesis (25) and reducing PCNA positive cells as well as altering PCNA gene expression (9). Despite these findings in the literature, our study did not observe any alteration regarding the proliferation rate. Regarding the apoptotic process, although there are studies that show genetic modulations arising from stress (26, 27), our data show no deregulation in BCL2 mRNA levels. BCL2 levels can provide good information due to its ability to inhibit induced apoptotic processes and act in balance with apoptosis-accelerating proteins, such as Bax (27).

The mechanisms of testosterone synthesis and regulation depend on several factors. Its bioconversion from the cleavage of cholesterol by the P450scc enzyme depends on adequate transport from the external mitochondria to the internal mitochondria, through the StAR protein. Studies prove that reproductive functionality and the synthesis of steroid hormones depend on good StAR gene expression, and regulated transcriptional and post-translational aspects (28). Endocrine changes arising from acute stress can lead to a reduction in the expression of StAR mRNA and as the stress period is prolonged, the stress adaptation mechanisms mediated by the HPA axis are able to resume their damage and increase gene expression (29). Although not supported by statistical analysis, the gene expression findings in our study may suggest that stress could lead to a re-

pression of the StAR gene. It is worth noting that the p-value found was borderline, likely due to the variation in StAR gene expression between the study samples. In view of this, we believe that a long period of stress, as performed in our study, may indeed lead to a decrease in StAR gene expression.

Damage to the male reproductive function resulting from stress is studied scientifically, since this issue afflicts the lives of many men. Factors that can mitigate its possible harmful effects are important, due to the increase in stress exposure in today's society (7, 19). In this aspect, the present study is the first to show that the consume of comfort foods during stressful periods can ameliorate the harmful effects caused by chronic stress. Other novel finding is that the tendency for consuming comfort food is increased during stress. The data presented in this study support a better understanding of the mechanisms of action and the deleterious effects of stress and show that, for some parameters, the use of a comfort agent (even if this is a non-healthy food) can ameliorate the damage caused.

Possibly, the chronic stress imbalances the oxidant / anti-oxidant conditions in testicular tissue, as well as it happens in other testicular conditions (30). The increase in in reactive oxygen species, and/or decrease in antioxidant production may be a consequence of the chronic stress and a cause of the morphological alterations observed. Studies verifying the testicular oxidative stress damage during chronic stress, as well as studies focusing on the use of antioxidant agents for ameliorating the stress-induced alterations, are warranted.

As this is an animal study, one of the limitations is the direct transposing for human pathology. As it is known, it would not be practical to perform testicular biopsy in stressed patients for verifying the morphological condition. Even so, this manuscript adds important clue that can be used in clinical practice: a patient with infertility concern can be helped by (moderately) consuming comfort food during stressful situations. This is a non-harmful clinical recommendation that (relying on the present study findings) ameliorate the stress-induced testicular damages, improving the fertility.

The chronic stress methodology used in the study is different from the stressful stimuli that people receive in their lives. Further, as it is a repetitive method, some adaptation may occur, although the study results proved the stress condition. Further studies with other (non-repetitive) stress-induction methods are necessary to corroborate the results of this study. Nonetheless, these results help to understand some aspects of the impact of stress on testes morphology, its relationship with food preference, and the effects of comfort food consumption during stress conditions.

CONCLUSIONS

The consume of comfort foods by chronic stressed rats partially prevented the stress-induced testicular morphological damage. This indicates that the use of comfort food during stressful situations can improve fertility. Also, the present study showed that induced chronic stress leads to an increased tendency to consume comfort food. Further, the study confirmed that chronic stress and the consumption of comfort foods resulted in morphological changes in the testes.

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CONFLICT OF INTEREST

None declared.

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Comparative Study of Gleason 7 (3+4) and (4+3) Prostatic Adenocarcinomas with Prognostic Criteria and Immunohistochemical Profiles of AMACR, PSA and Ki-67

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ABSTRACT

Background: To compare Gleason 7 (3+4) and (4+3) prostatic adenocarcinoma (PC) with different prognostic criteria through immunohistochemical analysis with anti-PSA, anti-Ki 67 and anti-AMARC antibodies.

Methods: We analyzed 221 surgical specimens from patients between 40 and 86 years-old (mean=63) with PC. The immunohistochemical study was performed with anti-PSA, anti-Ki 67 and anti-AMARC. The microscopic fields were photographed with an Olympus DP70 digital camera coupled to an Olympus BX51 microscope and archived in TIFF. Proportion and intensity criteria were used to quantify the anti-PSA antibody and for the anti-Ki 67 antibody, the quantification by similarity of this antibody in breast carcinomas. Anti-AMACR protein expression was based on four scores: negative, weak, moderate and strong. The statistical analysis was performed with the Graph Pad Prism 5 program.

Results: In the Gleason score 7 (3+4) we had 91.72% in pT2 and 8.27% in the pT3 group; 8.27% recurrences, of which 90.90% in the pT2 group. In the Gleason score 7 (4+3) we had 77.27% in the pT2 group and 22.72% in the pT3 group and 10.22% of relapses, of which 66.66% in the pT2 group and 33.33% in the pT3 group. In 6.81% of cases there was an increase in the anti-Ki 67 index and in 2.27% of the cases, there was an increase in the immunoexpression of anti-p53 when comparing Gleason score 7 (3+4) with Gleason score 7 (4+3).

Conclusion: Our study confirmed differences in the Gleason score 7 (3+4) and Gleason score 7 (4+3) of PC when comparing prognostic criteria. Anti-Ki 67 and anti-PSA antibody immunostaining showed a positive correlation as the Gleason score 7 increased from (3+4) to (4+3).

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INTRODUCTION

The classification of prostatic adenocarcinomas is still based on Gleason's histopathological classification, which, despite having undergone modifications, remains a well-established indicator that has supported the test of time (1, 2). In 2013, a new system composed of grade groups of 1 to 5 was developed by the Johns Hopkins Hospital and validated in a large multi-institutional and multimodal study by the International Society of Urological Pathology (ISUP) in 2014 (3, 4).

The new grading system proves to be more accurate than the Gleason system. The Gleason system with its primary and secondary patterns is a subjective and complicated classification system, considering that the classification systems used for other tumors are usually simplified, ranging from grade 1 to 3 (well, moderately and poorly differentiated) or low, intermediate or high grade. The current classification proposed by ISUP and WHO (World Health Organization) uses a grade group 1 for Gleason 6 and a grade group 2 for Gleason (3+4), making common prognostic and therapeutic proposals possible (3, 4). Similarly, classification in grade group 4 for Gleason 8 and grade group 5 for Gleason 9 or 10 allows for better stratification and future studies to determine whether PC grade group 5 will require more intensive therapy (3, 4).

In addition to the histopathological grading, the set of factors that determine the pathological staging is of prognostic importance, such as the invasion of the prostatic capsule, the impairment of the surgical resection margin, the impairment of the urethral and vesical margins and the invasion of seminal vesicles (5-7).

Currently, the established prognostic factors for prostate cancer (PC) are the TNM staging of the tumor (primary tumor, regional lymph nodes and distant metastases) of the AJCC (American Joint Committee on Cancer) (8), status of surgical margins, level of serum PSA and Gleason score (2).

The aim of this study was to compare Gleason 7 (3+4) and Gleason 7 (4+3) adenocarcinomas with different prognostic criteria: impairment of the surgical margin of resection, impairment of the vesical margin, impairment of the urethral margin and impairment of seminal vesicles through an immunohistochemical analysis with anti-PSA, anti-Ki 67 and anti-AMARC antibodies.

MATERIAL AND METHODS

The project was submitted and approved by the Ethics Committee (CAAE number 12685413.6.0000.5259 of the State University of Rio de Janeiro) and is in accordance with the Institution's ethical standards for experiments with human materials.

We retrospectively analyzed 221 surgical specimens of patients (aged 40 to 86, mean=63 years old) with diagnosis of prostatic adenocarcinoma submitted to radical prostatectomy between January 2015 and January 2021.

As inclusion criteria, only cases with histopathological diagnosis of prostatic acinar adenocarcinoma Gleason 7 (3+4) and Gleason 7 (4+3) were considered. As exclusion criteria were considered the ductal pattern adenocarcinomas, other histopathological variants of prostate cancer and prostate adenocarcinomas with histopathological evidence of previous treatment.

The specimens were sent to the Pathological Anatomy Laboratory, fixed in block by immersion in 10% buffered formalin for 24 hours. The surgical margins were marked with India ink and the prostate was separated into two lobes, right and left, and respective anterior and posterior quadrants, from which samples were taken for histological analysis. Also, fragments of the vesical (upper) and urethral (lower) limits were removed.

The removed fragments were accommodated in plastic cassettes and processed for inclusion in paraffin. The samples were dehydrated in increasing baths of ethanol, diaphanized in xylene and impregnated in liquid paraffin with subsequent hardening at room temperature.

Histologic techniques

After routinely processed for paraffin embedding, 5-µm thick sections are obtained at 200-µm intervals. Sections are stained with hematoxylin-eosin to assess the integrity of the tissue.

The immunohistochemical analysis of the prostate fragments is done with anti-PSA (prostate-specific antigen, clone EP109, Biocare), anti-Ki 67 (Molecular immunology Borstel 1, Clone MIB-1, Agilent) and anti-AMARC (alpha-methylacyl-coenzyme A racemase, P504s, clone 13H4, Cell score). The antibodies are revealed with the use of a Mouse Rapid Staining Kit (Sto Stock #1, Quik-1 - Sigma Chemical Co., St. Louis, USA), containing a secondary antibody, peroxidase, 3% hydrogen peroxide and the chromogen AEC (3-amino-9-ethyl-carbazole).

Anti-PSA is a protease of the kallikrein family produced by the ductal epithelium and prostatic acinar. Anti-PSA antibody exhibits cytoplasmic labeling in more than 95% of prostatic carcinomas, but its immunoreaction decreases as the Gleason grade increases (9).

Anti-Ki 67 is a monoclonal antigen that interacts with the human nuclear Ki 67 antigen, present in all active phases of the cell cycle (phases G1, S, G2 and M), not being present only in phase G0. Anti-Ki 67 antibody labeling is therefore nuclear and expresses cell proliferation, useful in mitotic counting (10).

Anti-AMACR is a mitochondrial and peroxisomal enzyme involved in the metabolism of branched chain of fatty acids and bile acid (11).

Quantification Techniques

The microscopic fields were photographed, under the same conditions and by the same senior pathologist, using an Olympus DP70 digital camera (Olympus America, Inc., Melville, New York) with a resolution of 2,040 1,536 pixels, directly attached to an Olympus BX51 microscope and filed in TIFF.

The criterion for interpreting the protein expression of anti-AMACR included four scores: negative, weak (weak or apical granular cytoplasmic staining), moderate (diffuse granular cytoplasmic staining), and strong (diffuse intense cytoplasmic staining). Only moderate and strong markings were considered positive (12).

Proportion and intensity criteria were used to quantify the anti-PSA antibody based on the quantification by similarity of this antibody in hormone receptors (estrogen and progesterone) (13).

The criteria for interpretation of the anti-PSA immunostaining in patterns 3 and 4 prostate adenocarcinomas were as follows:

- Proportion: 0: unmarked; 1: less than 1%; 2: between 1 and 10%; 3: between 10% to 33%; 4: between 33 to 66%; 5: above 66%.

- Intensity: 0: no marking; 1: light; 2: moderate; 3: intense.

- Total score: sum up to 2: negative; sum greater than 2: positive. (13) (Table-1).

The anti-Ki 67 antibody quantification criterion was used based on the similarity quantification of this antibody in breast carcinomas (14).

The criterion for interpretation of the anti-Ki 67 immunostaining in prostate adenocarcinomas with Gleason patterns 3 and 4 used was the cutoff point of 14% (14).

Statistical analysis

All parameters were statistically processed and tabulated. The Student t-test was used for comparison of quantitative data between negative vs. positive result ($p<0.05$). The chi-square test was used to verify associations between categorical variables and negative vs. positive result ($p<0.05$). The statistical analysis was performed with the Graph Pad Prism 5 program (Version 5).

RESULTS

In the Table-2 we can observe the AJCC Pathological Classification of Gleason 7 (3+4) and Gleason 7(4+3) prostatic adenocarcinomas and the demographic data of our sample.

In the Gleason 7 score (3+4) we had 55.63% of patients distributed in pT2 and 36.09% in pT2R1 according to the AJCC classification, that is, 91.72% of

Table 1 - Quantification of anti-AMARC, anti-PSA and anti-Ki67 antibodies in prostatic adenocarcinomas.

GLEASON	AMARC	PSA	KI 67
Pacient 1- Gl 3	weak (-)	P5 + I 3= 8 (+)	< 14%
Pacient 1 - Gl 4	weak (-)	P5 + I 3= 8 (+)	> 14%
Pacient 2 - Gl 3	weak (-)	P 5 + I 3= 8(+)	< 14%
Pacient 2 - Gl 4	moderate (+)	P5 + I 3= 8 (+)	< 14%
Pacient 3 - Gl 3	weak (-)	P 5 + I 2= 7 (+)	< 14%
Pacient 3 - Gl 4	weak (-)	P 5 + I 3= 8 (+)	14%
Pacient 4 - Gl 3	weak (-)	P 4 + I 2= 6 (+)	< 14%
Pacient 4 - Gl 4	weak (-)	P5 + I 3= 8 (+)	14%
Pacient 5 - Gl 3	moderate (+)	P 5 + I 2= 7 (+)	< 14%
Pacient 5 - Gl 4	moderate (+)	P5 + I 3= 8 (+)	< 14%
Pacient 6 - Gl 3	weak (-)	P 5 + I 1= 6 (+)	< 14%
Pacient 6 - Gl 4	weak (-)	P 5 + I 2= 7 (+)	14%
Pacient 7 - Gl 3	weak (-)	P 5 + I 3= 8 (+)	< 14%
Pacient 7 - Gl 4	weak (-)	P5 + I 3= 8 (+)	< 14%
Pacient 8 - Gl 3	moderate (+)	P 5 + I 2= 7 (+)	14%
Pacient 8 - Gl 4	moderate (+)	P 5 + I 1= 6 (+)	14%
Pacient 9 - Gl 3	weak (-)	P 5 + I 2= 7 (+)	< 14%
Pacient 9 - Gl 4	moderate (+)	P5 + I 3= 8 (+)	> 14%
Pacient 10 - Gl 3	weak (-)	P 2 + I 1= 3 (+)	< 14%
Pacient 10 - Gl 4	weak (-)	P3 + I 2= 5 (+)	< 14%
Pacient 11 - Gl 3	weak (-)	P 5 + I 3= 8 (+)	< 14%
Pacient 11 - Gl 4	weak (-)	P 5 + I 3= 8 (+)	< 14%
Pacient 12 - Gl 3	weak (-)	P 5 + I 3= 8 (+)	< 14%
Pacient 12 - Gl 4	weak (-)	P5 + I 2= 7 (+)	> 14%
Pacient 13 - Gl 3	weak (-)	P 5 + I 3= 8(+)	< 14%
Pacient 13 - Gl 4	weak (-)	P5 + I 3= 8 (+)	< 14%
Pacient 14 - Gl 3	moderate (+)	P 5 + I 3= 8(+)	< 14%
Pacient 14 - Gl 4	weak (-)	P5 + I 3= 8 (+)	< 14%
Pacient 15 - Gl 3	weak (-)	P3 + I 2= 5 (+)	< 14%
Pacient 15 - Gl 4	weak (-)	P3 + I 2= 5 (+)	< 14%

Table 2 - The table shows the AJCC Pathological Classification of Gleason 7 (3+4) [A] and Gleason 7 (4+3) [B] prostatic adenocarcinoma.

