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EDITORIAL
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Vol. 50 (2): 115-118, March - April, 2024
doi: 10.1590/S1677-5538.IBJU.2024.02.01

In this issue we will celebrate 50 years of the International Brazilian Journal of Urology

Luciano A. Favorito [1, 2]

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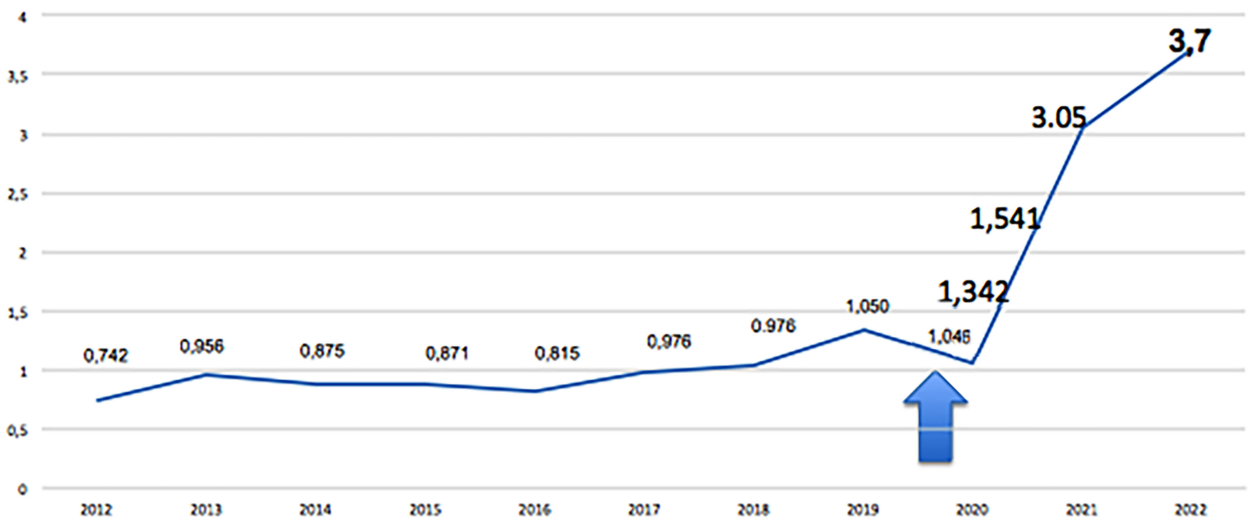
The March-April number of *Int Braz J Urol* is the 27nd under my supervision and is very special. In 2024 the Int Braz J Urol celebrate **50 years** of foundation. I would like to thank our former editors, doctors Alberto Gentile, Lino L. Lens, Rubem Arruda, Gilberto M. Goes, Sami Arap, Nelson R. Neto Jr., Sergio Aguinaga, Francisco Sampaio, Miriam Dambros and Sideny Glina. In Figure-1 we can observe the operating time of the former editors in the last 50 years. I highlight the importance of Prof. Francisco Sampaio that internationalized our Journal and Prof. Sidney Glina that adopted the submission system. In the cover of this edition, we can observe the new symbol of our Journal. In Figure-2 we observe the evolution of the impact factor of Int Braz J Urol in the last years. In 2023 we had the **impact of 3.7** the biggest of our history.

Figure 1 - In this figure we can observe the operating time of the former editors of International Brazilian Journal of Urology in the last 50 years.

ATUAL EDITOR

Luciano Alves Favorito
(2020 –)

Figure 2 - The figure shows the evolution of the impact factor of Int Braz J Urol in the last years.



In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Bladder Cancer, Uroanatomy, Hormonal reposition, Infection, Enuresis, ChatGPT in urology, Research in Urology, Endourology and Testicular Cancer. The papers came from many different countries such as Brazil, USA, Canada, Italy and Germany, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Glina and collegues from Brazil, presented in page 119 (1) a nice systematic review about statins and decrease of testosterone in men and concluded that the statins use causes a decrease in total testosterone, not enough to cause a drop below the normal range and also determines increase in FSH levels. No differences were found in LH, Estradiol, SHBG and Free Testosterone analysis.

Dr. Dutra and collegues from Brazil, presented in page 136 (2) a important systematic review about the treatment of monosymptomatic enuresis (MNE) in children and adolescents and concluded that Parasacral transcutaneous electrical nerve stimulation can reduce the occurrence of wet nights in children and adolescents with MNE. However, it is not a complete cure for the condition, except for one study that reported a 27% cure rate among patients. To determine the most effective protocol for this treatment, more high-qual- ity research is needed. Comprehensive evaluation of its effectiveness will require larger samples and more sessions.

Dr. Talizin and collegues from Brazil, performed in page 152 (3) a nice systematic review about the postoperative antibiotic prophylaxis for percutaneous nephrolithotomy and risk of infection and concluded that there is no benefit associated with the use of post- operative antibiotic prophylaxis until nephrostomy tube withdrawal in patients undergoing percutaneous nephrolithotomy (PCNL). We recommend that antibiotic prophylaxis should be administered only until the induction of anesthesia in PCNL.

Dr. Miranda e Morais and collegues from the Urogenital Resarch Unit from Brazil performed in page 164 (4) a nice narrative review about the kidney collecting system anatomy applied to endourology and concluded that the knowledge of intra-renal collecting system divisions and variations as the angle between the renal pelvis and lower infundibula, position of the calices in relationship with renal edge and the diameter and position of the calyces are important for the planning of minimally invasive renal surgeries.

Dr. Fu and collegues from USA performed in page 178 (5) an interesting study about the risk factors for perioperative outcomes in Intracorporeal Urinary Diversion (ICUD) and Extracorporeal Urinary Diversion (ECUD) with Robotic cystectomy and concluded that Robotic cystectomy with ICUD results in shorter hospitalizations and lower intraoperative transfusion rates compared to ECUD, without differences in operative time, high-grade postoperative complications, or readmission rates. These findings can inform clinical decision-making, highlighting ICUD as a potentially more favorable option in ap- propriate settings.

Dr. Braga and collegues from Brazil and Canada performed in page 192 (6) a nice study about the use of ChatGPT in Urology and its Relevance in Clinical Practice and concluded that ChatGPT simulated general knowledge on the researched topics. Regarding Enuresis, the provided definition was partially correct, as the generic response allowed for misinterpretation. For VUR, the response was considered appropriate. For pMU it was partially correct, lacking essential aspects of its definition such as the diameter of the dilatation of the ureter. Unnecessary exams were suggested, for Enuresis and pMU. Regarding the treatment of the conditions mentioned, it specified treatments for Enuresis that are ineffective, such as bladder training. Therefore, ChatGPT responses present a combination of accurate information, but also incomplete, ambiguous and, occasionally, misleading details.

Dr Beatrice and collegues from USA, Italy, Germany and Brazil performed in page 199 (7) a nice study about smoking Characteristics and Years Since Quitting Smoking of US Adults Diagnosed with Lung (LC) and Bladder (BC) Cancer: A National Health and Nutrition Examination Survey Analysis and concluded that BC patients exhibit a prolonged latency period between smoking cessation and cancer diagnosis compared to LC patients. Despite smoking status evaluation in microhematuria, current risk stratification models for urothelial cancer do not incorporate it. Our findings emphasize the significance of long-term post-smoking cessation surveillance and advocate for integrating smoking history into future risk stratification guidelines.

The Editor-in-chief expects everyone to enjoy reading this special number.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Do statins decrease testosterone in men? Systematic review and meta-analysis

Felipe Placco Araujo Glina [1], Leonardo Lopes [1], Rodrigo Spinola e Silva [1], Eduardo Augusto Correa Barros [1], Bruno Biselli [2], Sidney Glina [1]

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ABSTRACT

Purpose: Statins are one of the most prescribed classes of drugs worldwide to treat hypercholesterolemia and dyslipidemia. By lowering the level of cholesterol, the use of statin could cause a reduction in testosterone levels.