	Cases		%		Age		Recurrence		White		Brown		Black	
	[A]	[B]	[A]	[B]	[A]	[B]	[A]	[B]	[A]	[B]	[A]	[B]	[A]	[B]
pT2	74	51	55.63	57.95	40-86	51-82	7	4	50	31	10	4	3	0
pT2 R1	48	17	36.09	19.31	46-77	55-71	3	2	29	8	3	4	0	0
pT3a	1	3	0.75	3.40	76	52-69	0	0	1	2	0	1	0	0
pT3a R1	6	6	4.51	6.81	54-75	56-71	1	2	3	5	1	0	1	0
pT3b	2	5	1.50	5.68	54-66	57-76	0	1	1	4	0	1	0	0
pT3b R1	2	6	1.50	6.81	61-70	59-76	0	0	1	4	0	0	0	0

[A] Gleason 7 (3+4); [B] Gleason 7 (4+3)

patients in pT2. In this Gleason 7 score (3+4) we had only 8.26% of patients in T3.

In the Gleason 7 score (4+3) we had 57.95% of patients distributed in pT2 and 19.31% in pT2R1, that is, 77.26% of patients in pT2 and 22.70% in T3. In this Gleason score 7(4+3), pT3 was more expressive when compared to the pT2 group.

As for recurrences in the Gleason score 7 (3+4), we had a total of 11 cases (8.27%), of which 90.90% in pT2 of the AJCC and only 9.09% in pT3. In the Gleason score 7 (4 +3) we had a total of 9 recurrences (10.22%), of which 66.66% in pT2 and 33.33% in pT3. In this Gleason score 7(4+3), pT3 values were higher when compared to pT2.

As for the color of the patients, both Gleason 7 (3+4) and (4+3) scores showed a predominance of the white race, 82.52% and 84.37%, respectively. In white individuals, both in the Gleason scores 7 (3+4) and (4+3), were distributed in pT2 in the percentages of 58.82% and 57.40%, respectively.

In the Gleason score 7 (3+4) the browns were distributed in pT2 in the percentage of 71.42% and blacks were distributed in pT2 in 75% of cases and in pT3aR1 in 25%.

In the Gleason score 7 (4+3) the browns were distributed in pT2 and pT2R1 in the percentage of 40% for both.

In 6.81% of the cases there was an increase in the anti-Ki 67 index and in 2.27% of the cases there was an increase in the immunoexpression of anti-p53 when comparing Gleason score 7 (3+4) areas with Gleason score 7 (4+3) areas.

In our study, 6.81% of cases showed increased immunostaining of tissue anti-PSA when compared to Gleason score 7 (3+4) with 7 (4+3) and only 2.27% of cases showed decreased PSA labeling when compared these two scores (Figure-1).

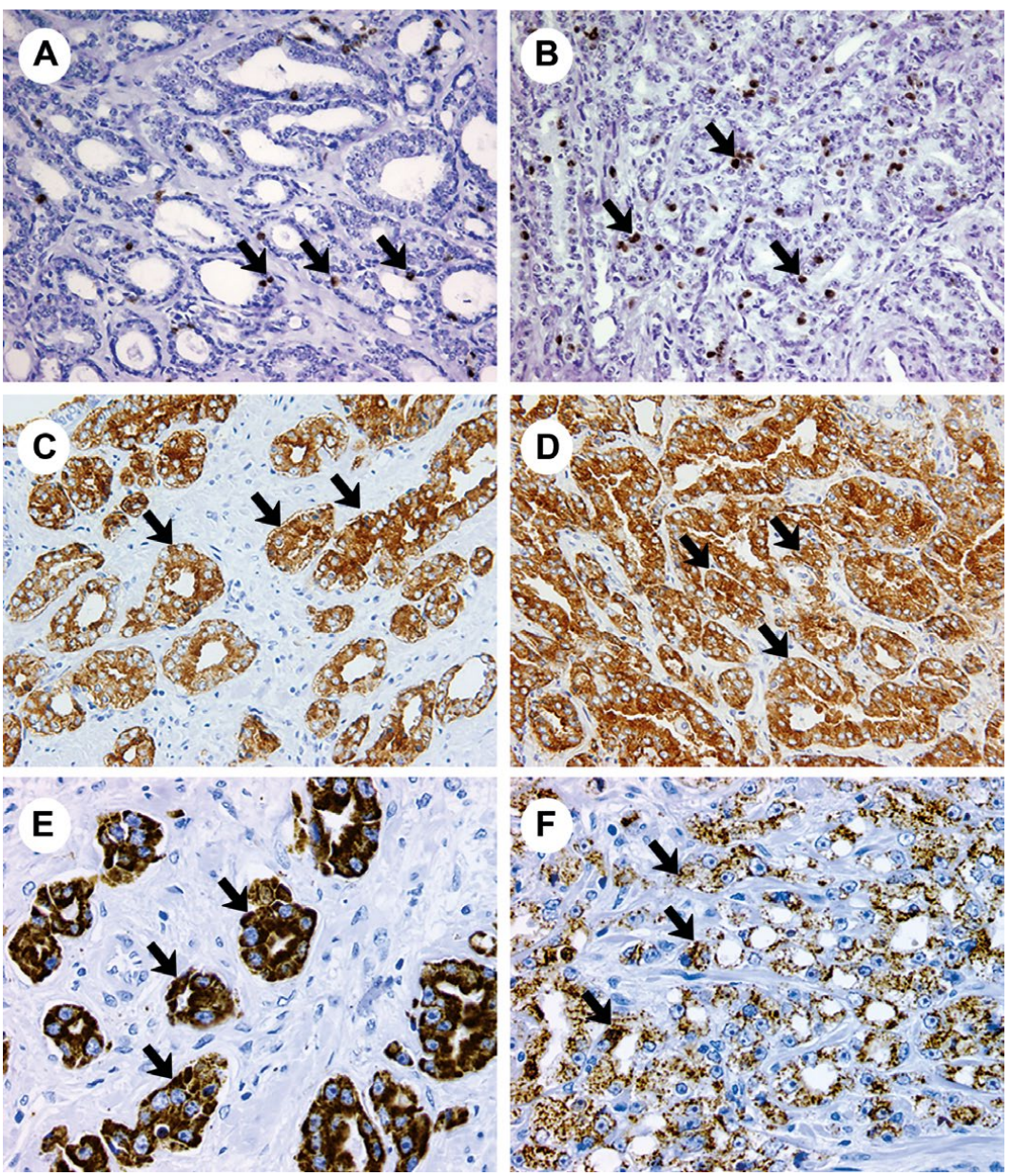
We did not find a correlation between anti-AMARC and anti-Ki 67 immunostaining.

DISCUSSION

The AJCC methodology uses the TNM classification (T-tumor extension, N-node involvement and M-presence or absence of metastases) to group patients. TNM staging in combination with tumor grade and PSA are considered standard for PC and used in the therapeutic decision (15).

The histological grade of PC is an important, if not the most important, factor in the prognosis of clinically localized PC. For over forty years the Gleason classification was the standard classification used in the CP, based on its primary and secondary patterns from 1 to 5 and scores resulting from the sum of these patterns. In 2014 WHO and ISUP formally changed the Gleason classification and adopted a group grade system for CP. Such classification ranges from 1 to 5, where group 1 is similar to Gleason score 6, grade 2

Figure 1 - The Figure show the immunoexpression for Ki 67, PSA and AMARC in prostatic adenocarcinoma. A) Photomicrograph of anti-Ki 67 antibody (arrow) in Gleason 3 prostate adenocarcinoma (X200); B) Photomicrograph of anti-Ki 67 antibody (arrow) in Gleason 4 prostate adenocarcinoma (X200); C) Photomicrograph of immunoexpression for anti-PSA antibody (arrow) in Gleason 3 prostate adenocarcinoma (X200); D) Photomicrograph of anti-PSA antibody in Gleason 4 prostate adenocarcinoma (X400); E) Photomicrograph of anti-AMARC antibody (arrow) in Gleason 3 prostate adenocarcinoma (X200) and F) Photomicrograph of anti-AMARC antibody (arrow) in Gleason 4 prostate adenocarcinoma (X200).



group similar to Gleason score 7 (3+4), grade 3 group is similar to Gleason score 7 (4+3), grade 4 group is similar to Gleason score 8, and grade 5 group is similar to Gleason score 9 and 10. The eighth edition of the AJCC uses this classification (15).

The Gleason score 7 is a heterogeneous group both morphologically and in its biological behavior, so the Gleason score 7 (3+4), grade group 2, has a much more favorable prognosis than the 7 (4+3) grade group 3. This division of Gleason 7 scores implies different therapeutic strategies, especially in relation to radiotherapy (15).

Black patients have a worse prognosis for PC, related to dietary, nutritional and health factors (16, 17), although, in our results, 75% of blacks are distributed in the Gleason score 7 (3+4) pT2.

As for the color of the patients, both Gleason scores 7 (3+4) and (4+3) showed a predominance of the white race, 82.52% and 84.37%, respectively.

Prognostic factors are divided into clinical and biological. Clinical factors include PSA dosage, imaging findings, and evaluation of prostate biopsies. Biological factors are another category of prognostic factors. With recent advances in molecular biology the concept of oncogene and tumor suppressor genes are dominating tumorigenesis research and may provide new tumor markers, with special attention to anti-p53 and anti-Ki 67 (18). Verma et al., 2015 (18) in their article showed a strong relationship between the expression of anti-p53, a tumor suppressor protein, and anti-Ki 67, a cell proliferation marker, with the increase in the Gleason score, which is important for the prognosis of PC (19). Anti-p53 is an antibody homologous to anti-p63 and in benign lesions it shows discontinuous nuclear immunostaining (20).

According to Tretiakova et al. 2016 (21) the anti-Ki 67 index increases in patients with pT3/pT4 stages of the disease when compared to pT2 stages. Our results were similar, although we did not have cases of pT4 stage in these scores. Our work corroborates these results. In 6.81% of the cases there was an increase in the anti-Ki 67 index and in 2.27% of the cases there was an increase in the immunoexpression of anti-p53 when comparing Gleason score 7 (3+4) areas with Gleason score 7 (4+3) areas.

Recently, anti-AMARC overexpression has been demonstrated in localized and metastatic PC, as well as in high grade prostatic intraepithelial neoplasms, but not in normal glands, suggesting that it may be an important tumor marker (22).

Anti-PSA antibody has decreased sensitivity in poorly differentiated prostatic carcinomas, so it should be decreased in Gleason pattern 4 adenocarcinomas when compared to pattern 3 (23). In the work of Missaoui et al. 2016 (24) 78% of PCs showed anti-PSA expression. Cytoplasmic expression in tumor cells ranged from 30 to 100%.

In our study, 6.81% of the cases showed increased immunostaining of tissue anti-PSA when comparing the groups of Gleason score 7 (3+4) with that of Gleason 7 (4+3) and only 2.27% of the cases showed a decrease in labeling of PSA when comparing these two groups.

CONCLUSIONS

Our work confirmed differences in the Gleason 7 (3+4) and Gleason 7 (4+3) scores of prostatic carcinomas when compared to the AJCC/TNM prognostic criteria.

These differences are clearer when the groups are separated only into pT2 and pT3 of the AJCC/TNM classification.

These differences corroborate with the difference in biochemical recurrence/disease-free survival after radical prostatectomy according to ISUP/WHO grade 2 and 3 groups.

Anti-Ki 67 and anti-PSA antibody immunostaining showed a positive correlation as the Gleason score 7 increased from 3+4 to 4+3.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The Effect of Detethering Surgery on the Bladder Function and Psychology of Children with Primary Tethered Cord Syndrome

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ABSTRACT

Purpose: Currently, detethering surgery (DS) is the modality most extensively utilized to treat primary tethered cord syndrome (TCS). Disappointingly, some children without bladder impairment showed a deterioration of bladder function after surgery, which critically influences the health-related quality of life. It was hypothesized that the DS might have a significant effect on bladder function and psychology. Therefore, the purpose of this study was to investigate the effect of DS on bladder function and quality of life in children with primary TCS.

Materials and Methods: A retrospective study of 83 patients aged 6 to 10 years who were diagnosed with TCS and underwent DS between 2022 and 2023. The urodynamic parameters and score, psychological-behavioral profile, and lower urinary tract symptoms were compared before and after DS. Additionally, the patients were divided into the normal group and the abnormal group according to the preoperative urodynamics parameters.

Results: A total of 66 children fulfilled the criteria, with a mean age at surgery of 89.5 ± 13.7 months. There were statistically significant differences in bladder detrusor sphincter synergy and urodynamic score and no statistically significant difference in the remaining urodynamic parameters and psychological-behavioral items before and after DS. The proportion of bladder dysfunction that improved or did not worsen after surgery was higher in the Abnormal group than in the Normal group. Nevertheless, the detection rate of each psychological behavior abnormality in children with TCS was higher compared with that of normal children, both preoperatively and postoperatively.

Conclusions: DS could not considerably ameliorate pre-existing bladder dysfunction and patients exhibiting non-progressive bladder dysfunction could be treated conservatively with close observation. TCS plagues patients all the time even if detethering. Psychological counseling for children with TCS should be strengthened after DS.

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INTRODUCTION

Tethered cord syndrome (TCS) is presumed to be a diverse clinical entity characterized by the increased tension of the conus medullaris or cauda equina due to a comparatively low-lying level. Overstrain of the spinal cord could lead to "traction" ischemia and impaired oxidative metabolism, manifesting a constellation of clinical symptoms and signs of tension-induced cord dysfunction, predominantly back pain, orthopedic deformities, neurological deficits, and intestinal and urological disturbances (1). TCS is usually divided into primary and secondary TCS. The primary TCS is commonly seen in children and most of them show the different forms of congenital spinal closure disorders. The secondary form is an acquired pathology caused by previous operations, scar tissue development after open dysraphism closure, inflammation, or neoplasia (2, 3).

Primary TCS is one of the main causes of neurogenic bladder and its clinical manifestations include different types of low urinary tract symptoms (LUTS). Currently, DS is one of the invasive procedures to treat primary TCS but the results are controversial (4-7). Bowman and colleagues (5) reported that 64% of patients showed improvements in voiding function after DS. On the other hand, Valentini et al. (6) demonstrated that early DS was unable to halt preoperative urodynamic impairment, and radical surgery carried a high risk of new neuro-urological deterioration in chaotic lipoma and terminal myelocystocele. Additionally, some children suffering from primary TCS diagnosed by MRI, without LUTS, showed a bladder impairment after DS, which critically influenced the health-related quality of life (4). No doubt, current patients' treatment selection is suboptimal, leading to over- or under-treatments. Obviously, further observation and research on the therapeutic effect of DS from the perspective of bladder function and quality of life is warranted.

It was hypothesized that a DS might have a significant effect on bladder function and psychology. In this study, children with primary TCS were investigated and followed up after DS. The therapeutic impact of surgery on bladder function was assessed by comparing urodynamic parameters pre- and post- detethering. Moreover, LUTS and psychological behavior modification in patients were quantitatively evaluated by questionnaires. Ultimately, we investigated the effect of DS on bladder function in children with primary TCS.

MATERIAL AND METHODS

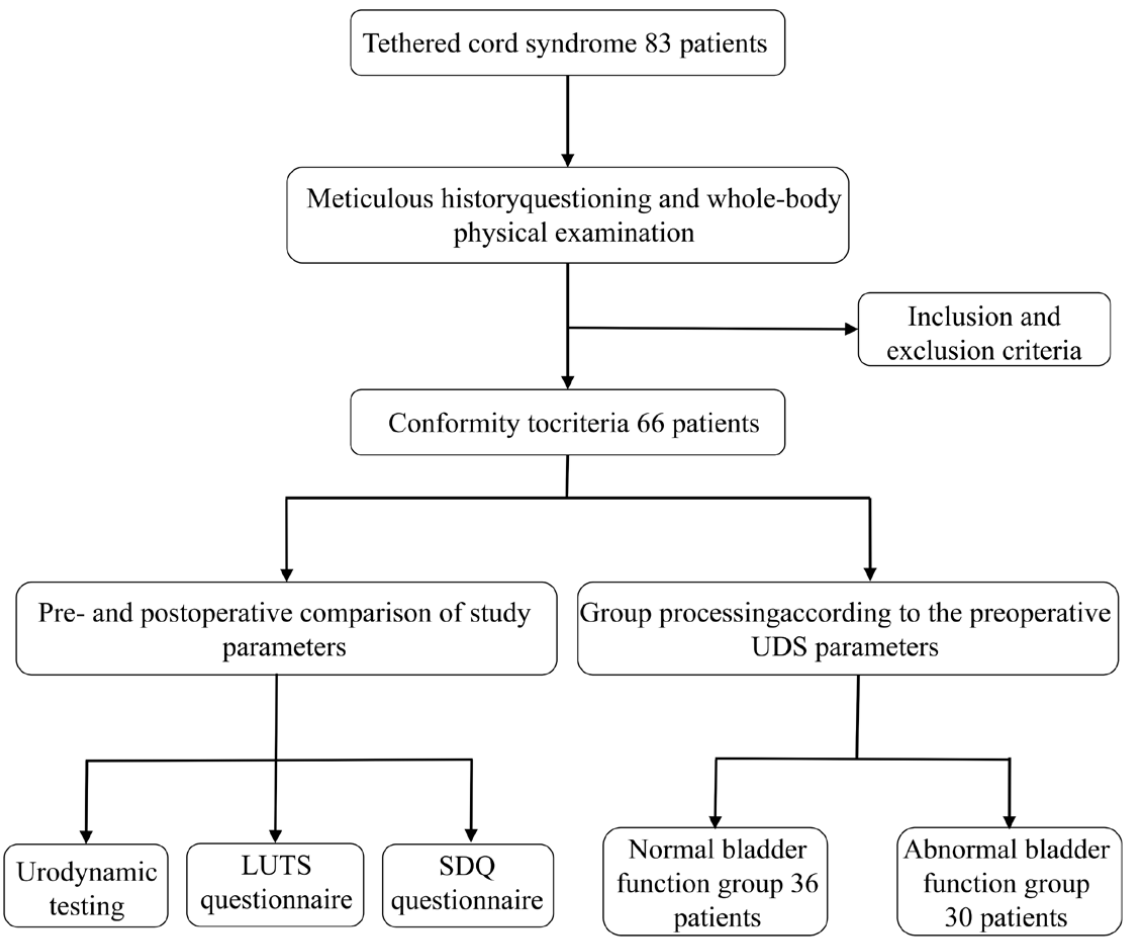
Patient spectrum

A total of 83 children aged 6 to 10 years with primary TCS consulted in the Pediatric Urodynamic Center of the First Affiliated Hospital of Zhengzhou University from October 2022 to December 2023 were retrospectively reviewed. This study was approved by the hospital Ethics Committee (IRB 2018-NY-86). Primary TCS was diagnosed in children after spinal MRI (fatty or thickened filum signals/conus medullaris located caudal to L2). At the time of the initial clinic visit, each case underwent meticulous history questioning and whole-body physical examination. Detailed historical information should pay attention to surgical history, medications, family history, voiding habits, and whether the patient ever experienced urologic symptoms. Physical examination includes the dorsal spine, cutaneous stigmata, and the lower extremity motor and sensory function. Sensory assessment should cover pinprick, tactility, and proprioception. Evaluation for defecation is also imperative. The flow chart is shown in Figure-1.

The patients were included after meeting the following criteria: [1] Children 6 to 10 years old diagnosed with primary TCS based on clinical symptoms, signs, and imaging (spinal cord cone located below the L2 vertebral body on MRI); [2] Underwent DS for the first time; [3] Urodynamic testing within 1 month prior to surgery (8); [4] Comprehensive case data and cooperated with follow-up for more than 3 months.

Exclusion criteria: [1] Underwent multiple DS; [2] Children with other significant comorbidities, such as myelitis, Guillain-Barre syndrome, and myasthenia gravis, shared similar symptoms with primary TCS and affected the determination of postoperative efficacy; [3] Diagnosed with primary TCS but with other diseases leading to urinary tract malformations, skeletal developmental malformations, and bowel malfunction; [4] Incomplete urodynamic parameters and case data before and after surgery and missing visits.

Figure 1 - The flow chart of the study.



Surgical procedure and conservative therapy

All patients underwent total resection of spinal lipomas by the same group of neurosurgeons. The patient was placed in the prone position, and intravenous inhalation anesthesia was routinely administered. The subcutaneous lipoma was separated up to the vertebral defect, and the vertebral plate was incised at the head of the defect to expose the normal anatomy, and then the subcutaneous lipoma was progressively removed from head to tail and into the spinal canal cavity. The spinal cord and cones were detached from the dura matter where they were attached by cutting with microscopic scissors to release the embolism. The end filaments were then explored and cut off if infiltrated with fat. Finally, the split spinal cord was closed with interrupted sutures, the dura was closed tightly, and the paraspinal muscles, lumbosacral fascia, subcutaneous fat, and skin were sutured.

Patients were selected for appropriate treatment options such as clean intermittent catheterization, anticholinergics, clean intermittent catheterization combined with anticholinergics, and behavioral therapy (pelvic floor muscle training, etc.) before and after surgery, according to the patient's urodynamic findings and symptoms (9, 10).

STUDY PARAMETERS

Urodynamic testing

Urodynamics (UDS) constitutes an indispensable modality for urologists to assess the function of lower urinary tract. Moreover, UDS is administered according to the methods recommended by the International Children's Continence Society (ICCS) (11). The UDS parameters included maximum flow rate (Qmax), post void residual (PVR), maximum cystometric bladder capacity (MCC), bladder compliance (BC), and detrusor activity (detrusor instability or hyperreflexia). In addition, the detrusor-sphincter synergy during voiding was assessed by recording the EMG activity of the external anal sphincter with perineal surface electrodes. Pre- and postoperative Qmax, PVR, MCC, BC, detrusor activity, detrusor-sphincter synergy, and UDS scores (Table-S1) were compared in children with primary TCS. Meyrat et al. introduced for the first time that the UDS score could be used as an objective tool for UDS interpretation (12). The urodynamic scores were as follows: MCC, BC, detrusor activity, and detrusor-sphincter synergy were graded and summed up to obtain UDS score. MCC, BC, detrusor activity, detrusor-sphincter synergy quantified values >1, and UDS score >4 were abnormal (13).

LUTS questionnaire

Patients were quantitatively appraised for LUTS according to the Lower Urinary Tract Dysfunction Research Network Symptom Index-29 (LURN SI-29) (14). The LURN SI-29 calculates a total score based primarily on five brief scales measuring urgency, incontinence, voiding difficulty, nocturia, and pain, plus nine separate questions about frequency, nocturnal urgency, sensation, incomplete emptying, dribbling after urination, bifurcation of urine flow, and overall distress. Total scores were positively correlated with LUTS and higher scores mean worse symptoms. The reliability of the scale has been verified and could provide granular and precise information about LUTS (15). In the study, the children and parents completed questionnaires based on the patients' LUTS symptoms with the help of a professional medical practitioner. In an initial examination of the reliability of the LURN SI-29, all scales had internal consistency (Cronbach's alpha) greater than 0.7 (15-17).

Strengths and Difficulties Questionnaire (SDQ)

The questionnaire was completed by the children's families under the guidance of medical professionals. SDQ comprises 25 items distributed into five scales. Emotional problems, conduct problems, hyperactivity, and peer interaction problems, with higher scores considered abnormal, were added together to obtain a total difficulty score; pro-social behavior, with lower scores considered abnormal. SDQ has been extensively evaluated and widely applied to assess behavior disorders. The reliability and validity of SDQ make it a friendly screening measure of psychosocial problems for children and adolescents (18-20). The Cronbach's alpha for this questionnaire was 0.784 (18, 21, 22). The threshold values of abnormality for each factor were total difficulty score ≥ 17, emotional problems ≥ 5, conduct problems ≥ 4, peer interaction problems ≥ 4, hyperactivity ≥ 7, and pro-social behavior ≤ 4; the normal level was defined as total difficulty score ≤ 13, emotional problems ≤ 3, conduct problems ≤ 2, hyperactivity ≤ 5, peer interaction problems ≤ 2, and pro-social behavior ≥ 6; the middle range was the borderline status. In administering the SDQ questionnaire to patients, emotional problems, conduct problems, hyperactivity, peer interaction problems, pro-social behavior, and total difficulty scores of the questionnaire were categorized into normal and abnormal groups according to their scores as required, with the former comprising both normal and borderline scores. The questionnaire was completed by the children's families under the guidance of medical professionals.

Group processing

Children with primary TCS were divided into two groups according to the preoperative UDS parameters: The normal bladder function group (Normal group) and the bladder dysfunction group (Abnormal group). The postoperative urinary system of the children in the two groups were analyzed according to the alterations of the postoperative UDS parameters.

Normal bladder function was defined as UDS score ≤4, and improved bladder dysfunction was described as a decreased UDS score (13). According to preoperative symptoms and postoperative clinical outcomes, lower extremity pain, motor dysfunction, and intestinal tract dysfunction were classified as improvement (symptoms improved), stability (no change in symptoms but no progression), ineffectiveness (failure to control the disease and continued progression), and aggravation (symptoms worsened), with improvement and stability as effective treatment and ineffectiveness and aggravation as ineffective treatment (23).

Statistical Analysis

SPSS 22.0 software was used for statistical analysis of the data. The differences of each parameter of UDS and each index of LURN SI-29 were tested for normality at $P < 0.05$ and conformed to non-normally distribution, expressed as median and quartiles [M (P25, P75)], with Wilcoxon matched-pairs signed rank test. Each entry of the SDQ questionnaire before and after surgery in children with primary TCS was tested with McNemar's test. Count information of Normal and Abnormal groups was expressed as frequency and rate (%), and comparisons were made using the Pearson chi-square test. Two-sided test, test level α=0.05, $P < 0.05$ was considered statistically significant.

RESULTS

Baseline information

A total of 66 children fulfilled the criteria, comprising 35 male cases and 31 female cases (Table-1 and Table-S2). Age at operation ranged from 71 to 120 months, with a mean age of 89.5 ± 13.7 months. Follow-up time ranged from 3 to 10 months, with a mean follow-up duration of 4.6 ± 2.0 months. Cutaneous stigmata such as hyperpigmentation and hypertrichosis were present in 52 patients (78.8%). 35 (53.0%) patients presented with preoperative lower extremity disorders, and 19 (28.8%) patients presented with preoperative intestinal tract dysfunction. There were 44 patients with preoperative bladder dysfunction, including 7 patients (15.9%) with constipation and 9 patients (20.5%) with fecal incontinence.

Table 1 - Characteristics of patients undergoing detethering surgery for tethered cord syndrome.

TCS Type		Sacral Cutaneous Findings		Lower Extremity Dysfunction		Intestinal Tract Dysfunction		Bladder Dysfunction	
Type	n (%)	Symptom	n (%)	Symptom	n (%)	Symptom		Symptom	n (%)
Transitional LMMC	33 (50.0)	Hyperpigmentation	29 (43.9)	Normal	31 (47.0)	Normal	47 (71.2)	Normal	22 (33.3)
Dorsal LMMC	14 (21.2)	Normal	14 (21.2)	Weakness of both feet	20 (30.3)	Constipation	11 (16.7)	Urinary incontinence	20 (30.3)
Filum terminale lipoma	11 (16.7)	Tufts of hair	14 (21.2)	Clubfoot	11 (16.7)	Fecal incontinence	9 (13.6)	Weak stream	11 (16.7)
Caudal LMMC	9 (13.6)	Sacral mass	14 (21.2)	Ankle deformity	2 (3.0)			Enuresis	11 (16.7)
		Dimple	10 (15.2)	Plantar flexion weakness	2 (3.0)			Dysuria	9 (13.6)
		Skin tag	5 (7.6)	Left leg weakness	2 (3.0)			Urgency	8 (12.1)
								Urine hesitation	2 (3.0)

LMMC = lipomyelomeningocele

Comparison of UDS pre- and post detethering

Preoperatively, a considerable proportion of cases presented with aberrant MCC (51.5%), BC (65.1%), detrusor activity (81.8%), detrusor-sphincter synergy (63.6%), and UDS scores (60.6%). Postoperatively, a larger number of cases exhibited abnormal MCC (60.6%), BC (72.7%), detrusor activity (90.9%), detrusor-sphincter synergy (77.3%), and UDS scores (75.8%). The patients' UDS scores before and after surgery were: improved (21, 31.8%), unchanged (14, 21.2%), and worsened (31, 47.0%). The urodynamic parameters, including Qmax, PVR, MCC, BC, and MCC (% of CV norm), showed no statistically significant differences before and after detethering. The UDS scores, including MCC, BC, and detrusor activity, showed no statistically significant differences before and after detethering. However, significant differences were observed in bladder detrusor sphincter synergy and urodynamic score (Table-2).

The variations of LUTS, hydronephrosis, and urinary tract infection pre- and post detethering

In order to further corroborate the change in LUTS following surgery, quantitative scoring of patients' LUTS was performed and compared before and after the procedure. The results revealed that there were statistically significant differences in urinary urgency, incontinence, voiding difficulty, urinary pain, and total score. Postoperative follow-up demonstrated deteriorations in urinary incontinence, urgency, dysuria, and overall LUTS score. However, nocturia did not exhibit a statistically significant difference between preoperative and postoperative follow-up, indicating that it did not improve (Table-2). Preoperative hydronephrosis 12 patients (18.2%), postoperative reduced to 7 patients (10.6%); Preoperative urinary tract infection 8 patients (12.1%), postoperative reduced to 3 patients (4.5%).

Psycho-behavioral changes pre- and post-detethering

Grounded on qualitative analysis of the SDQ data before and after the surgery, we determined whether the children's psychological behavior improved or deteriorated. Statistical results showed that emotional problems, character problems, hyperactivity, peer interaction problems, engaging in pro-social behavior, and total difficulty score did not altered (All $P > 0.05$, Table-2).