The objective was to evaluate whether the continued use of statins in patients with hypercholesterolemia causes a deficiency in testosterone and other sex hormones.

Materials and Methods: Systematic Review with Meta-analysis, performed in Embase, Medline and Cochrane databases, until May 2023; PROSPERO CRD42021270424protocol. Selection performed by two independent authors with subsequent conference in stages. Methodology based on PRISMA statement. There were selected comparative studies, prospective cohorts (CP), randomized clinical trials (RCT) and cross-sectional studies (CSS) with comparison of testosterone levels before and after statin administration and between groups. Bias analysis were evaluated with Cochrane Tool, The Newcastle-Ottawa Scale (NOS), and using the Assess the Quality of Cross-sectional studies (AXIS) tool.

Results: There were found on MedLine, Embase and Cochrane, after selected comparative studies, 10CP and 6RCT and 6CSS for the meta-analysis. In the Forrest plot with 6CSS, a correlation between patients with continuous use of statins and a reduction in total testosterone was evidenced with a statistically significant reduction of 55.02ng/dL (95%CI=[39.40,70.64],I^2=91%,p<0.00001).In the analysis with 5RCT, a reduction in the mean total testosterone in patients who started continuous statin use was evidenced, with a statistical significance of 13.12ng/dL (95%CI=[1.16,25.08],I^2=0%,p=0.03). Furthermore, the analysis of all prospective studies with 15 articles showed a statistically significant reduction in the mean total testosterone of 9.11 ng/dL (95%CI=[0.16,18.06],I^2=37%,p=0.04). A reduction in total testosterone has been shown in most studies and in its accumulated analysis after statin use. However, this decrease was not enough to reach levels below normal.

Conclusion: Statins use causes a decrease in total testosterone, not enough to cause a drop below the normal range and also determines increase in FSH levels. No differences were found in LH, Estradiol, SHBG and Free Testosterone analysis.

ARTICLE INFO

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INTRODUCTION

Statins are one of the most prescribed medications worldwide for lowering cholesterol. Therefore, they are efficient for the primary and secondary prevention of cardiovascular diseases (CVD) (1, 2). Because cholesterol is one of the precursors of adrenocortical and gonadal hormones, there is a concern that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may impair testosterone production and other sex hormones (3, 4). This could lead eventually to hypogonadism in men. Defined as low levels of total serum testosterone (less than 300 ng / dL) and free testosterone (less than 5 ng / dL) in combination with clinical symptoms such as low sex drive, fracture associated with osteoporosis and erectile dysfunction, or two or more of the following symptoms: sleep disturbances, depressed mood, lethargy, or decreased physical performance (5). The male hypogonadism can thus affect the function of multiple organs and the quality of life of patients.

Conflicting evidence on the subject appears in studies in the medical literature. The study by Bernini GP 1998 evaluated in 8 patients using statins for 24 weeks that there was no change in the testosterone level nor the spermogram (6). The Braamskamp MJ et al. 2015 study evaluated children with familial hypercholesterolemia for 10 years using any statin and compared them with siblings who were not using the medication and found no difference in hormone levels (7). However, in the study by Baspınar O et al. 2016, a correlation was seen between the fall in low-density lipoprotein cholesterol levels in patients using statin with the fall in the levels of total and free testosterone, in addition to exposing an association with the impairment of erectile function assessed by the IIEF-5 questionnaire. Thus, lower cholesterol levels were directly associated with lower testosterone levels and lower IIEF-5 scores (8). Other studies have shown indirect signs of significant hormonal changes, with a drop in PSA in patients without prostate cancer and an increased risk of gynecomastia in men using statins (9, 10). In the cross-sectional study by Stanworth RC et al. 2009, it was not correlated the decrease in testosterone with signs and symptoms of hypogonadism, assessed by ADAM questionnaire, even though it showed a statistically significant reduction in total testosterone and SHBG (11).

Due to the contradictory findings in the literature, the hypothesis of this study is that continuous use of statins may lead to decreased levels of testosterone and other sex hormones in patients with hypercholesterolemia, potentially resulting in hypogonadism. The primary objective is to assess whether continued use of statins in patients with hypercholesterolemia causes a decrease in testosterone levels. The secondary aim is to evaluate the hormonal axis, including free testosterone, estradiol, LH, FSH, and SHBG, with the chronic use of statins.

METHODS

Registration and protocol:

PROSPERO CRD42021270424 protocol registration

Eligibility criteria

Methodology based on the PRISMA 2020 statement (12). Inclusion criteria: Male patients with hypercholesterolemia or dyslipidemia or with cardiac indication for statin use. Intervention: continuous use of any type of statin such as atorvastatin, fluvastatin, lovastatin, rosuvastatin, pravastatin and others. In its various dosages as long as above the established minimum. Comparison: before and after statin use, comparison between control or placebo groups. Outcomes: Hormonal evaluation with total testosterone, free testosterone, FSH, LH, Estradiol, SHBG. Use of a questionnaire to assess sexual function. Study design: Prospective and retrospective comparative studies. Among them are randomized clinical trial (RCT), prospective cohort (PC), cross-sectional study or ecological study (CSS). Search Period: All articles published up to the date of the last search. Language: there was no language restriction. Exclusion Criteria: Patients under 18 years old. Studies that showed divergence between results and measurement units. Articles with incompletely displayed results or not submitted to peer-review journals.

Information sources

The search was carried out in MEDLINE through PubMed, Embase and Cochrane Central. The review was carried out in all databases in May 2023. Gray searches were carried out by the authors in the references of the selected articles.

Search strategy

Search strategy performed by author FPAG and revised by LSL. Strategy performed based on PICO acronym (patient, intervention, comparison, and outcome) and study objective using MESH terms. Conducted preliminary search with selection of articles to improve the search with terms found. After performing a definitive search. If during the search any article was found in the gray search that was not included in the search, the search strategy was updated.

Pubmed search strategy: (Testosterone OR androgen OR hypogonadism OR gonadotropin OR Gonadal Steroid Hormones OR Sex Hormone OR Sex Steroid Hormones) AND (CS-514 OR statin OR simvastatin OR atorvastatin OR fluvastatin OR lovastatin OR rosuvastatin OR pravastatin OR 3-hydroxy- methylglutaryl-CoA reductase).

Cochrane search strategy: (Testosterone OR androgen OR hypogonadism OR gonadotropin OR Gonadal Steroid Hormones OR Sex Hormone OR Sex Steroid Hormones) AND (CS-514 OR statin OR simvastatin OR atorvastatin OR fluvastatin OR lovastatin OR rosuvastatin OR pravastatin OR 3-hydroxy- methylglutaryl-CoA reductase).

Embase search strategy: (Testosterone OR androgen OR hypogonadism OR gonadotropin OR Gonadal Steroid Hormones OR Sex Hormone OR Sex Steroid Hormones) in Title Abstract Keyword AND (CS-514 OR statin OR simvastatin OR atorvastatin OR fluvastatin OR lovastatin OR rosuvastatin OR pravastatin OR 3 hydroxy methylglutaryl CoA reductase) in Title Abstract Keyword - in Trials (Word variations have been searched).

Selection process

The article selection process was carried out in stages in order to screen the articles by double selection. Selection performed from outside paired by two authors in the stages of selection by title, abstract and full text. No automation method was used in the process. Selections were based on eligibility criteria. When an article disagreed, a third author decided.

Data collection process

Data extraction was also performed by two different authors separately, RSS and FPAG. After extraction, the data were compared with each other, and the PICO table and the results table were created in an excel spreadsheet. Any misunderstanding, a third author resolved, LSL. There was no automation of the process.

Articles that had more than one comparison group were selected, the groups that fit the selection criteria, even if there were more than two selectable groups.

Data items

The information collected was: Authors, Study year, Study country, Number of patients, Follow-up, Study design, Drug used, Drug dose, Dropouts, Total Testosterone, Free Testosterone, FSH, LH, Estradiol, SHBG, Prolactin and Erectile Dysfunction. Erectile dysfunction and hypogonadism were assessed using validated questionnaires such as *the International Index of Erectile Function* short form (IIEF-5) (13) and *Androgen Deficiency in Aging Male* (ADAM) questionnaire(14), respectively.

In case there was any information exposed in an incomplete way, it was tried to contact the authors of the articles through e-mail. If there was no response, the data was reported as not provided.

Study risk of bias assessment

To assess the risk assessment of each study, a different questionnaire was used depending on each study design. For the Randomized Clinical Trials, the Cochrane Collaboration's Tool (15) was used, for the Prospective Cohorts the Newcastle-Ottawa Scale (NOS) (16) and for the Cross-sectional Studies the AXIS tool (Assess the Quality of Cross-sectional studies) (17). Questionnaires were applied independently by two authors in each article, RSS and FPAG.

Effect measures

Data were extracted in their means and standard deviations. When the data was exposed only in confidence intervals, a conversion of the same type of standard deviation was performed. The measurement units were converted for standardization and possible comparison of variables. Total testosterone and free testosterone were evaluated in ng/dL; FSH and LH in UI/L; Estradiol in pg/mL and SHGB in nmol / L.

Synthesis methods/ Reporting bias assessment

Review Manager® software, version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2020). A meta-analysis of continuous variables was used in the reverse variation test, the mean difference (MD) with a 95% confidence interval (CI) was calculated. The results were generated in graphs (18).

To assess heterogeneity, both the graphic of the forest plot and I^2 were analyzed. When this value was less than 50%, heterogeneity was considered low and acceptable, and the fixed model was used for analysis. When I^2 was greater than 50%, heterogeneity was considered important. Studies that caused heterogeneity were removed so that further meta-analyses could be conducted to assess the results, a sensitivity test. If there is true heterogeneity, the analysis model will be changed from fixed to random.

An additional analysis was performed, with the MetaDisc software (19), on the results of total and free testosterone in the statistically significant evaluations, to expose the results of the averages of the meta-analyzed groups and not just the difference between the groups. Only the values are exposed and not the graphics.

The presentation of the results was divided according to the different study designs. No other sub-analyses were performed.

Certainty of evidence

The GRADEpro tool was used to expose the degree of certainty of the evidence of the meta-analyzed and evaluated outcomes (20).

RESULTS

Study selection

A total of 2359 articles were retrieved in the database searches, of which 812 were from MedLine, 1373 from Embase and 174 from Cochrane. After removing the duplicates, 1032 articles remained, 42 being selected for full reading. Of these, 21 were excluded and 21 selected for systematic review and meta-analysis. The selection flowchart is shown in **Figure-1** (7-11, 21-36).

Study characteristics

The characteristics of the included studies are shown in **Table 1**. The review included a total of 9879 patients. Selected 21 articles with a total of 9879 patients. Among them, 5 randomized controlled trials (RCT) with 1104 patients, 10 prospective cohorts (PC) with 712 patients and 6 cross-sectional studies (CSS) with 8063 patients.(6, 37-56).

Risk of bias in studies

The risk of bias analysis was assessed using the The Newcastle-Ottawa Scale (NOS), AXIS tool and the Cochrane tool. The risks are shown in **supplementary file-1 in appendix.**

Results of syntheses

Total Testosterone

In the Forrest plot with 6 CSS, the correlation between patients with continuous use of statins and reduction in total testosterone was evidenced with a statistically significant reduction between groups of 55.02ng/dL (95% CI = [39.40, 70.64], I2 = 91 %, p < 0.00001), shown in **Figure-2** In the continuous statin use group, the mean total testosterone calculated was 409.56ng/dL (95% CI = [384.34, 434.79], p < 0.001) and in the control group, 470.70ng/dL (95% CI = [441.34 , 500.05], p < 0.001).

In the analysis with 5 RCTs, there was a reduction in the mean total testosterone in patients who started continuous use of statins, with a statistical significance of 13.12ng/dL (95% CI = [1.16, 25.08], I^2 = 0%,

Figure 1 - Flowchart of selected articles.

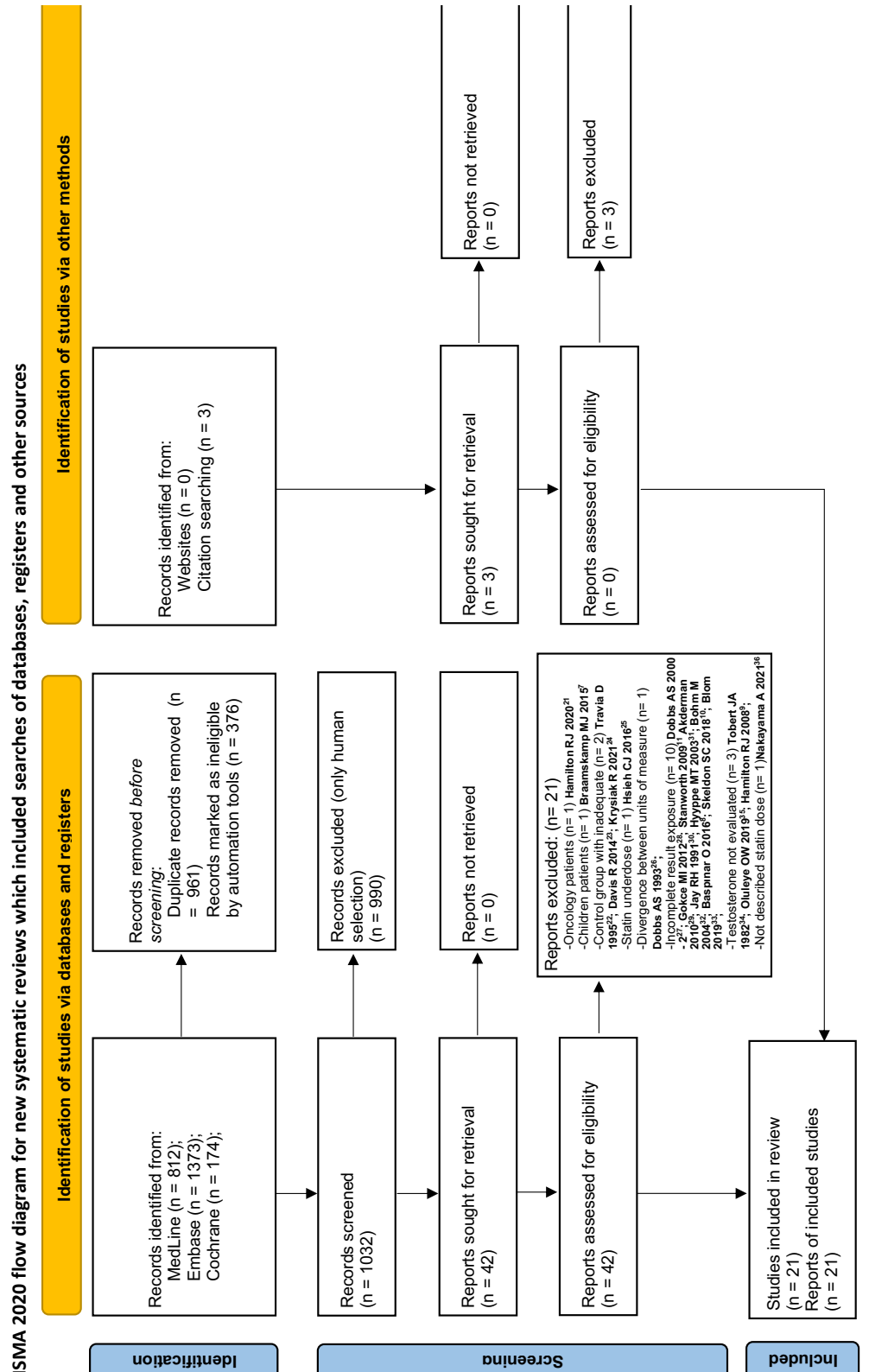


Table 1 - PC ProspecJve Cohort; RCT- Randomized Clinical Trial; CSS - Cross-secJonal study; SD Standard DeviaJon; Confidence Interval IC; LDL - Low-Density Lipoprotein; DM - Diabetes mellitus; SHA - Systemic Arterial Hypertension; CS - Can't Say; NA - Not Applicable; FSH - Follicle SJmulaJng Hormone; LH - Luteinizing Hormone; SHBG - sex hormone binding globulin; DHEA - Dehydroepiandrosterone; CV - Cardiovascular; CVD - Cardiovascular Disease;