The detection rates of abnormal preoperative scores were relatively high, with emotional problems, conduct problems, hyperactivity, peer interaction problems, pro-social problems, and total SDQ scores exhibiting abnormal rates of 53.0%, 18.2%, 28.8%, 40.9.%, 3.0%, and 36.4%, respectively. The detection rates of abnormal postoperative scores were found to be 54.5%, 21.2%, 25.8%, 39.4%, 3.0%, and 36.4%, respectively.

Group processing results

There were no statistically significant differences observed between the two groups for gender distribution, lower extremity pain and motor dysfunction, and intestinal tract dysfunction following surgery (all $P > 0.05$, Table-3). However, it was noteworthy that the proportion of patients exhibiting improved or stable bladder function post-surgery was higher in the Abnormal group compared to the Normal group ($\chi 2 = 10.482$, $P = 0.001$).

DISCUSSION

TCS is known to be a progressive disease, and bladder dysfunction is closely related to the development of the disease. Bladder wall thickness, urinary nerve growth factor value, and UDS can be used as indicators to predict disease progression All kinds of indexes such as the bladder wall thickness, urinary nerve growth factor values, UDS, etc can be used as a prediction index of disease progression (24, 25). Among them, the UDS is the gold standard method for determining the type and degree of bladder dysfunction in children with TCS and can be an objectively useful test for indirectly determining neurological function (26). The urodynamic manifestations of children with primary TCS are bladder dysfunction during the filling phase, the voiding phase, or both, with predominantly hyperactive urethral reflexes, DSD, reduced BC, anosognosia, and hypocontractility of the detrusor (12, 27). The abnormal urodynamic findings in the 66 children in our study were similar to those described above, mainly in terms of abnormalities in MCC, BC, detrusor activity, detrusor-sphincter synergy, Qmax, and PVR, and the changes in Qmax, PVR, MCC, BC, and detrusor activity

Table 2 - The UDS, LUTS and SDQ results before and after tethered cord syndrome.

	Variables	Preoperative M (P25, P75)	Postoperative M (P25, P75)	Z / X^2	P
Urodynamic testing	Qmax	12 (8.75, 15.00)	12.00 (5.75, 15.00)	-0.584	0.559
	PVR	20 (6.75, 50.00)	20.00 (5.00, 41.25)	-0.309	0.758
	MCC	221.00 (190.25, 2540.00)	221.00 (180.25, 259.00)	-0.348	0.728
	BC	23.00 (17.75, 25.00)	21.00 (16.75, 25.00)	-1.114	0.265
	MCC (% of CV norm)a	0.95 (0.79, 1.06)	0.89 (0.72, 1.03)	-1.818	0.069
UDS score	MCC	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	-1.009	0.313
	BC	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	-1.315	0.189
	Detrusor activity	2.00 (1.00, 3.00)	3.00 (1.00, 4.00)	-1.860	0.063
	Detrusor sphincter synergy	1.00 (0.00, 2.00)	1.00 (1.00, 2.00)	-2.561	0.010
	Overall score	4.00 (2.00, 7.00)	6.00 (3.75, 8.00)	-2.485	0.013
Lower Urinary Tract Dysfunction Research Network Symptom Index-29	Urinary urgency	0.00 (0.00, 16.67)	4.17 (0.00, 18.75)	-2.582	0.010
	Urinary incontinence	12.50 (0.00, 31.25)	16.67 (0.00, 50.00)	-2.060	0.039
	Voiding difficulty	5.00 (0.00, 41.25)	17.50 (0.00, 51.25)	-2.679	0.007
	Nocturia	0.00 (0.00, 0.00)	2.00 (0.00, 0.00)	-0.868	0.385
	Urinary pain	0.00 (0.00, 0.00)	0.00 (0.00, 12.50)	-2.066	0.039
	Total scores	13.28 (3.80, 29.43)	17.71 (11.07, 32.90)	-3.204	0.001
Strengths and Difficulties Questionnaire	Emotional problems			0.030	0.861
	Normal n (%)	31 (47.0)	30 (45.5)		
	Abnormal n (%)	35 (53.0)	36 (54.5)		
	Behavioral problems			0.192	0.662
	Normal n (%)	54 (81.8)	52 (78.8)		
	Abnormal n (%)	12 (18.2)	14 (21.2)		
	Hyperactive attention inability			0.153	0.696
	Normal n (%)	47 (71.2)	49 (74.2)		
	Abnormal n (%)	19 (28.8)	17 (25.8)		
	Peer relationship problems			0.125	0.723
	Normal n (%)	39 (59.1)	40 (60.6)		
	Abnormal n (%)	27 (40.9)	26 (39.4)		
	Social behavior			0.000	1.000
	Normal n (%)	64 (97.0)	64 (97.0)		
	Abnormal n (%)	2 (3.0)	2 (3.0)		
	SDQ score			0.131	0.717
	Normal n (%)	42 (63.6)	42 (63.6)		
	Abnormal n (%)	24 (36.4)	24 (36.4)		

UDS = urodynamics; LUTS = lower urinary tract symptoms; SDQ = Strengths and Difficulties Questionnaire; Q_{max} = maximum flow rate; PVR = post void residual; MCC = maximum cystometric bladder capacity; BC = bladder compliance

Table 3 - Comparison of the improvement or deterioration of children with TCS in the two groups after surgery.

Variables	Total (n = 66)	Normal group (n = 36)	Abnormal group (n = 30)	X^2	P
Gender				**2.512**	**0.113**
Boy (n, %)	29 (43.9)	19 (28.8)	10 (15.2)		
Girl (n, %)	37 (56.1)	17 (25.8)	20 (30.3)		
Lower limb sensory and motor dysfunction				0.084	0.772
Effective (n, %)	45 (68.2)	24 (36.4)	21 (31.8)		
Ineffective (n, %)	21(31.8)	12 (18.2)	9 (13.6)		
Bowel dysfunction				1.744	0.187
Effective (n, %)	43 (69.7)	26 (39.4)	17 (25.8)		
Ineffective (n, %)	23 (34.8)	10 (15.2)	13 (19.7)		
Bladder dysfunction				10.482	0.001
Effective (n, %)	34 (51.5)	12 (18.2)	22 (33.3)		
Ineffective (n, %)	32 (48.5)	24 (36.4)	8 (12.1)		

before and after the surgery were not significant. This further confirms that as primary TCS progresses it can lead to irreversible damage in bladder dysfunction.

The UDS score is obtained by summing the graded quantitative values of these four parameters, and its application complements the isolated parameters in assessing the overall picture of neurological dysfunction preoperatively or deterioration postoperatively (12). It has been shown that the combination of UDS scores and the values of the parameters reflect neurological dysfunction more comprehensively and accurately. The UDS scores are also considered to be a useful indicator of improvement or deterioration of bladder function (13). The difference between pre- and post-surgical UDS scores in children with primary TCS was statistically significant, and the quantitative scores were higher in the postoperative period than in the preoperative period. In addition, the results of the LUTS questionnaire further confirmed the deterioration of the patients' LUTS postoperatively. By comparing the UDS scores and the LUTS questionnaire, it was easy to find that the bladder function of the patients had an overall decreasing trend after surgery. This is on the one hand due to the older age of intervention when severe nerve damage existed. At this time, prophylactic DS has been unable to reverse the injury. On the other hand, it may be due to further progression of the disease or damage to the nerves by manipulation during surgery.

DS has been controversial, with the main point of contention being the need for prophylactic surgery in asymptomatic children. The arguments for prophylactic DS are that a certain (undefined) percentage of these patients will go on to develop symptomatic primary TCS (28). Although the procedure is tempting and efficacious, a few patients do not derive any improvement in long-standing. It was reported that seven children with unremarkable preoperative UDS developed bladder dysfunction subsequent to surgery with five (71.4%) culminating in permanent postoperative bladder dysfunction (6). McVeigh and colleagues came to a comparable conclusion that DS involved noteworthy hazards of spinal cord injury and high rates of retethering (29).

However, a related study of adult spinal embolism may also indirectly illustrate the presence of deterioration in bladder function over time in children with asymptomatic TCS exhibiting lower urinary tract symptoms during adulthood (30). It is undeniable that asymptomatic patients with primary TCS may experience deterioration of bladder function after surgery, but failure to operate in such patients may result in bladder dysfunction progressing to irreversible damage. Therefore, we divided 66 study subjects into normal and abnormal groups for comparative study, the improvement of bladder function in abnormal group after surgery was better than that in normal group, meanwhile, we compared gastrointestinal and lower limb symptoms, and there was no difference between normal and abnormal groups before and after surgery. Therefore, asymptomatic children should be carefully considered for surgery, and it is recommended to carry out prior conservative treatment before surgery and follow-up observation. Research on the beneficial effects of prophylactic DS in asymptomatic patients remains to be confirmed in large sample controlled, prospective studies.

In the era of individualized medicine, the clinical management of each patient should be thoughtfully considered. The ICCS recommends that the overall risk profile of DS should be carefully considered for asymptomatic patients or those with fixed, mild abnormalities (31). Surgery is only advocated if observation risks outweigh intervention. A meta-analysis on the treatment of TCS highlighted that abnormal UDS results can be used as supplementary evidence for the implementation of surgical intervention and that a more standardized treatment plan for bladder dysfunction in patients can be developed based on the UDS variations (32). In the study, 66.7% of patients with normal preoperative UDS had worsened UDS after surgery, whereas 71.4% of patients who presented abnormal preoperative UDS had improved or stabilized UDS. This illustrates that in terms of bladder function, surgical treatment is generally not recommended for children without preoperative bladder impairment, whereas the presence of abnormal preoperative UDS may be additional evidence for aggressive surgical intervention.

Children with primary TCS, as well as caregivers and medical practitioners, commonly had a multitude of concerns regarding neurogenic bladder, pharmacological management, and financial expenditure. The numerous and wide-ranging mental concerns plague patients all the time. Indeed, the pervasive and far-reaching nature of these concerns underscores the profound impact that primary TCS can have on the psychological well-being of pediatric patients and their families. It was reported that children and adolescents with lower urinary tract dysfunction appeared to be 2.6-fold more likely than normal to develop emotional and behavioral problems. Alternatively, the presence of constipation alongside bladder dysfunction further exacerbates the psychological symptoms (33). A population-based investigation showed that children with elimination disorders such as urinary and fecal incontinence were demonstrated as a nexus with anxiety and depression symptoms (34). These psychological disturbances hold a negative impact on management of urinary diseases, patient adherence to treatment, and overall clinical outcomes, thereby creating an ever-worsening cycle (35). To assess whether emotional and behavioral problems are more common in children and adolescents with primary TCS, our institution used the SDQ questionnaire to investigate whether surgery can alleviate the misery endured by patients. It was observed that children diagnosed with primary TCS exhibited significantly elevated rates of detection for all types of SDQ compared to their typically developing peers in this study. In particular, they displayed notably higher rates of emotional problems (52.5%) and peer relationship problems (39.3%), indicating a significant burden on their psychological well-being. The presence of lower limb deformities and the inability to control urination and defecation in children with primary TCS contributed to their alienation from peers or peer alienation. In turn, this could precipitate a cascade of negative psychological outcomes such as diminished self-worth and other mental health disorders. The findings indicated that the presence of primary TCS severely affected children's psychological behavioral problems. Moreover, there was no significant difference in psychological behavioral assessment pre- and post-surgery, possibly due to the incomplete resolution of symptoms, limited follow-up duration, and

insufficient attention to a family environment and psychological support and education. Therefore, healthcare professionals and patients' families should enhance psychological counseling and health education for children with primary TCS.

CONCLUSIONS

In the era of individualized medicine, it is imperative to meticulously contemplate the multidisciplinary clinical management of each patient with primary TCS. In terms of bladder function, for children with primary TCS who present abnormal or progressive bladder dysfunction, surgery is advocated; Children with primary TCS exhibiting normal or non-progressive bladder dysfunction could be treated conservatively with close observation. Notably, children with primary TCS have severe emotional and behavioral disturbances, leading to reduced treatment adherence. Psychological counseling and health education for children with primary TCS should be strengthened to ensure optimal care and delivery of the most favorable results, both preoperatively and postoperatively.

ABBREVIATIONS

TCS = Tethered cord syndrome
LUTS = Lower urinary tract symptoms
LMMC = lipomyelomeningocele
UDS = Urodynamics
ICCS = International Children's Continence Society
Qmax = Maximum flow rate
PVR = Post void residual
MCC = Maximum cystometric bladder capacity
BC = Bladder compliance
LURN SI-29 = Lower Urinary Tract Dysfunction Research Network Symptom Index-29
SDQ = Strengths and Difficulties Questionnaire

COMPLIANCE WITH ETHICAL STANDARDS

The studies involving human participants were reviewed and approved by The Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Ethical approval number. 2018-NY-86). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Research involving human research participants must have been performed in accordance with the Declaration of Helsinki.

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AVAILABILITY OF DATA AND MATERIAL

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The authors had equal contribution on this study

CONFLICT OF INTEREST

None declared.

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EXPERT OPINION

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From Double Helix to Double Trouble: Sperm DNA Fragmentation Unveiled – A Reproductive Urologist Perspective (AUA Bruce Stewart Memorial Lecture – ASRM 2024)

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COMMENT

I was truly honored to have been nominated by the Society of Male Reproduction and Urology (SMRU), led by Dr. Kathleen Hwang, the current president, and Dr. Matt Coward, the president-elect, to give the prestigious American Urological Association (AUA) Bruce Stewart Memorial Lecture at the 2024 American Society for Reproductive Medicine (ASRM) Annual Meeting, held in Denver, Colorado.

This nomination holds special significance for me. I was fortunate to become a charter member of SMRU when it was founded nearly 30 years ago. At that time, I was in training at the Cleveland Clinic, mentored by one of the true giants in this field, Dr. Anthony Thomas Jr., right after completing my urology residency at UNICAMP with another esteemed mentor, Prof. Nelson Rodrigues Netto Jr. These early influences were foundational to my career, and to this day, my SMRU membership certificate holds a special place on my office wall. It was signed by Dr. Marc Goldstein, the first president of SMRU, a figure I have always held in the highest regard. One of my fondest memories dates back from an AUA meeting around that time, where Dr. Goldstein chaired a session alongside Dr. Craig Niederberger. It was during this session that I delivered my first-ever oral presentation at an AUA meeting, discussing my research on varicocele and azoospermia (1). Reflecting on that moment and witnessing the evolution of this field over the past three decades, it was a profound honor to present a lecture on sperm DNA fragmentation, an area in which our group has worked actively (2).

INTRODUCTION

In the realm of male reproductive health, one pressing question persists: What if the greatest challenges we face are not rooted in a lack of knowledge but rather in the practical application of what we already understand?

This paper presents the author's expert opinion on sperm DNA fragmentation (SDF), a critical area where our understanding can directly influence reproductive success, and reflects the contents delivered during the lecture

mentioned in the author's note above. The first part discusses the basics of sperm chromatin, its structural components, and the significance of protecting paternal DNA during sperm maturation and transport. The second part elaborates on the mechanisms of sperm DNA damage, the role of oxidative stress, and how SDF testing helps identify patients at risk. It includes specific tests used to measure SDF and their relevance in clinical settings. The last part discusses strategies to minimize SDF, impact on male fertility and reproductive success, including lifestyle interventions, medical treatments (e.g., varicocelectomy), and the the use of testicular sperm in assisted reproductive technology (ART). This section highlights ours and other studies demonstrating the effectiveness of these interventions.