Study ID		Population			Comparation					Outcomes								
Author Yeay	Study Design	Country	Patient	Age Mean (SD or IC)	Comparison	Drugs and Groups	Dose (mg)	Nº patients	Follow Up (Months)	Total Testosterone (ng/dL)	Free Testosterone (ng/dL)	FSH (IU/L)	LH (IU/L)	Estradiol (pg/ml)	SHBG (nmol/L)	DHEA (µg/dL)	Sexual Function Questionnaire	ADAM
Purvis K 1992[37]	PC	Norway	Familial Hypercholesterolemia	31 (20-49)	Before/After	Simvastatin	40	19/19	3.5	✓	.	✓	✓	.	.	.	.	.
Bernini GP 1994[38]	PC	Italy	Mildly Hypercholesterolemic	34 (25 - 57)	Before/After	Simvastatin	10	8/8	6	✓	.	.	.	.	.	.	.	.
Azzarito C 1996[39]	PC	Italy	Hypercholesterolemia IIa	56.2 (±2.0)	Before/After	Simvastatin	20	8/8	12	✓	✓	✓	✓	✓	✓	✓	.	.
Segarra A 1996[40]	PC	Spain	Hypercholesterolemia in Chronic Kidney Disease	43(±15)	Before/After	Lovastatin	40	25/25	11	✓	.	✓	✓	.	.	.	.	.
Bernini GP 1998[6]	PC	Italy	Primary Hypercholesterolemia	48.8 (31-60)	Before/After	Pravastatin	20	8/8	6	✓	.	.	.	✓	.	✓	.	.
Santini SA 2003[41]	PC	Italy	Mild To Moderate Hypercholesterolemia and DM	64.7(±7.6)	Before/After	Atorvastatin	20	16/16	3	✓	.	.	.	.	✓	✓	.	.
Dogru MT 2008[42]	PC	South Africa	Uncontrolled Hyperlipidemia	44.7 (±7.1)	Before/After	Atorvastatin	40	74/74	12	✓	.	.	.	✓	.	✓	IIEF-15	.
Kocum TH 2008[43]	PC	Turkey	Men With Arterial Disease Coronary	59 (±9.6) 56 (±11.4)	Before/After and Between Groups	Atorvastatin	20 40	83/83 77/77	12	✓	✓	✓	✓	.	✓	.	.	.
Krysiak R 2014[44]	PC	Poland	Very High Cardiovascular Risk	53.9 (±3.8)	Before/After	Rosuvastatin	20	11/11	4.5	✓	✓	✓	✓	.	✓	✓	.	.
Krysiak R 2015[45]	PC	Poland	Coronary Disease After Statin: Increased Aminotransferase Or Creatinokinase	54.3 (±4.0)	Before/After and Between Groups	1- Atorvastatin 2- Rosuvastatin + Ezetimibe	20-40 5-10	12/12 15/15	4	✓	.	✓	✓	.	✓	✓	.	.
Kanat M 2009[46]	RCT	Turkey	DM and Coronary Disease Patients	45 (±10)	Before/After and Between Groups	1- Atorvastatin + Ezetimibe 2- Atorvastatin	10+10 80	50/50 48/48	3	✓	.	.	.	✓	.	✓	.	.
Mastroberardino G 1989[47]	RCT	Italy	Familial Hypercholesterolemia	42.5 (40-45)	Before/After and Between Groups	1- Lovastatin 2- Clofibrate	40 1500	8/8 8/8	1	✓	.	.	.	.	.	.	.	.
Dobs AS 2000 1[48]	RCT	USA	Hypercholesterolemia IIa Or IIb	41 (±7.3) 41.2 (±6.4) 38.4 (±8.7) 40,2 (±7.5)	Before/After and Between Groups	1- Simvastatin 2- Simvastatin 3- Pravastatin 4- Placebo	20 40 40 CS	37/37 34/34 37/37 30/30	6	✓	✓	✓	✓	.	✓	.	.	.
Zhi-Guo C 2014[49]	RCT	China	Elderly Men With Osteopenia And Mild Dyslipidemia	80.8 (±6.8)	Before/After and Between Groups	1- Atorvastatin 2- Lifestyle guidance only	10 NA	32/32 32/32	12	✓	.	.	.	.	.	.	.	.
Berberoglu Z 2009[50]	RCT	Turkey	DM with Evident CVD Or CV Risk Factor	60.8 (±7.1) 61.3 (±8.0) 60 (±7.8) 62.2 (±7.5)	Before/After	1-LDL < 70 - Simvastatin 2- LDL < 100 - Simvastatin 3- LDL < 70 - Atorvastatin 4- LDL < 100 - Atorvastatin	35.7 32.7 37.3 34.4	9/9 15/15 10/10 9/9	3	✓	.	.	.	.	.	✓	.	.
Keyser CE 2015[51]	CSS	Netherlands	Rotterdam Study Men	64.1 (±8.1) 64.6 (±9.7)	Between Groups	1- Using Statin 2- Non Statin User	CS NA	577 3441	NA	✓	✓	.	.	✓	✓	✓	.	.
Hall SA 2007[52]	CSS	USA	USA Population Base	57.9 (±1.3) 45.5 (±0.5)	Between Groups	1- Using Statin 2- Non Statin User	CS NA	237 1575	NA	✓	✓	.	✓	.	✓	✓	.	.
Mondul AM 2010[53]	CSS	USA	USA Population Base	60 42	Between Groups	1- Using Statin 2- Non Statin User	CS NA	41 1275	NA	✓	✓	.	.	✓	.	.	.	.
Corona G 2010[54]	CSS	Italy	Men with Sexual Dysfunction	60.9 (±7.6) 60.8 (±7.3)	Between Groups	1- Using Statin 2- Non Statin User	CS NA	244 244	NA	✓	✓	.	.	.	.	.	ANDROTEST	.
Medras M 2014[55]	CSS	Poland	Poland Region Population Base	58.6 (±7.6) 57.9 (±5.6)	Between Groups	1- Using Statin 2- Non Statin User	20 NA	38 151	NA	✓	✓	✓	✓	✓	✓	✓	.	.
Jarari AM 2018[56]	CSS	Libyan	DM And DM and SHA Men Taking Statin	45.5 (±8.2) 46.8 (±7.1) 44.4 (±5.0) 45.0 (±2.5) 46.5 (±3.1) 44.6 (±4.5) 44.3 (±3.7) 45.9 (±3.8)	Between Groups	1- Non Statin User 2- Using Statin 3- DM Non Statin User 4- DM with Statin <1y 5- DM with Statin >1y 6- DM and SHA Non Statin User 7- DM and SHA with Statin <1y 8- DM and SHA with Statin >1y	NA CS NA CS CS NA CS CS	30 30 30 30 30 30 30 30	NA	✓	.	.	.	.	.	.	.	.

p=0.03). In the group before statin use, they had a mean testosterone of 411.60ng/dL (95% CI = [335.85, 487.34], p < 0.001) and after the use of 395.14ng/dL (95% CI = [321.38, 468.91] , p < 0.001).