Importance of Sperm DNA Fragmentation

In recent years, there has been a growing interest in studying human sperm chromatin, which comprises a complex mix of DNA and proteins. This structure holds not only genetic information but also crucial epigenetic signals necessary for creating healthy offspring (3). The proper packaging of sperm chromatin is vital to protect the paternal genome during its journey through the male and female reproductive systems, ensuring its delivery intact to the oocyte (4).

Sperm chromatin can suffer damage at various stages: during spermiogenesis, as it traverses the epididymis and even post-ejaculation. This damage can arise from multiple factors, including protamination failure, oxidative stress, and apoptosis. Notably, oxidative stress—primarily induced by high levels of reactive oxygen species (ROS)—significantly contributes to chromatin damage (5-7).

It is critical to recognize that sperm chromatin damage is a broad term that encompasses various structural defects. Sperm DNA fragmentation is a more specific term that refers to breaks in the DNA strands, which can be classified as single-strand or double-strand breaks (6, 8).

There is a robust association between oxidative stress and SDF, as human sperm are particularly vulnerable to free radical attacks (9, 10). These attacks compromise both the plasma membrane and the DNA within the sperm's nucleus and mitochondria, often leading to weakened DNA structures and strand breaks (6, 8).

In clinical practice, various factors contribute to oxidative stress, including medical conditions like varicocele, genital infections, advanced paternal age, unhealthy lifestyle choices, chronic illnesses, and environmental toxins (4, 8, 11-13) (Figure-1). These factors promote an increased oxidative stress environment within the male reproductive system. Notably, SDF levels are consistently found to be higher in infertile men than in fertile controls and semen donors (14).

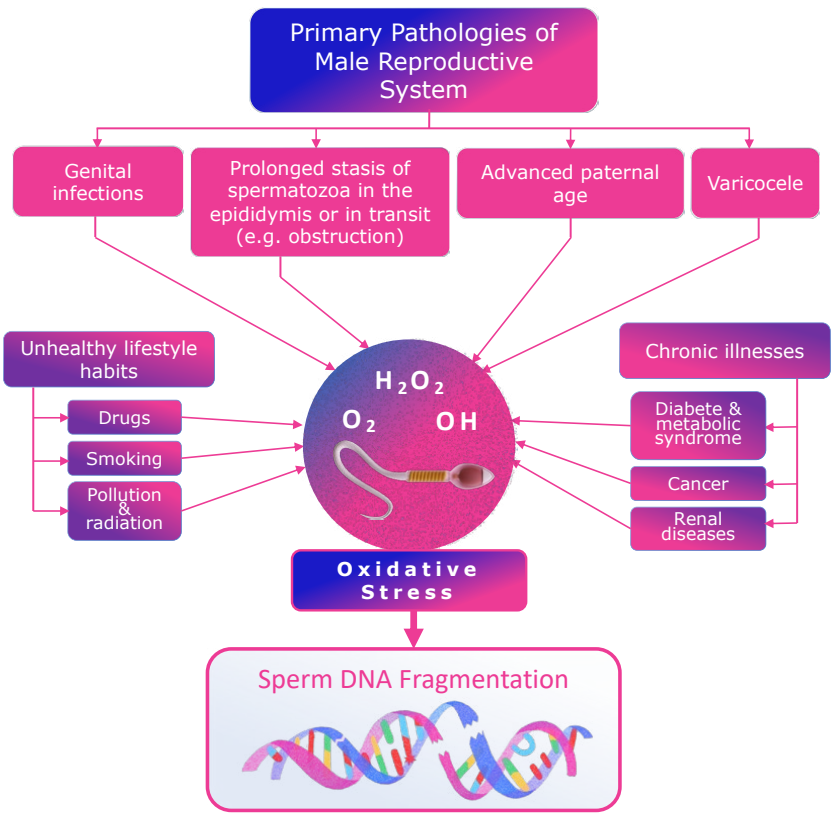
Diagnosing and Managing Infertility through Sperm DNA FragmentationTesting

In our clinic, where we routinely screen for SDF, more than 50% of patients exhibit rates exceeding 20%, which we consider the threshold indicating pathological SDF (15). Furthermore, around 25% of patients present with fragmentation rates above 30%, where the negative implications for reproductive outcomes become particularly pronounced (Figure-2).

Pathological SDF is commonly found in men with abnormal basic semen analysis parameters (16). However, it is also prevalent in male partners of couples facing unexplained infertility (8). For instance, a patient may present with basic semen analysis parameters within the reference ranges, have no apparent history of conditions affecting fertility, and display normal findings upon physical examination yet still possess pathological SDF that contributes to infertility (17).

Going back to oxidative stress, the hypothesis proposed by Professor Aitken and his research team from Australia presents an intriguing explanation of how oxidative stress leads to DNA fragmentation in human sperm (18). They suggest that the genesis of the problem begins during the late stages of spermatogenesis, where defective sperm with weakened chromatin are produced. These sperm, characterized by fragile DNA, become highly susceptible to oxidative attacks from both exogenous and endogenous sources, particularly hydrogen peroxide originating from the mitochondria. This process ofen results in DNA strand breaks that can be identified through specific laboratory tests.

Figure 1 - Clinical factors associated with increased oxidative stress in the male reproductive system that may contribute to sperm DNA fragmentation.



Measurement of Sperm DNA Fragmentation

Sperm DNA fragmentation can be quantified using several well-established tests, including the TUNEL assay, the sperm chromatin structure assay (SCSA), the sperm chromatin dispersion test (known as the Halo test), and the alkaline Comet assay (6, 8, 19-21) (Figure-3). These methods can be categorized into two main types: those that utilize enzymatic reactions to label DNA breaks, such as TUNEL, and those that employ controlled DNA denaturation to reveal breaks, like SCSA, SCD, and Comet assays. While these tests measure the overall SDF level in a sample, they do not specify whether the breaks are in single or double DNA strands.

One critical point is that because each test employs a different method to detect DNA breaks, results obtained from one assay may not always align with those from another. Nevertheless, there is a strong correlation between the results from SCSA, TUNEL, alkaline Comet, and SCD tests when it comes to classifying patients as having normal or pathological sperm DNA fragmentation levels (22). Overall, research indicates a high level of agreement between laboratories *concerning SDF measurement* (23, 24).

Additionally, SDF levels in consecutive ejaculates display low biological variability. In a recent study, we evaluated the reliability of the SCD test for measuring SDF, specifically concerning the consistency of results obtained from the same patient at different time points (25). For this, we analyzed two semen samples collected from the same individuals, with a three-month interval between collections. We found that 80% of the patients remained in the same classification—either normal or pathological SDF — across both analyses. The results demonstrated a high intraclass correlation coefficient, reflecting strong agreement between the two as-

Figure 2 - Prevalence of elevated sperm DNA fragmentation (SDF) among patients attending ANDROFERT, a tertiary center for reproductive medicine. The graph in the upper left quadrant illustrates the distribution of patients according to SDF levels. The graphs in the upper right quadrant show the proportion of patients with pathological SDF levels (above 20% on the top and above 30% on the bottom). The graph in the lower right quadrant depicts the proportion of patients with pathological SDF levels (i.e., >20%) among couples with unexplained infertility. The photomicrograph in the lower left quadrant displays the sperm chromatin dispersion test (SCD; Halo test), with arrows indicating individual spermatozoa lacking halos, signifying the presence of SDF (abnormal). In the central portion of the figure, two spermatozoa exhibit well-defined halos, indicating the absence of DNA fragmentation (normal).

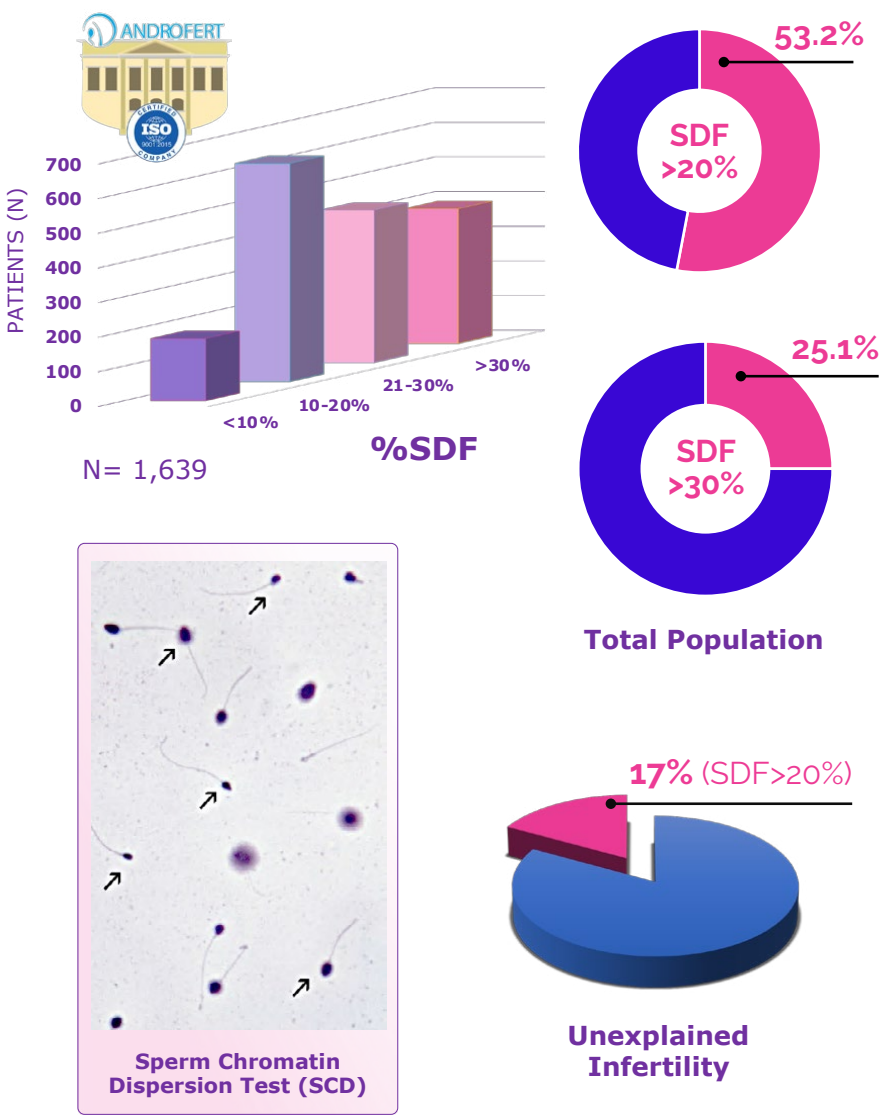
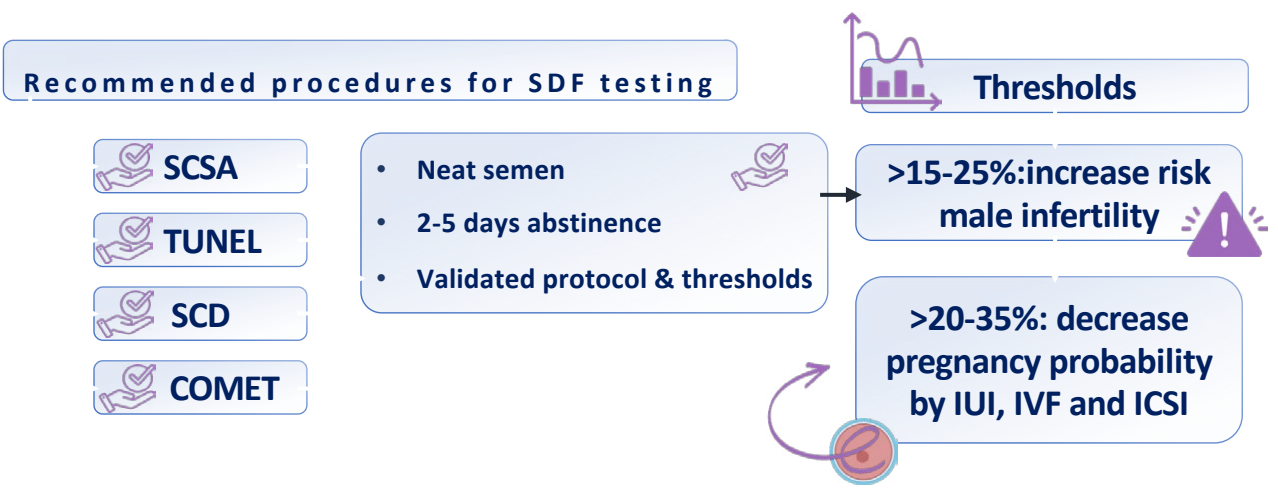


Figure 3 - Key technical aspects of sperm DNA fragmentation (SDF) testing. SDF should be measured using SCSA, TUNEL, SCD, or alkaline Comet following established and validated protocols. The analysis must be conducted on neat semen collected after an abstinence period of 2 to 5 days, ideally between 2 and 3 days. All four methods (SCSA, TUNEL, SCD, and alkaline Comet) provide valuable insights into infertility risk and the likelihood of reproductive success. Abbreviations: TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling, SCSA: sperm chromatin structure assay, SCD: sperm chromatin dispersion, Comet: single-cell gel electrophoresis, IUI: intrauterine insemination, IVF: in vitro fertilization, ICSI: intracytoplasmic sperm injection.



sessments, with only a minimal difference in SDF rates between the samples. Based on these results, we concluded that a single analysis is generally sufficient to assess SDF levels for most patients. However, for individuals with borderline levels, we recommend considering a confirmatory test, particularly when making treatment decisions. It is also worth mentioning that ejaculatory abstinence has a notable impact on SDF levels; notably, longer abstinence periods are associated with increased levels of SDF (26, 27).

Regarding SDF level thresholds, values exceeding the 17 to 26% are associated—dependent on the assay used—indicate an increased risk for male infertility (8, 19). Similarly, levels surpassing the 20 to 36% range correlate with an increased risk of adverse pregnancy outcomes, particularly in assisted reproduction scenarios (8, 19). While these cutoffs are informative, it is crucial to acknowledge that they are not infallible, especially when predicting pregnancy outcomes. The predictive value of SDF testing is influenced by the fertility status of the female partner, which warrants further discussion. There is yet to be a universally accepted gold-standard test for SDF. Each method has unique characteristics and may exhibit *distinct* clinical thresholds *depending* on the measured outcomes. Therefore, clinicians considering incorporating SDF testing into clinical practice should select the method that aligns best with their specific circumstances, taking into account factors like test availability, turnaround time, *to obtain reports* and costs. Furthermore, identifying optimal thresholds tailored to their patient population *should be also considered.*

When conducting SDF testing, several key considerations must be remembered (Figure-3). First, SDF should be measured using one of the four validated methods previously discussed. It is essential to adhere to established protocols to ensure the accuracy and reliability of the results. Second, for accurate diagnosis and treatment planning, the analysis must be performed on the neat semen collected after a recommended abstinence period of 2 to 5 days, with an optimal duration of 2 to 3 days to minimize the risk of false positives. Third, it is critical to maintain a consistent abstinence period when

the test is employed to monitor the effects of treatments aimed at reducing SDF. This consistency helps ensure the reliability of the results. Lastly, when performed correctly, all four methods can provide valuable insights into infertility risk and the likelihood of reproductive success, aiding in informed clinical decision-making. A detailed discussion about the technical aspects of SDF testing can be found elsewhere (8).