Furthermore, analysis of all prospective comparative studies with 15 articles showed a statistically significant reduction in mean total testosterone of 9.11ng/dL (95% CI = [0.16, 18.06], I^2 = 37%, p = 0.04), shown in **Figure-3** In the group before statin use, they had a mean testosterone of 427.83ng/dL (95% CI = [362.25, 493.41], p < 0.001) and after the use of 416.86 ng/dL (95% CI = [365.68, 468.04] , p < 0.001).

Figure 2 - Total testosterone - Cross-sectional studies.

Study or Subgroup	Control Mean	Control SD	Control Total	Statin Mean	Statin SD	Statin Total	Weight	Mean Difference IV, Random, 95% CI
Corona 2010	467	199	244	381	147	244	9.6%	86.00 [54.96, 117.04]
Hall 2007	445.3	8.1	1575	394.3	16	237	15.5%	51.00 [48.92, 53.08]
Jarari 2018	520	110	30	460	80	30	6.2%	60.00 [11.33, 108.67]
Jarari 2018	480	99	30	420	50	30	7.8%	60.00 [20.31, 99.69]
Jarari 2018	420	90	30	310	130	30	5.1%	110.00 [53.42, 166.58]
Jarari 2018	420	90	30	380	50	30	8.3%	40.00 [3.16, 76.84]
Jarari 2018	480	99	30	340	130	30	4.9%	140.00 [81.53, 198.47]
Keyser 2015	490.3	76.8	3441	426.9	82.9	577	15.1%	63.40 [56.17, 70.63]
Medras 2014	472	21.7	151	429	49	38	13.4%	43.00 [27.04, 58.96]
Mondul 2010	511	4.2	1275	516	42.6	41	14.0%	-5.00 [-18.04, 8.04]
Total (95% CI)			**6836**			**1287**	**100.0%**	**55.02 [39.40, 70.64]**

Heterogeneity: Tau^2 = 407.84; Chi^2 = 101.68, df = 9 (P < 0.00001); I^2 = 91%
Test for overall effect: Z = 6.90 (P < 0.00001)

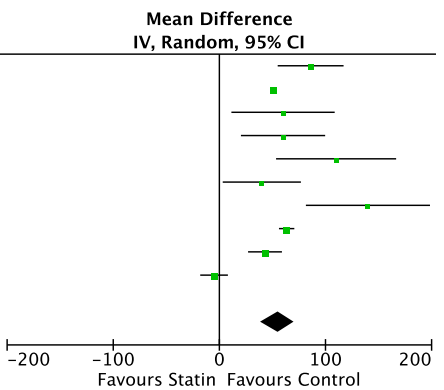
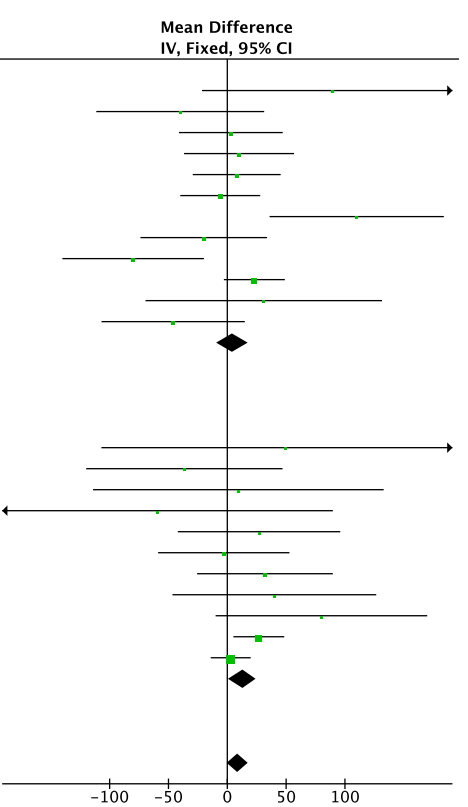


Figure 3 - Total testosterone - Before and After - All Prospective Comparative Studies: Prospective Cohort and Randomized Clinical Trial.

Study or Subgroup	Before Statin Mean	Before Statin SD	Before Statin Total	After Statin Mean	After Statin SD	After Statin Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 CP								
Azzarito 1996	513	133	8	424	88	8	0.7%	89.00 [-21.51, 199.51]
Bernini 1994	410	50	8	450	90	8	1.6%	-40.00 [-111.34, 31.34]
Bernini 1998	513	46	8	510	44	8	4.1%	3.00 [-41.11, 47.11]
Dogru 2008	490	150	74	480	140	74	3.7%	10.00 [-36.75, 56.75]
Kocum 2008	447	131	83	439	114	83	5.7%	8.00 [-29.36, 45.36]
Kocum 2008	426	109	77	432	106	77	6.9%	-6.00 [-39.96, 27.96]
Krysiak 2014	420	110	11	310	60	11	1.5%	110.00 [35.95, 184.05]
Krysiak 2015	300	80	15	320	70	15	2.8%	-20.00 [-73.79, 33.79]
Krysiak 2015	320	70	12	400	80	12	2.2%	-80.00 [-140.14, -19.86]
Purvis 1992	738	34.6	19	715	46.1	19	11.9%	23.00 [-2.92, 48.92]
Santini 2003	355	167	16	324	119	16	0.8%	31.00 [-69.48, 131.48]
Segarra 1996	375	57.7	25	421	144.2	25	2.2%	-46.00 [-106.88, 14.88]
Subtotal (95% CI)			**356**			**356**	**44.0%**	**4.01 [-9.48, 17.50]**
Heterogeneity: Chi^2 = 25.24, df = 11 (P = 0.008); I^2 = 56%								
Test for overall effect: Z = 0.58 (P = 0.56)								
1.1.2 RCT								
Berberoglu 2009	465.8	202.5	9	416.2	128.2	9	0.3%	49.60 [-106.98, 206.18]
Berberoglu 2009	411.5	113.7	10	448	72.1	10	1.2%	-36.50 [-119.94, 46.94]
Berberoglu 2009	359.3	162.3	15	349.9	182.3	15	0.5%	9.40 [-114.12, 132.92]
Berberoglu 2009	418.6	141	9	477.9	179.3	9	0.4%	-59.30 [-208.32, 89.72]
Dobs 2000	555	149	37	528	154	37	1.7%	27.00 [-42.05, 96.05]
Dobs 2000	493	122	37	496	123	37	2.6%	-3.00 [-58.82, 52.82]
Dobs 2000	511	138	34	479	102	34	2.4%	32.00 [-25.68, 89.68]
Kanat 2009	210	240	48	170	190	48	1.1%	40.00 [-46.60, 126.60]
Kanat 2009	280	270	50	200	180	50	1.0%	80.00 [-9.95, 169.95]
Mastroberardino 1989	509.9	29.7	8	483.1	9.5	8	17.2%	26.80 [5.19, 48.41]
Zhi-Guo 2014	306.6	42.1	32	303.7	25.1	32	27.8%	2.90 [-14.08, 19.88]
Subtotal (95% CI)			**289**			**289**	**56.0%**	**13.12 [1.16, 25.08]**
Heterogeneity: Chi^2 = 8.79, df = 10 (P = 0.55); I^2 = 0%								
Test for overall effect: Z = 2.15 (P = 0.03)								
Total (95% CI)			**645**			**645**	**100.0%**	**9.11 [0.16, 18.06]**
Heterogeneity: Chi^2 = 35.01, df = 22 (P = 0.04); I^2 = 37%								
Test for overall effect: Z = 1.99 (P = 0.05)								
Test for subgroup differences: Chi^2 = 0.98, df = 1 (P = 0.32), I^2 = 0%								



In the Forrest plot in the analysis with 3 PC, an increase in the mean total testosterone was evidenced, without significant significance, in patients on continuous use of statins and compared with patients in the control group of -3.04 ng/dL (95% CI = [-60.72, 54.65], I^2 = 92%, p = 0.92), shown in **Figure-4.**

Free Testosterone

In the Forrest plot with 5 CSS, there was a correlation between patients on continuous use of statins and the reduction in free testosterone with a statistically significant reduction of 0.60 ng/dL (95% CI = [0.56, 0.64], I2 = 0%, p<0.00001), shown in **Figure-5** In the continuous statin use group, the calculated mean free testosterone was 7.32ng/dL (95% CI = [5.26, 9.38], p < 0.001) and in the control group, 6.64ng/dL (95% CI = [2.88 , 10.40], p < 0.001).