At Androfert, the SCD test (i.e., the Halo test) is used to assess SDF. We advise patients to maintain an ejaculatory abstinence period of 2 to 3 days before providing a semen specimen to ensure optimal test accuracy (8). Each test is conducted with positive and negative controls, and we always perform a basic semen analysis concurrently with the SDF testing. We employ a cutoff of 20% to differentiate between normal and pathological sperm DNA fragmentation, with values exceeding 30% categorized as especially high (Figure-2).

Negative Impact of Sperm DNA Fragmentation on Reproductive Success

The potential adverse effects of SDF on human reproduction are significant and warrant careful consideration. To fully understand these implications and to accurately interpret the existing literature, it is essential to revisit the underlying pathophysiology, particularly the hypothesis proposed by Aitken and colleagues (18). They suggest that oxidative stress can lead to the formation of base adducts, such as 8-oxo-deoxyguanosine, indicative of DNA damage.

To repair the damaged bases, sperm utilize the enzyme 8-oxoguanine glycosylase (OGG1), which removes the oxidized base. However, this repair process results in an abasic site destabilizing the DNA strand, increasing the likelihood of strand breaks. When oxidative stress is excessive, OGG1 can become overwhelmed, leaving persistent lesions on the DNA that may cause mutations (18) (Figure-4).

Unfortunately, sperm lack the necessary tools for complete DNA repair. Instead, they depend on the oocyte's cellular machinery to sperm DNA damage following fertilization and before syngamy (28). If the oocyte is unable to adequately repair the inflicted DNA damage, the resulting zygote may respond through a non-apoptotic mechanism that slow down paternal DNA replication (28). This impairment can lead to adverse outcomes such as poor embryo development, implantation failure, miscarriage, and an increased risk of congenital disabilities in the offspring—some of which may not manifest until future generations (28, 29).

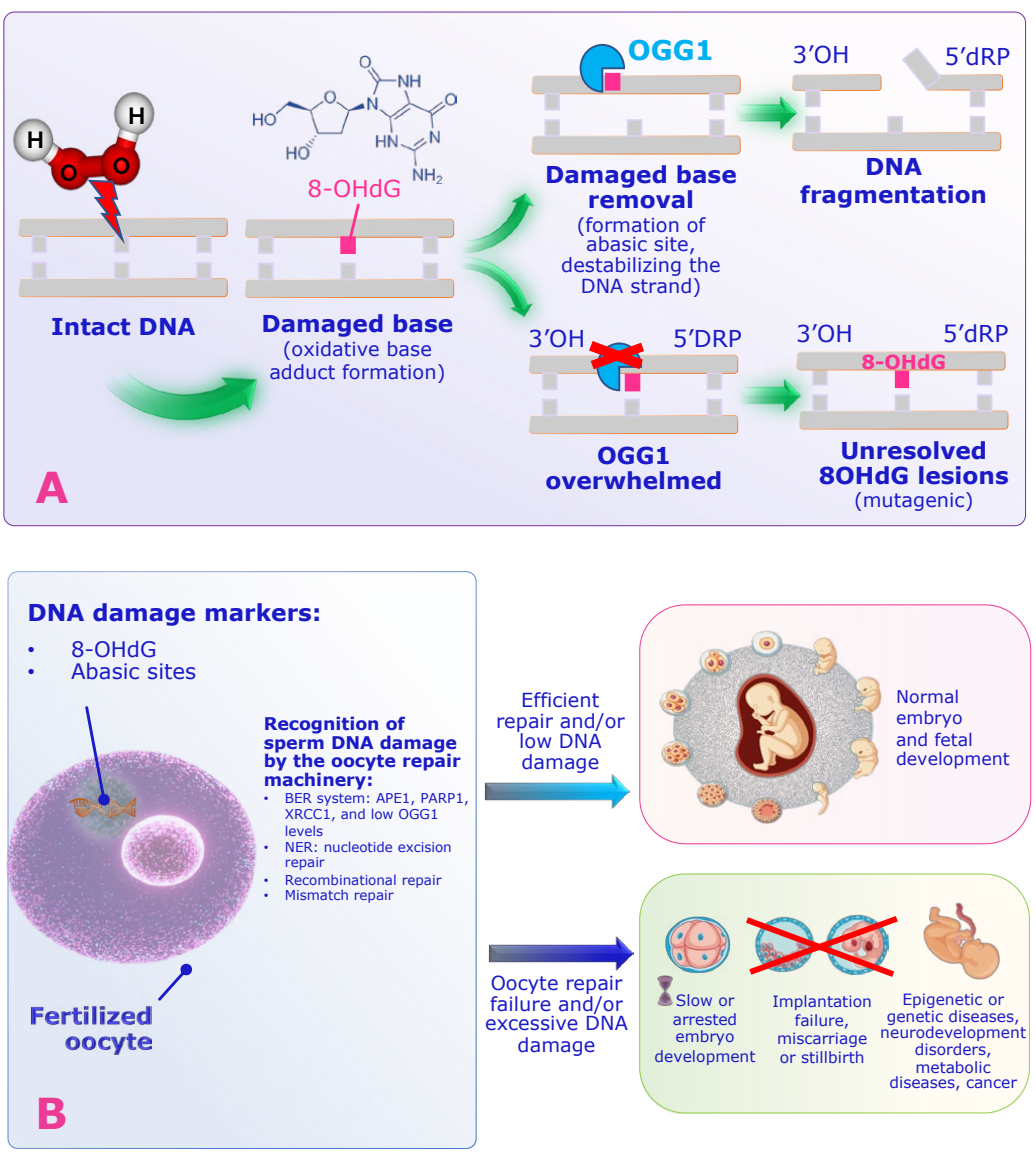
The most substantial evidence linking SDF to reproductive outcomes is derived from animal studies, which often experience fewer confounding variables than human studies. For instance, a groundbreaking investigation by Yanagimachi and colleagues demonstrated that sperm DNA integrity deteriorates during epididymal transit (30). In a mouse model utilizing these defective sperm with abnormal chromatin for ICSI, there was a notable increase in chromosomal abnormalities within embryos and a corresponding decrease in both implantation and live birth rates (30). Additional research found that inducing oxidative DNA damage in epididymal sperm was associated with higher miscarriage rates and developmental defects in mouse offspring (31).

Translating these findings to human studies, elevated SDF has been associated with extend timeframes to achieve natural conception (32). Meta-analyses reveal that couples experiencing recurrent pregnancy loss (RPL) exhibit significantly higher SDF levels S fertile couples (33, 34).

Regarding the impact of SDF on IUI outcomes, meta-analyses consistently indicate that the risk of pregnancy failure more than doubles when sperm from men with elevated SDF levels are used (35, 36). Furthermore, when assessing IVF and ICSI outcomes, our group's recent review of existing meta-analyses found that while two analyses reported minimal negative impacts of SDF on pregnancy rates, eight identified significant negative effects on conventional IVF outcomes without affecting ICSI results (37). Additionally, two studies reported significant negative consequences in both conventional IVF and ICSI. Along these lines, when it comes to miscarriage rates in IVF/ICSI pregnancies, the correlation remains consistent; high sperm DNA fragmentation levels are associated with an elevated risk of miscarriage in both conventional IVF and ICSI procedures (38-40).

While it is essential to critically evaluate the

Figure 4 - The Aitken and De Iuliis hypothesis for the origin of DNA fragmentation in human sperm. A) Free radicals' attack, especially from hydrogen peroxide, can lead to the formation of base adducts, such as 8-oxo-deoxyguanosine, indicative of DNA damage. Sperm utilize the 8-oxo guanine glycosylase (OGG1) to repair these damaged bases. This process creates an abasic site that destabilizes the DNA strand and increases the risk of strand breaks. Excessive oxidative stress can overwhelm OGG1, resulting in persistent DNA lesions (e.g., 8-OHdG) that may cause mutations. B) As sperm lack the mechanisms for complete DNA repair, they rely on the oocyte's cellular machinery to further repair sperm DNA damage post-fertilization and before syngamy. If the oocyte fails to repair this damage adequately, the zygote may undergo a non-apoptotic mechanism that impairs paternal DNA replication. This impairment can lead to adverse outcomes, including poor embryo development, implantation failure, miscarriage, and an increased risk of congenital disabilities in the offspring. Abbreviations: OGG1: 8-oxi guanine glycosylase, 8-Oxo-dG: 8-oxo-deoxyguanosine, APE1: DNA (apurinic/apyrimidinic site) endonuclease 1, 5'dRP: 5-terminal deoxyribose phosphate, BER: Base excision repair, APE1: DNA (apurinic/apyrimidinic site) endonuclease 1, PARP1: poly (ADP-ribose) polymerase-1, XRCC1: x-ray cross-complementing protein.



current knowledge and acknowledge that the evidence linking SDF to adverse effects on human fertility is not entirely conclusive, we must also adopt a clinical perspective. The impact of SDF on reproductive outcomes primarily hinges on the interplay between the severity of DNA damage and the oocyte's capacity to repair it effectively. Unfortunately, many of our patients present with factors such as advanced maternal age or diminished ovarian reserve. When these issues coincide with elevated SDF levels, the potential implications for fertility become particularly concerning.

Holistic Approaches to SDF Testing

Given the robust association between SDF and male infertility—and the potential detrimental effects on reproductive outcomes—many experts now consider SDF analysis a frontline diagnostic procedure. Our clinical guidelines advocate for testing in specific scenarios, including cases of varicocele, unexplained and idiopathic infertility, recurrent miscarriage, situations involving assisted conception, and fertility counseling, particularly when there are known risk factors for high oxidative stress, and when freezing sperm for fertility preservation (8). The results obtained from these tests can play a pivotal role in guiding management decisions.

The latest WHO semen analysis manual has also acknowledged the significance of SDF testing, incorporating it into the extended semen examination panel (41). This panel comprises advanced tests that may be utilized in clinical practice at the laboratory's discretion or upon the clinician's request.

Despite the growing recognition of SDF testing, it is essential to note that its role as a frontline diagnostic tool remains contentious. The 2021 ASRM/AUA male infertility guidelines, recently updated, do not endorse SDF testing as a routine component of the initial infertility evaluation for couples (42, 43). However, they do suggest it for couples with a history of recurrent pregnancy loss (RPL). Conversely, the updated 2024 European Association of Urology (EAU) guidelines take a broader approach by strongly recommending SDF testing for couples with RPL, whether resulting from natural conception or ART (44, 45). They also advise testing for men with unexplained infertility.

The strong correlation between high SDF levels and RPL has led authoritative organizations, such as the European Society for Human Reproduction and Embryology (ESHRE) and the Australasian Reproductive Endocrinology and Infertility Consensus Expert Panel, to include SDF testing in their evaluations for couples experiencing RPL (46, 47). The Australasian guidelines have even introduced an algorithm to assist clinicians in treatment decisions based on SDF results (47).

The key guidelines' statements and recommendations concerning SDF testing are summarized in Table-1.

While the AUA/ASRM guidelines' cautious stance against the routine use of SDF testing is understandable—primarily due to the limited evidence supporting its predictive value for pregnancy—it is vital to recognize that SDF is not solely a matter of fertility. There is a burgeoning concern regarding the potential health implications of high SDF levels for the resulting offspring. If SDF is not entirely repaired in the oocyte, it may lead to genetic or epigenetic mutations in the embryo, which could have long-term effects on the child's health (29). These concerns include potential alterations in cardiometabolic health, neurodevelopmental disorders, and even childhood cancers, which may extend into future generations (29, 48).

We now understand that most *de novo* mutations in our species originate from the paternal genome, often arising from defective DNA damage repair mechanisms (49, 50). In a recent article, I posited that while ART, particularly ICSI, can enable couples to conceive without addressing the underlying causes of male infertility, it is not without risks, especially when using sperm from men with elevated SDF levels (51).

New evidence continues to emerge regarding the negative effects of high SDF. A recent study examining birth outcomes from IVF and ICSI, utilizing data from the Swedish National Registry, found a strong association between SDF and adverse events such as preterm birth and preeclampsia (52). These detrimental outcomes are recognized as potentially influenced by paternal factors, given that the placenta is genetically derived from both the mother and the father. However, until now, the precise mechanisms underlying these associations have remained elusive. This study underscores the

Table 1 - Guidelines' recommendations for sperm DNA fragmentation testing.

Guideline [Year]	Statement	Grade of Recommendation/ Level of evidence
SFRAG guidelines [2021]	Situations for considering SDF testing: ▪ Varicocele ▪ Unexplained and idiopathic infertility ▪ Pregnancy loss, especially when recurrent ▪ When assisted conception is contemplated ▪ For fertility counseling, particularly when there are risk factors for high oxidative stress ▪ When freezing sperm for fertility preservation	Ranging from conditional[1] to strong[2] recommendation; evidence level[3] ranging from B to D
WHO semen analysis manual [2021]	SDF is an extended semen examination (advanced test) that may be used clinically in certain situations* by choice of the laboratory or at the special request of the clinician.	NA
AUA/ASRM male infertility guidelines [2021; updated 2024]	SDF analysis is not recommended in the initial evaluation of the infertile couple; For couples with recurrent pregnancy loss, men should be evaluated with SDF.	Moderate recommendation; evidence level C
EAU guidelines on sexual and reproductive health [2021; updated 2024]	Perform SDF testing in the assessment of couples with recurrent pregnancy loss from natural conception and failure of ART or men with unexplained infertility.	Strong recommendation; evidence level 2a
ESHRE guidelines on recurrent pregnancy loss [2018; updated 2022]	Assessing SDF in couples with recurrent pregnancy loss could be considered for diagnostic purposes.	Conditional
Australasian recurrent pregnancy loss clinical management guideline [2024]	SDF testing is suggested to evaluate the contribution of the male factor in recurrent pregnancy loss. The guideline proposes management strategies in the presence of pathological SDF levels, including lifestyle modifications, assessment of varicocele, use of antioxidants, and IVF with advanced sperm selection techniques.	Evidence levels ranging from 1 to 3

*Not specified;

NA = not applicable; SDF = sperm DNA fragmentation; ART = assisted reproductive technology; WHO: World Heath Organization; AUA: American Urological Association; ASRM: American Society for Reproductive Medicine; EAU: European Association of Urology; ESHRE: European Society for Human Reproduction and Embryology.

critical role that SDF may play in these outcomes.

Strategies to Minimize SDF Impact

From the extensive body of evidence we have discussed, I strongly advocate including SDF analysis as an integral component of best clinical practices to benefit our patients and their children. Identifying pathological SDF is essential, as it opens avenues for therapeutic interventions to reduce fragmentation levels (Figure-5).

Numerous interventions have been explored in this context (15). Notably, the insights gained from measuring SDF levels are most valuable when integrated with a comprehensive male evaluation conducted by a qualified reproductive urologist or andrologist. This evaluation should encompass a thorough medical history, physical examination, and any necessary diagnostic tests to identify and potentially address conditions adversely affecting sperm DNA quality or to optimize ART usage (53, 54).