In the Forrest plot in the analysis with 2 PC, an increase in the mean of free testosterone in patients who started continuous statin use of -0.17 ng/dL was evidenced (95% CI = [-0.54, 0.19], I^2 = 93%, p = 0 .35), without statistical significance, shown in **Figure-6.**

Figure 4 - Total Testosterone - Statin X Control - Prospective Cohort.

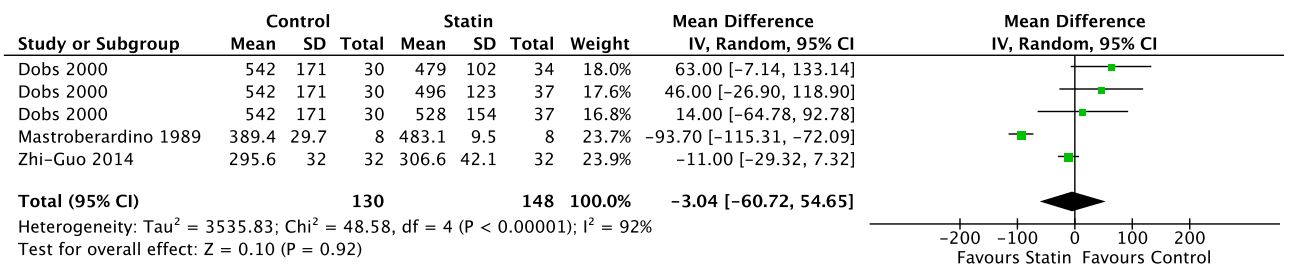


Figure 5 - Free Testosterone - Cross-sectional Studies.

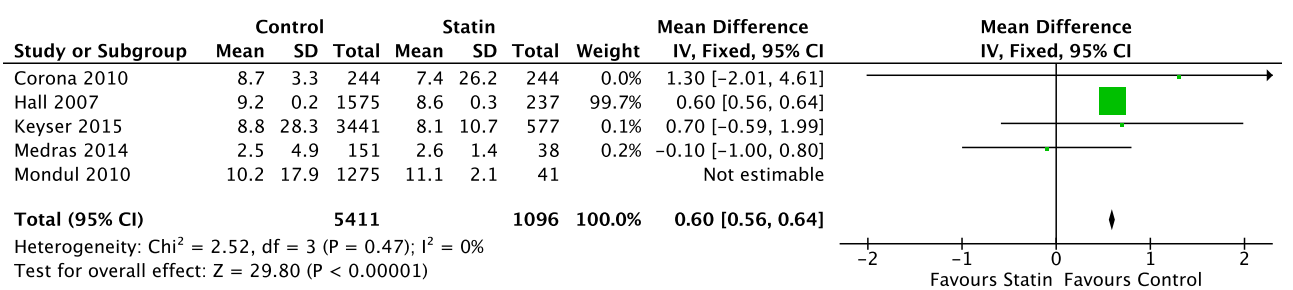
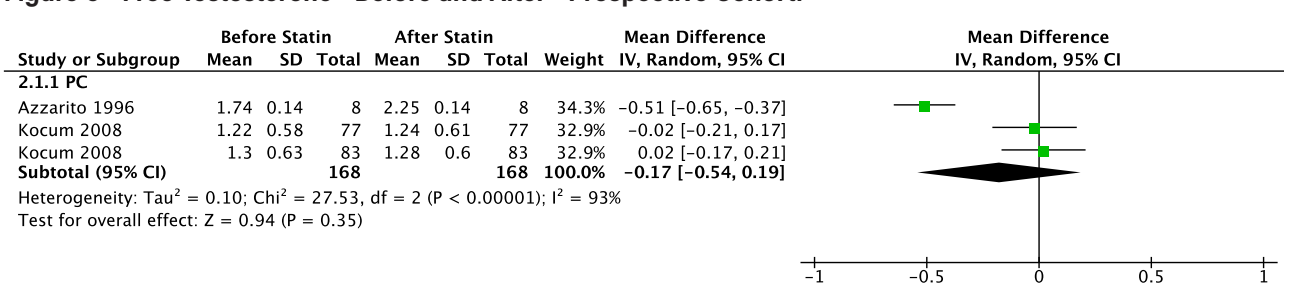


Figure 6 - Free Testosterone - Before and After - Prospective Cohort.



FSH

The Forrest plot with 6 PC showed an increase in the mean FSH in patients who started continuous statin use of -0.39 UI/L (95% CI = [-0.59, -0.19], I^2 = 28%, p = 0.0002), with statistical significance. Furthermore, the analysis of all prospective comparative studies with 6 articles showed a statistically significant increase in the mean FSH of -0.35 UI/L (95% CI = [-0.54, -0.15], I^2 = 19%, p = 0.0005), shown in **Figure-7.**

LH

In the Forrest plot with 2 CSS, there was evidence of a correlation between patients with continuous statin use and a statistically significant increase in LH of -0.29 UI/L (95% CI = [-0.45, -0.12], I2 = 5%, p <0 .0008), shown in **Figure-8.**

In the Forrest plot with 5 PC, an increase in the mean LH was evidenced in patients who started continuous statin use of -0.04 UI/L (95% CI = [-0.44, 0.36], I^2 = 70%, p = 0.85), without statistical significance. Furthermore, in the analysis of all prospective comparative studies with 6 articles, a statistically non-significant reduction in the mean LH of 0.05 UI/L was evidenced (CI 95% = [-0.25 , 0.34], I^2 = 64%, p = 0 .76), shown in **Figure-9**.

Estradiol

In the Forrest plot with 2 CSS, a correlation between patients with continuous use of statins and

Figure 7 - FSH - Before and After - All Prospective Comparative Studies: Prospective Cohort and Randomized Clinical Trial.

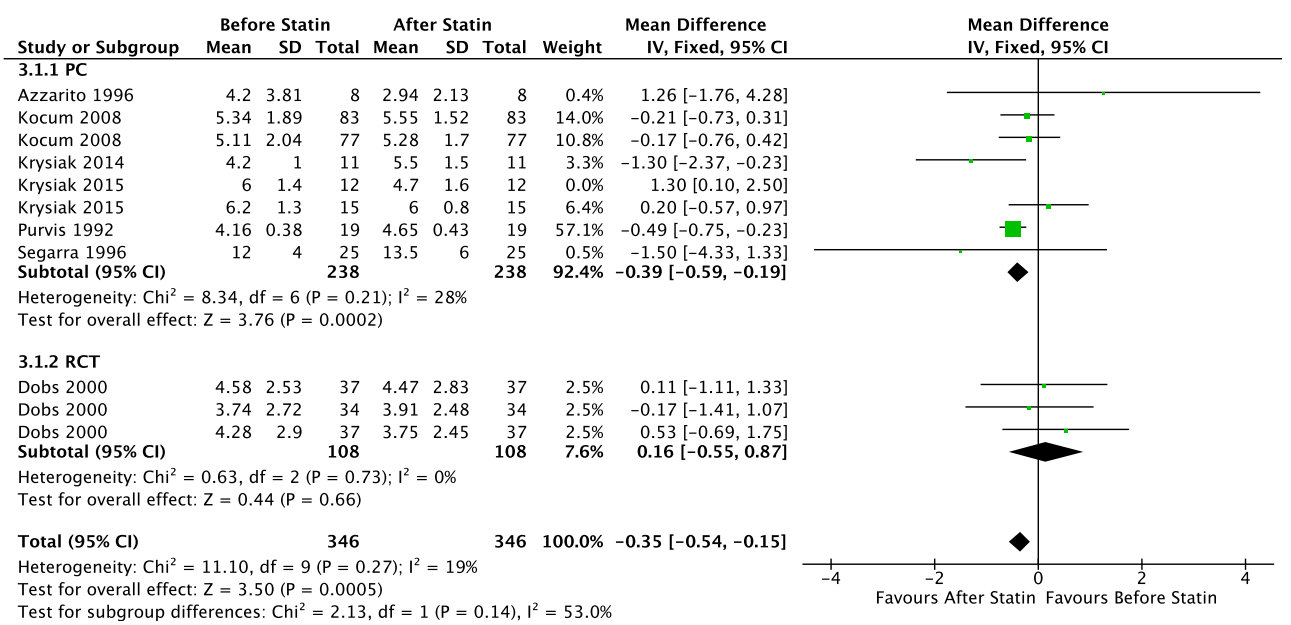
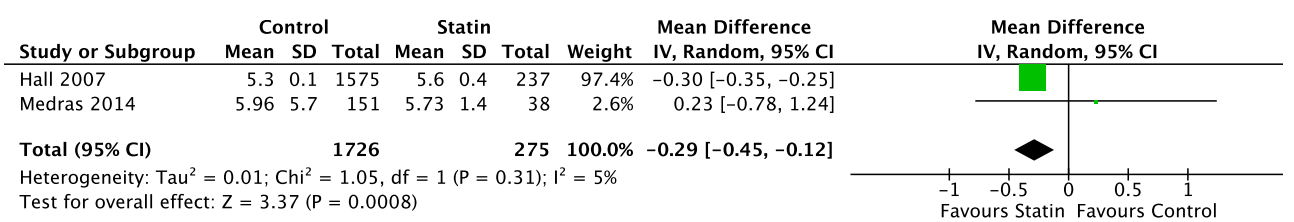


Figure 8 - LH - Cross-sectional studies.



a decrease in Estradiol without statistical significance of 0.39 pg/mL was evidenced (CI 95% = [-1.74, 2.52], I2 = 93%, p =0. 72), shown in **Figure-10**.

In the Forrest plot with 3 PC, an increase in the mean estradiol in patients who started continuous statin use of -3.14 pg/mL was evidenced (95% CI = [-6.82, 0.54], I^2 = 49%, p = 0.09), without statistical significance. Furthermore, the analysis of all prospective comparative studies with 4 articles showed a statistically non-significant increase in the mean estradiol of -0.43 pg/mL (95% CI = [-5.38, 4.52], I^2 = 78%, p = 0.86), shown in **Figure-11**.

SHBG

In the Forrest plot with 3 CSS, there was a correlation between patients with continuous use of statins and a decrease in SHBG without statistical significance of 0.93 nmol/L (95% CI = [-4.32, 6.17], I2 = 99%, p =0, 73), shown in **Figure-12.**

In the Forrest plot with 4 PC, a reduction in the mean SHBG in patients who started continuous statin use of 0.13 nmol/L was evidenced (95% CI = [-1.53, 1.79], I^2 = 0%, p = 0.88), without significance statistics, shown in **Figure-13.**

Certainty of evidence

The summary of evidence and findings are displayed in the GRADE20 table in the **supplementary file 2 in appendix.**

Figure 9 - LH - Before and After - All Prospective Comparative Studies: Prospective Cohort and Randomized Clinical Trial.

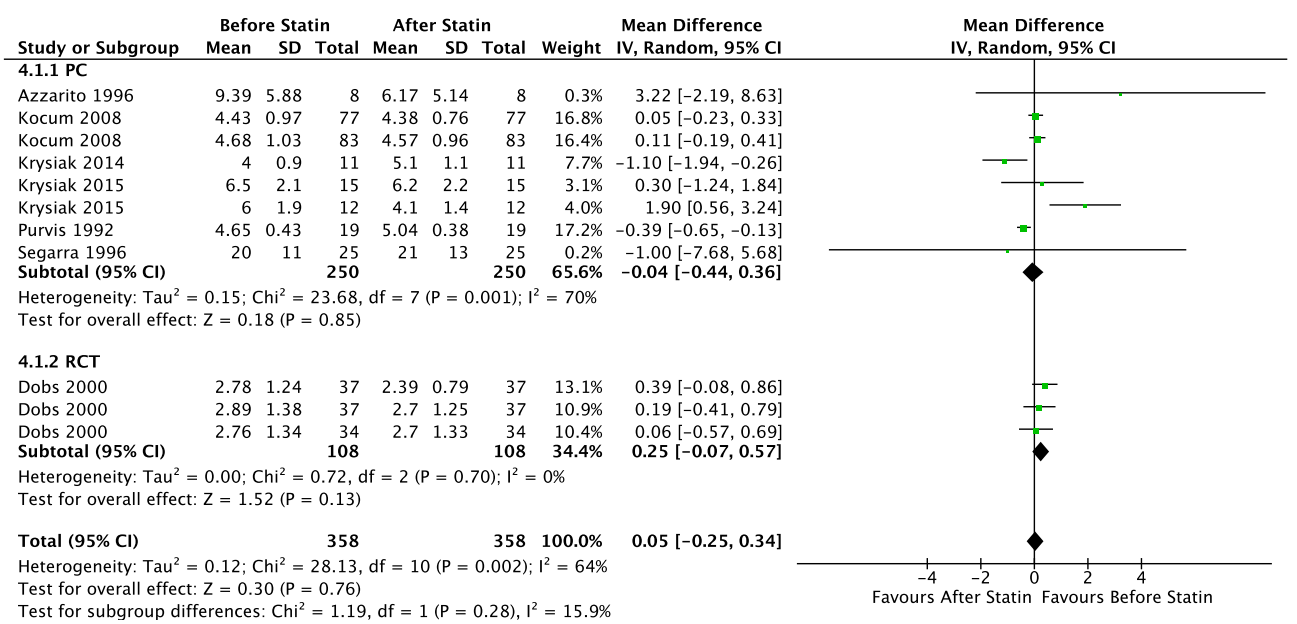


Figure 10 - Estradiol - Cross-sectional studies.

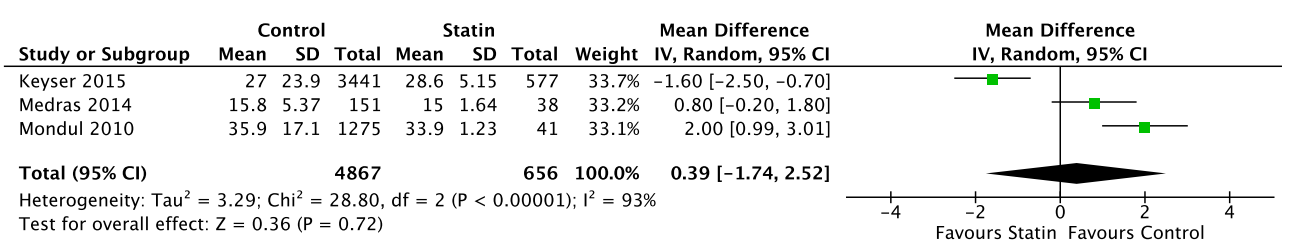


Figure 11 - Estradiol - Before and After - All Prospective Comparative Studies: Prospective Cohort and Randomized Clinical Trial.