For example, in a prospective single-arm pilot study, we investigated the effects of a three-month lifestyle intervention combined with daily antioxidant intake (55). Following the guidelines set forth by the Danish Health Authority, participants were instructed to reduce red meat consumption, increase their intake of fruits and vegetables, limit sugary beverages and alcohol, and engage in daily exercise. Additionally, the intervention included commercially available oral antioxidants. The study included couples with a history of unsuccessful IVF/ICSI attempts where the male partners had pathological SDF levels. We compared the changes in SDF post-intervention with those in a control group that did not undergo the intervention. The results demonstrated a mean reduction in levels of approximately 7 percentage points after the intervention, compared to only a 0.4% change in the controls. These preliminary findings suggest that lifestyle modifications combined with antioxidant supplementation can effectively lower SDF levels.

Furthermore, varicocele management is another crucial intervention area, given its association with oxidative stress and (11, 12, 56). In our systematic review and meta-analysis, which encompassed 19 studies, we examined the effects of varicocelectomy on levels (57). The findings indicated that treating a clinical varicocele significantly reduced levels, with an average relative decrease of 30% from baseline. Additionally, a meta-regression analysis revealed that this reduction was more pronounced in men with higher baseline SFD levels, particularly those exceeding 20%.

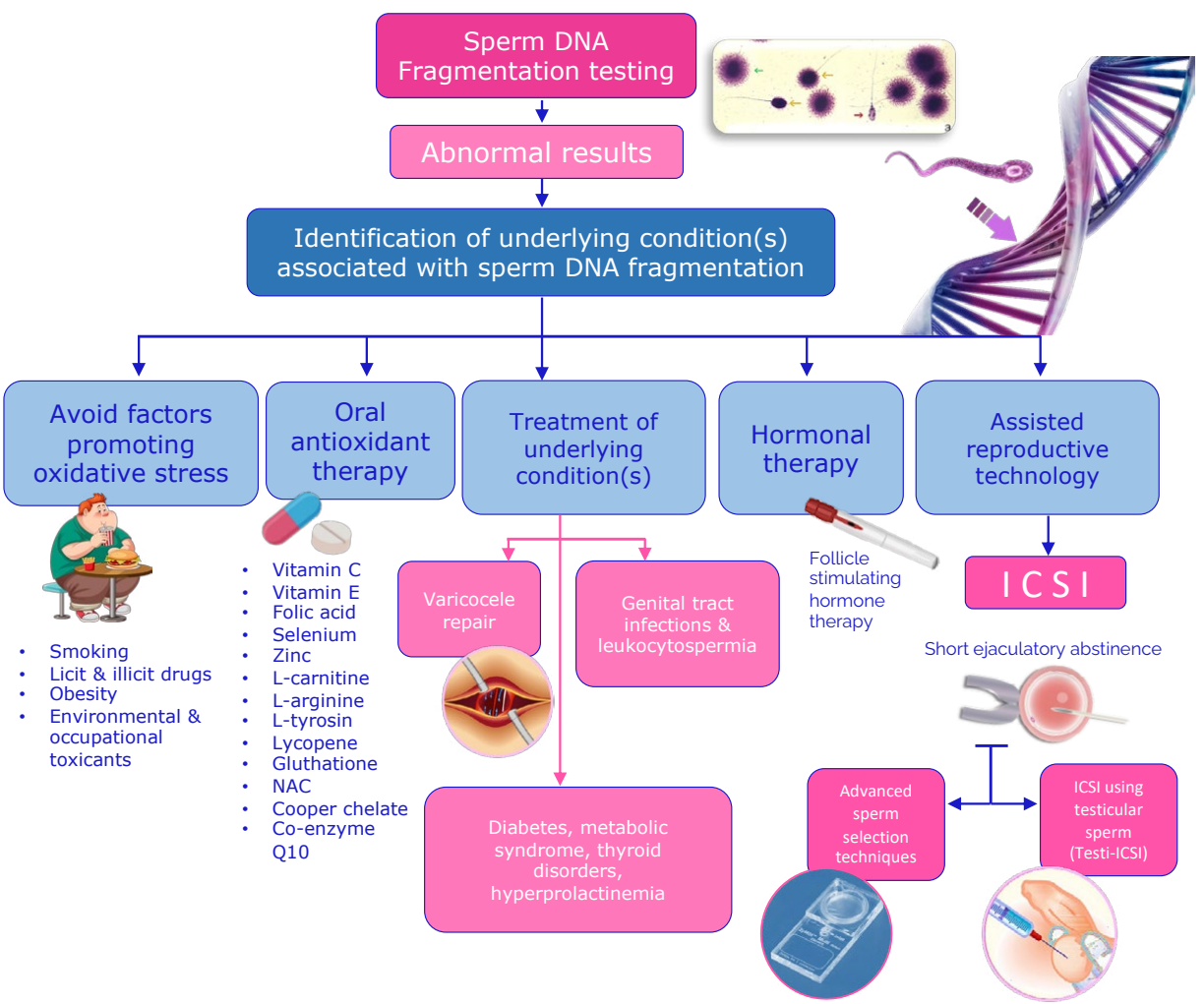
In the study mentioned above, we also analyzed pregnancy outcomes, and found that postoperative SDF levels were significantly lower in patients from couples who achieved pregnancy than those who did not (57). This underscores the potential for reducing SDF to enhance pregnancy rates in men with clinical varicoceles. To address a clinical varicocele, we employ microsurgical techniques, utilizing intraoperative Doppler ultrasound to improve precision during the procedure (58-60).

In the context of ART, simple measures such as encouraging frequent ejaculations and ensuring that the patient provides a semen sample on the day of oocyte retrieval—following a short abstinence period of as little as one day—can make a significant difference (61, 62). These straightforward steps may help improve sperm DNA quality and the likelihood of successful outcomes in ART.

Another promising avenue for men with high SDF undergoing ICSI involves the use of testicular sperm (63-66). This approach may be advantageous due to the significantly lower levels of DNA damage present in testicular sperm compared to those that have undergone the typical journey through the epididymis, vas deferens, and ejaculate (67, 68). The critical factor seems to be related to avoiding oxidative stress encountered by sperm as they traverse the male reproductive system and following ejaculation (65, 69).

In a prospective observational study involving 172 couples with male partners diagnosed with idiopathic oligozoospermia and high SDF, we found that utilizing testicular sperm for ICSI, as opposed to ejaculated sperm, yielded significant improvements in outcomes (70). Specifically, using testicular sperm reduced the rates of miscarriage and increased the chances of live birth. Notably, we determined that for every five couples requiring testicular sperm, one additional successful live delivery was obtained. Moreover, when comparing SDF

Figure 5 - Clinical and laboratory strategies to mitigate the effects of pathological sperm DNA fragmentation of male fertility and human reproduction. A comprehensive male evaluation by a qualified reproductive urologist or andrologist is crucial for identifying and addressing conditions associated with poor sperm DNA quality. Several interventions have been explored to reduce SDF rates, including lifestyle modifications, oral antioxidant supplementation, varicocele repair, treatment of clinical and subclinical male genital infections, and exogenous FSH therapy. Additional strategies in the context of assisted conception include frequent ejaculations, short ejaculatory abstinence, advanced sperm preparation techniques (e.g., hyaluronic acid and microfluidics), the preference for intracytoplasmic sperm injection (ICSI) over intrauterine insemination and conventional in vitro fertilization (IVF), and the use of testicular sperm for ICSI.



levels between testicular and ejaculated sperm within the same patients, we found that testicular sperm exhibited an approximately 80% reduction in fragmentation levels (70). This remarkable finding underscores the importance of minimizing oxidative stress during the maturation and transport of sperm.

This vital knowledge has been highlighted in the 2024 updated ASRM/AUA male infertility guidelines for the first time, underscoring the importance of considering SDF in clinical practice (43). According to the guidelines, clinicians may consider the utilization of testicular sperm in nonazoospermic males with elevated SDF index.

Preliminary evidence also suggests that advanced laboratory techniques, such as using hyaluronic acid and microfluidics, hold promise for isolating sperm with lower DNA fragmentation levels for assisted conception (71, 72). However, it is crucial to recognize that even if these innovative techniques are validated to improve outcomes, they should never replace comprehensive male evaluations. Neglecting thorough assessments would mean missing unique opportunities to identify and treat underlying conditions that may adversely affect sperm DNA quality.

CONCLUSIONS

It is essential to highlight several key takeaways regarding SDF and its impact on male infertility. First, high SDF is a significant factor that can increase the risk of infertility and adverse outcomes in IUI and ART, particularly when combined with factors such as advanced female age or poor oocyte quality. Therefore, it is imperative to consider all these factors to gain a complete understanding of the implications of SDF on reproductive success. Second, infertility is inherently a couple's issue. Relying solely on the assessments of one partner provides an incomplete picture. A holistic approach that includes evaluations of both partners is essential for effectively addressing infertility. Third, while SDF testing offers valuable insights into gamete quality, it should not be considered a substitute for basic semen analysis or comprehensive andrological evaluations. Instead, it represents one crucial component of a multifaceted approach to reproductive health. Finally, incorporating SDF testing into ART clinics is not just a good idea; it is an essential aspect of good clinical practice. This approach improves the care we provide and ensures that we offer our patients the most comprehensive and effective treatments possible.

To close, there are compelling reasons to amplify our focus on male infertility care. Our objective should be to achieve a balance in the attention already given to female infertility, ensuring optimal outcomes for the couples we serve. Achieving this goal will require fertility clinics to prioritize interdisciplinary collaboration with reproductive urologists and andrologists. Together, we can deliver the most thorough and effective care to our patients, ultimately enhancing their chances of successful reproduction.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Walking Among Pioneers – Sperm DNA Fragmentation and a Growing Focus on Male Factor Infertility

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COMMENT

Ask a medical student to name some pioneers in medicine, and you may hear about Louis Pasteur, Marie Curie, Alexander Fleming, or Jonas Salk. Ask a surgeon, and you'll hear about Joseph Lister, Harvey Cushing, or Michael DeBakey. Most urologists will also mention heroes from the early 20th century such as Hugh Hampton Young, Frederic Foley, or Charles Huggins and the Nobel Prize. Most of the greatest innovations in medicine and urology were before the turn of the last century.

The field of reproductive urology and male infertility, on the other hand, is still in the dawn of its era. The first child conceived using in vitro fertilization (IVF) technology was born in 1978, and Gianpiero Palermo first described intracytoplasmic sperm injection (ICSI) in 1992. IVF with ICSI was the catalyst that provided the first real opportunity for men with severe male factor infertility to become biological fathers. Shortly thereafter, Peter Schlegel described the microdissection testicular sperm extraction (micro-TESE) in 1999, representing the single greatest advancement in the surgical treatment of severe male factor infertility of our lifetimes. Many of the pioneers of our subspecialty are still currently in practice in 2024.

The Society for Male Reproduction and Urology (SMRU) was founded in 1995 by Marc Goldstein and Dorrie Lamb with the mission "to promote the advancement of our understanding of male reproductive physiology and management of male infertility by providing a forum for the dissemination of both basic and clinical research information and support of educational programs." As a Society, one of the highest honors we have is the coveted invitation for the American Urological Association (AUA)'s Bruce Stewart Lecture, given annually at the American Society for Reproductive Medicine (ASRM) Congress. The 2024 AUA Bruce Stewart Lecture was given at the ASRM Congress on October 23, 2024, in Denver, Colorado, USA, by Dr. Sandro Esteves, titled "From Double Helix to Double Trouble: Sperm DNA Fragmentation Unveiled" (1).

Dr. Esteves is a true pioneer in the field. He is a founding member of the SMRU, and he is the founder of the world's first (and still only) comprehensive center of reproductive medicine with a primary focus on caring for couples with male factor infertility. With over 350 peer-reviewed publications, his contributions to the field of reproductive urology through innovative research are immeasurable. His most substantial work has come in the area of sperm DNA fragmentation and its influence on a couple's infertility. In fact, no other researcher across the globe has made a greater impact on this critically important topic than Dr. Esteves.

In the accompanying manuscript, reflecting Dr. Esteves's lecture mentioned above, sperm DNA fragmentation and its timely relevance for the field of reproductive medicine is described in perfect detail. He lends his research group's expertise in a friendly, helpful voice that only he can do. He makes the concepts crystal clear for the reader, even providing enough detail for implementation into one's clinical practice if they have yet to do so. Although the recognition of sperm DNA integrity is one of the most important innovations in the field of male reproductive urology in the 21st century, sperm DNA fragmentation testing is only one tool in a growing armamentarium of diagnostics we now have to characterize male factor infertility beyond the semen analysis. Dr. Esteves concludes in this manuscript that, ultimately, finding a balance between the attention provided to female and male factor infertility is the best path to the most optimal outcomes for the couples we serve.

I encourage all of my reproductive urology colleagues worldwide to join the ASRM and the SMRU (https://connect.asrm.org/smru/aboutus/membershipbenefits) so that they can access the latest research, education, and opportunities for growth as reproductive medicine providers. As President of the SMRU from 2024-2025, I extend heartfelt congratulations to Dr. Sandro Esteves, the 2024 AUA Bruce Stewart Lecturer for the ASRM Congress. The field of male reproductive medicine is young, allowing the next generation of leaders to always be walking among pioneers like Dr. Esteves.

Figure - Photograph of Dr. Sandro Esteves receiving a recognition plaque from Dr. Robert Brannigan, honoring his exceptional contributions as the 2024 ASRM Reproductive Urology Keynote Lecturer.

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Advancing Telesurgery Connectivity Between North and South America: the first Remote Surgery Conducted Between Orlando and São Paulo in Animal Models

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COMMENT

The 2001 Lindbergh operation, telesurgery between Strasbourg (France) and New York (USA), was a milestone in surgery history, showing the feasibility of transatlantic telesurgery and the beginning of the robotic surgery era. However, despite this success, the widespread adoption of remote surgery was limited for many years by technological limitations and economic constraints (1, 2). In this context, advancements in robotic systems, 5G networks, and fiber-optic infrastructure have reignited interest in this area (3–5). The rapid advancement of telesurgery technology presents an unprecedented opportunity to address global healthcare disparities and revolutionize surgical education (6). However, despite this technological progress, the literature still lacks articles and studies about long-distance remote surgeries using these new technologies (7).

In this scenario, since December 2023, our group has been performing trials and remote connections with several centers worldwide (8, 9). Consequently, we conducted a pioneering telesurgery procedure connecting São Paulo (Brazil) to Orlando (USA) on September 3rd, 2024. In this trial, the animal model (live porcine) was located in Orlando, while the surgeon (MCM) operated remotely from São Paulo using the MicroPort® MedBot™ Toumai robotic platform (Shanghai MicroPort MedBot Group Co., Ltd.). This milestone achievement marks the first telesurgery robotic procedure between these two cities located in opposite parts of America (North and South) and opens new avenues for future studies on remote surgical connectivity inside the American Continent. Moreover, it underscores the immense potential that telesurgery holds in transforming global healthcare delivery, approximating the expertise of remote surgeons to improve operative outcomes, as addressed by our team in previous articles (5).

Before conducting our study, the research project received approval from the Nicholson Center's Animal Care Committee (Celebration, FL, USA). All procedures strictly adhered to institutional ethical standards and regulatory requirements, following the Institutional Animal Care and Use Committee (IACUC) guidelines (10). The study followed the EQUATOR and ARRIVE reporting guidelines for research involving animal models (11). One surgeon from our team (MCM) traveled to São Paulo, Brazil to operate on the console, while our team stayed in Orlando (USA) to manage the

patient cart and porcine model. Under general anesthesia, the animal was initially positioned in right lateral decubitus, and the robotic trocars were placed along the paramedian abdominal line, as routinely done in robotic surgery training in animal models. We used four robotic trocars, and one assistant trocar positioned between the second and third robotic trocars. Instruments, including scissors, bipolar forceps, and Cadiere forceps, were inserted under direct visualization.

The procedure began with dissection of the left renal hilum, isolating the renal artery and vein, which were then clamped with Bulldog clamps for warm ischemia. A round defect was created on the anterior surface of the kidney, followed by suturing of the parenchyma using barbed sutures, secured with hem-o-lok clips at the edges. Once the suture was complete, the Bulldog clamps were removed, hemostasis was confirmed, and a radical nephrectomy was performed by ligating the renal artery and vein with hem-o-lok clips. The same steps were performed on the contralateral kidney. Total operative time was 35 minutes on the right side (warm ischemia 12 minutes) and 37 on the left (warm ischemia 13 minutes). No complications or robotic faults were recorded during the procedure. The verbal communication between both centers was also optimal, and surgeons could control the robot independently from each center's console during several surgery steps, highlighting the tremendous potential of telesurgery in minimizing complications and training robotic surgeons remotely.

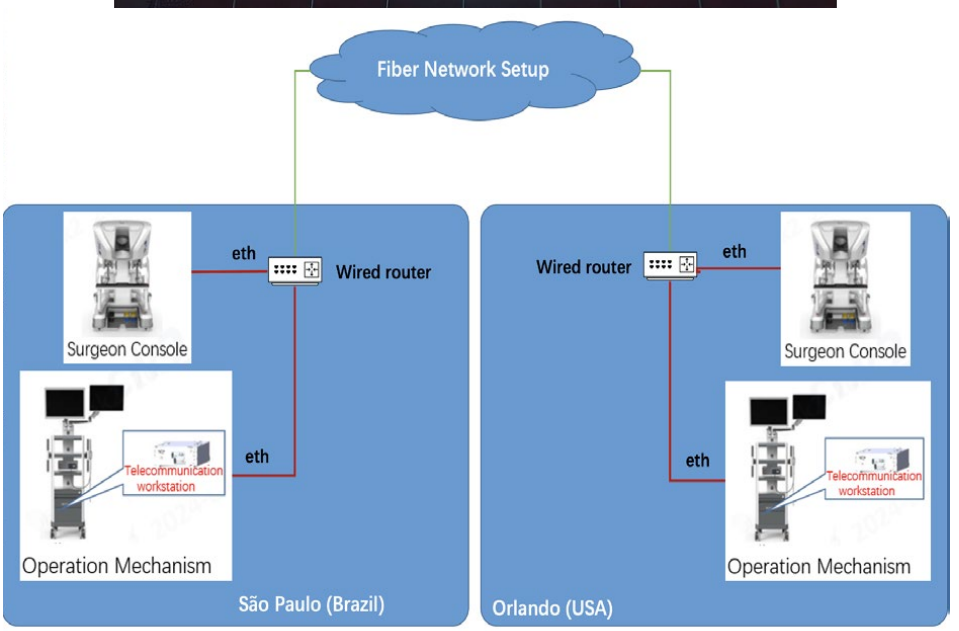
It is essential to emphasize that distance plays a critical role in assessing the optimal telesurgery connection between two centers. In our study, the fiber distance between São Paulo and Orlando is approximately 8,000 kilometers, resulting in a round-trip signal distance of nearly 16,000 kilometers. Given that the speed of light through fiber-optic cables is around 200,000 km/s, the theoretical minimum round-trip time (RTT) due to distance alone is approximately 80 milliseconds. Our study used corporate Ethernet in the hospitals, then terrestrial fiber between hospitals and landing stations (i.e. Orlando – Miami and Fortaleza – Sao Paulo); and the middle-segment was covered by submarine fiber (Miami – Fortaleza), illustrated in Figure-1. The average round-trip of 120 ms (118-150 ms) with no frame loss, indicating high connection quality. Note that telesurgery latency is influenced by more than just distance, as other network variables also play a role. No intraoperative complications or robotic malfunctions occurred during the procedures, demonstrating the system's reliability and the optimal performance of the Toumai robot under these conditions.

Considering that Brazil is a continental country, the fifth biggest area in the world, with several remote and underserved areas, the humanitarian implications of telesurgery are profound. Currently, millions of individuals in underserved regions of the world lack access to timely, high-quality surgical care. Geographical barriers, a shortage of skilled healthcare professionals, and limited infrastructure contribute to significant disparities in healthcare access, eventually leading to suboptimal surgical outcomes in these areas. In this scenario, the new platforms with telesurgery capabilities have the potential to mitigate these barriers by enabling expert surgeons to perform complex procedures remotely, offering their skills and expertise to regions where local healthcare systems may be insufficient (7). This technology can effectively bridge the gap between patients and advanced medical care, bringing critical surgical interventions, small procedures, and even biopsies to those who need them most, regardless of their location.

In this context, several articles in the literature described the benefits of Telementoring and Teleproctoring in surgical training and emergency scenarios (12, 13). Remote surgical interventions could be lifesaving in situations where access to care is restricted by natural disasters, conflict zones, resource-limited settings, and areas such as neurovascular, cardiology, and oncology, where time to intervention is crucial. As technology evolves, telesurgery could become an essential tool for global humanitarian missions, helping to alleviate the burden of surgical diseases in remote and low-resource areas (2).

In addition to its humanitarian impact, telesurgery holds significant promise in medical education. Traditionally, surgical training has been limited by geographical proximity and the availability of experienced mentors (6). With the advent of remote surgery, these constraints are diminished, allowing for real-time collaboration and mentorship between

Figure 1-Trail-SP-Orlando.



surgeons in different parts of the world simultaneously. Now, expert surgeons can supervise, guide, and assist in complex procedures remotely, fostering a global community of surgical practices. This creates opportunities for knowledge exchange and skill enhancement that were previously unattainable. Medical institutions worldwide could leverage telesurgery for remote proctoring and training programs, enabling students and professionals to observe or participate in surgeries performed by leading experts without the need for physical relocation. This opportunity will also minimize the travel of experts, proctors, and invited professors to perform cases in other cities because these connections will be enabled by a robot with telesurgery capabilities. Furthermore, patients will save resources by having the opportunity to undergo a surgical procedure in their city next to their families instead of traveling to other centers or paying for the expenses of a proctor travelling from a different city or country.

Our telesurgery study between São Paulo and Orlando serves as a compelling example of how this technology can be applied in practice with optimal connectivity. During the procedure, the surgeon in São Paulo could remotely control the surgical robot in Orlando, maintaining optimal communication with the local team. This real-time collaboration between teams on different continents exemplifies the potential for international surgical partnerships in several surgical fields. More importantly, it highlights how remote surgery can overcome geographical limitations, offering the possibility of expert care and mentorship access across vast distances.

While the initial success of this procedure is promising, the implementation of telesurgery on a global scale will require further advancements in technology, robust telecommunications infrastructure, and transparent regulatory frameworks. In this context, a collaborative community of experts should be involved in the implementation, maintenance and responsible evolution of remote surgery following optimal ethical standards (7). This community involves medical societies, medical councils, engineers, surgeons, robotic companies, telecommunication entities, local governments, legal experts, and all stakeholders involved with remote procedures. Before any remote surgery, it is crucial to have these specialists and stakeholders involved in consenting and orienting the patient regarding the next steps of that surgical approach. The establishment of standardized protocols and guidelines for remote surgery will be critical to ensure patient safety and maintaining the quality of care (7, 14, 15). Furthermore, latency, data security, and interoperability remain key challenges that must be addressed by experts to ensure safe and effective implementation. In this context, after our extensive experience with telesurgery in Asia operating in several centers, our collaborative community created the 10 commandments for a safe and ethical exploration of telesurgery (Table-1) (7).

Telesurgery, as previously mentioned, represents a transformative innovation with the potential to improve healthcare access, reduce disparities, and enhance surgical education worldwide. Our recent procedure between São Paulo (Brazil) and Orlando (USA) marks a significant step forward in the development of telesurgical capabilities between North and South America, demonstrating that such connections are not only feasible but also offer immense potential for future applications in several surgical fields. However, despite the optimism, we should acknowledge that several steps are yet to come until these results can be translated to human trials, such as guidelines, regulations, connectivity studies, and the involvement of local medical societies and committees for a safe and ethical application of remote surgery. By continuing to explore and refine this technology, we have the opportunity to create a more equitable healthcare system where advanced surgical care and training are available to all, irrespective of geographical constraints.

Table 1 - Telesurgery collaborative community 10 commandments for the ethical and safe exploration of telesurgery.

1. **Prioritize Patient Safety and Efficacy**: Ensure that all robotic and networking systems meet the highest standards of safety and efficacy through rigorous testing, certification, and regular monitoring. Ensure that all medical staff have adequate training and certification in telesurgery
2. **Maintain Transparency, Honesty & Consent:** Provide clear, truthful, and accessible information about the capabilities, limitations, risks and economics associated with robotic telesurgery to patients and the public. Obtain, explicit consent about the remote nature of the surgery and the teams involved.
3. **Foster Human Interaction and Empathy**: Despite the remote delivery method of robotic telesurgery, ensure that human empathy and patient comfort are prioritized by involving compassionate medical staff in the patient care process.
4. **Adhere to Ethical Medical Practices**: Maintain the highest standards of medical ethics, including respecting patient autonomy, doing no harm, providing the best possible care and having telesurgical approvals from national, trans-national and international regulatory bodies. Initial telesurgeries ought to be performed under an IRB/investigational protocol monitored by an administrative body.
5. **Establish Clear Accountability and Liability**: Define and communicate the shared responsibility and liability among all parties involved in robotic telesurgery, including the local and remote surgical teams and hospitals, device manufacturers, and telecommunication providers.
6. **Uphold Data Privacy and Security**: Implement robust cybersecurity measures and adhere to international data protection laws to safeguard sensitive patient information stored, processed and transmitted in real-time against unauthorized access and breaches.
7. **Promote Accessibility and Equity**: Make robotic telesurgery accessible and affordable to all individuals, regardless of geographic location or socioeconomic status, to prevent healthcare disparities nationally and globally.
8. **Encourage International Collaboration and Standardization**: Work towards harmonizing regulatory and ethical telesurgery standards across borders to facilitate international cooperation and consistency in robotic telesurgery practices.
9. **Promote Continuous Education and Training**: Ensure ongoing professional development and training for all medical professionals involved in robotic telesurgery to keep pace with technological advancements and ethical considerations.
10. **Promote Innovation of Safe & Trusted Telesurgery Technologies:** Ensure continuous innovation in telesurgery, robotics and connectivity technologies. Encouraging the development and application of emerging technologies such as artificial intelligence and real time surgical imaging.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

RECONSTRUCTIVE UROLOGY

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Editorial Comment: Targeting Heme in Sickle Cell disease: New Perspectives on Priapism Treatment

Tammyris Helena Rebecchi Silveira [1], Fabiano Beraldi Calmasini [2], Mariana Gonçalves de Oliveira [1], Fernando Ferreira Costa [3], Fábio Henrique Silva [1]

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COMMENT

Ischemic priapism, also called low-flow or ischemic priapism, is associated with decreased venous return with vascular stasis, which causes tissue hypoxia. In this type of priapism, venous drainage is delayed. It is usually painful due to ischemia. Ischemic priapism is associated with a high risk of fibrosis of the corpora cavernosa and impotence (1). In this interesting narrative review from Brazil the authors shows some interesting aspects of the priapism treatment (2) and concluded that the dysfunction of the nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) pathway in erectile tissues as a critical mechanism in developing priapism in Sickle cell disease. Pharmacological treatments should ideally target the pathophysiological basis of the disease. Agents that reduce excess free heme in the plasma have emerged as potential therapeutic candidates for priapism treatment.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Comparing the Technological and Intraoperative Performances of Da Vinci xi and DaVinci 5 Robotic Platforms in Patients Undergoing Robotic-Assisted Radical Prostatectomy

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ABSTRACT

Introduction: In the last two decades, several Da Vinci robotic platforms have been released in the market, revolutionizing the field of robotic-assisted surgery (1, 2).The system has seen numerous modifications, with several Da Vinci® robotic models being introduced, each featuring ongoing technological advancements in ergonomics,instrumentation,high-definition imaging, EndoWrist™ technology, and single-port surgery capabilities (3, 4).Building on this, the new generation Da Vinci 5 robot promises significant hardware and software improvements, with the potential for enhanced operative performance (2, 5). In this video, we will illustrate several technical advancements of the Da Vinci 5.

Material and methods: We performed a video compilation comparing the Da Vinci 5 and Da Vinci Xi during radical prostatectomy. The video will highlight the technical modifications of the new platform, showcasing the advancements and improvements in the Da Vinci 5 system. Additionally, this video will illustrate key aspects of the surgery, including anterior bladder neck access, lateral bladder dissection from the prostate, posterior prostate dissection and anastomosis.

Surgical technique: We performed our RARP technique with our standard approach in all patients (6-8). With this new platform, we maintained our conventional technique without any modifications or adaptions from the trocar placement until anastomosis. The beginning of the case is performed as usual, we first identify the anterior bladder neck and then complete its dissection with Maryland and Scissors. Then, we proceed to the posterior bladder neck dissection, seminal vesicles control and nerve-sparing. In sequence, we control the prostate arterial pedicles with hem-o-lok clips and then we perform the apical dissection until dividing the urethra. Finally, we perform the hemostasis, posterior reconstruction (Rocco's technique) and anastomosis with barbed suture.

Results: The Da Vinci 5 features several key upgrades. The first part of our video described the console, patient cart, and energy tower modifications. The console has been ergonomically redesigned for a flat neck posture to decrease muscle fatigue, and the handgrip now includes a rubber surface for better grip (9). The patient cart, similar to the previous generation, has updated helm interfaces and integrated commands with the console and vision tower. In sequence, we described the instrument modifications and the step-by-step technique showing the DV5 and DV-Xi. Force feedback instruments provide three degrees of tactile feedback, enhancing tissue manipulation. A new security system ensures instruments can only be inserted when clear of tissues and obstructions, reducing the risk of errors. Another modification regards the ability to switch instruments and camera.

Conclusion: While using and evaluating the DV5 in more than 100 cases, we noticed some improvements in the ergonomics and digital interface. The intraoperative performance was similar among the platforms and all procedures were performed without intraoperative complications or problems with the system. However, we are still evaluating the long-term outcomes and potential clinical advantages provided by this new platform.

CONFLICT OF INTEREST

None declared.

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re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

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The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

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1) Do not embed the figures in the text, but supply them as separate files.
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Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not embed in Word or PowerPoint.
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Papers published in periodicals:

- Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

- Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

- Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

- Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

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The **Ideal Manuscript** may not exceed 2500 words.

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Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

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- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
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- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
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