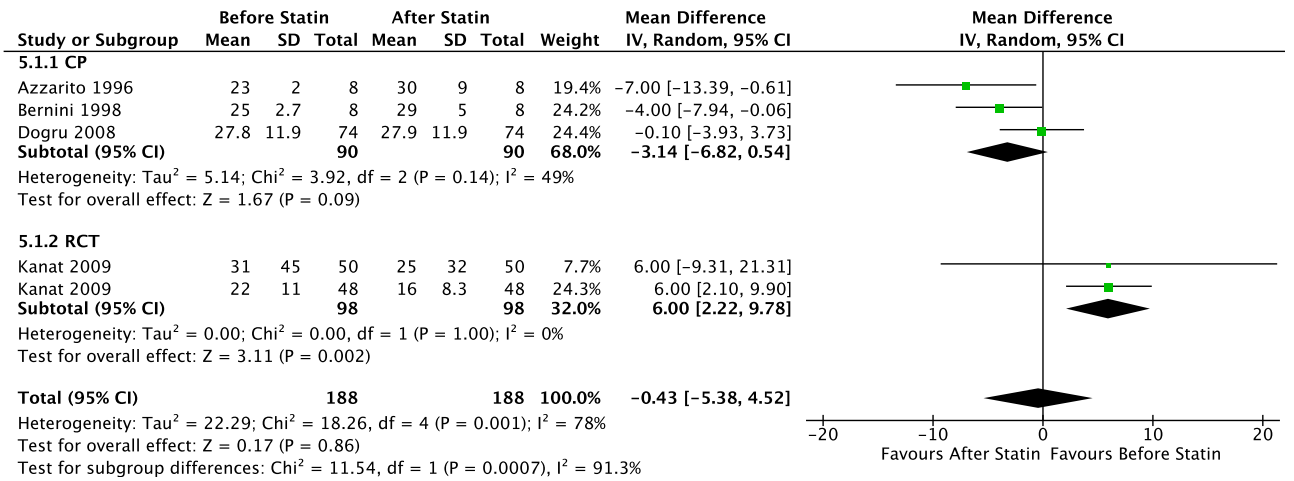


Figure 12 - SHBG - Cross-sectional studies.

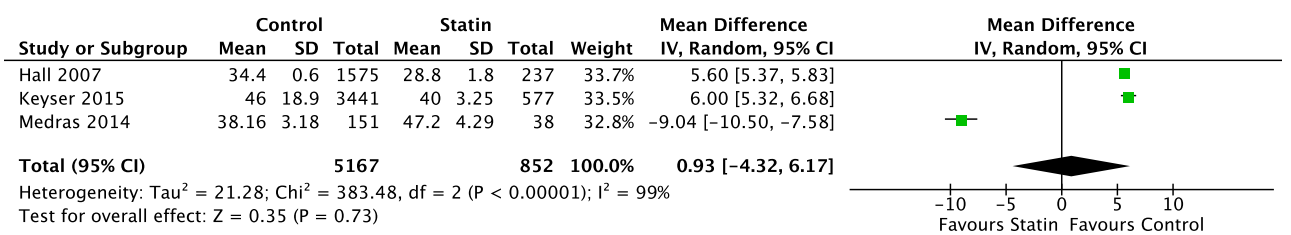
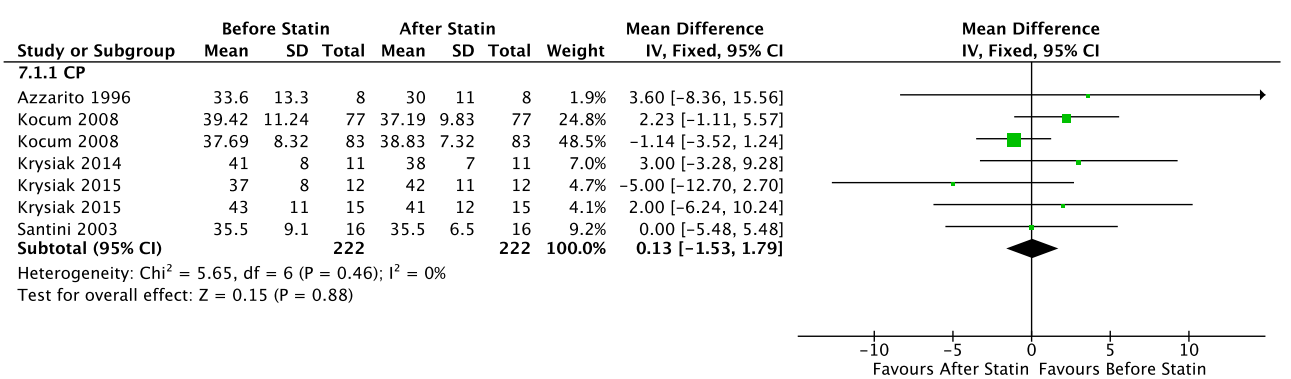


Figure 13 - SHBG - Before and After - Prospective Cohort.



DISCUSSION

This study is a comprehensive systematic review and meta-analysis on the subject, which assesses the role of statins use on male hormones, both in the individual and populational context. Thus, in order not to commit any ecological fallacy, it was only accepted as significant evidence, the analyzes that, when there were population studies, had their statistical result in agreement with the prospective

studies. In addition, the review included all medications in the statin class used in the articles, without selecting one drug over the others, as previous reviews on the subject did, thus allowing for the effect of the class as a whole. Twenty-one articles were included with a total of 9,879 patients evaluated.

Total Testosterone was seen to decrease its mean at all levels of evidence, with the exception of the comparison between groups in the prospective studies. However, this analysis was hampered due to the low number of articles and patients evaluated, shown in the GRADE evidence summary. Therefore, it is possible to affirm that the statin use causes a decrease in the total levels of testosterone. However, these levels on average did not reach below normality, with the exception of Kannat et al. 2009 data, which were already below normality before starting the medication (46).

There was a decrease in Free Testosterone in the cross-sectional study, but no statistical difference was seen in prospective studies, as there was an important decrease in the number of studies that analyzed the variable. Therefore, it is not possible to state that statin causes a decrease in free testosterone.

Analysis of FSH showed a statistically significant increase in the hormone after statin use. As for the analysis of LH, Estradiol and SHBG, it was not possible to identify statistically significant differences (57).

The limitations of the study were the quality of the data, the mode of exposure of the variables, the variability of the medication, the exposure time and the lack of clinical evaluations. For example, patients with metabolic syndrome and obesity are at risk of testosterone deficiency and usually take statins, and those situations were not evaluated in the studies.

Data quality was a limiting factor, as some articles presented the hormonal outcome as a secondary outcome. In addition, the large variability of data measurement units was one of the possible biases, as it was the cause of the inconsistency of the data in the articles, being a reason for the exclusion of some articles. To homogenize the data, it was necessary to convert units, which generate a limitation and a potential error. For this, the conversion was performed and verified repeatedly by more than one author.

The analysis of several drugs grouped, in different doses and different exposure times can be a potential limiting factor of the evidence, but all the articles included used validated drugs, in their therapeutic dose and with a minimum period of 3 months. Furthermore, the study was unable to establish a correlation between the extent of reduction in total cholesterol levels and the decrease in total testosterone levels. Only a few groups of articles were selected, since not all groups fit the eligibility criteria.

It was not possible to assess sexual function and signs and symptoms of hypogonadism as studies did not assess these data.

Limitations of the human selection process, which include potential selection or analysis errors, were mitigated by employing the methodology recommended by PRISMA, as outlined in the methodology section (12).

Regarding practice implications, the results indicate that statin administration is associated with a decrease in testosterone levels. While this decrease is statistically significant, its clinical relevance may not be substantial. However, in patients at high risk or exhibiting symptoms of hypogonadism or ADAM, statins may contribute to clinical symptoms. Concerning future research directions, there is a necessity for further investigation into the potential relationship between statin use and clinical outcomes such as hypogonadism, ADAM, and erectile dysfunction. To elucidate more accurately the impact of statin or cholesterol reduction on testosterone levels and its clinical consequences, well-designed, multicentric randomized clinical trials are essential. These trials should include control groups of patients using benzofibrates and/or engaging in behavioral modifications like dietary changes and increased physical activity.

CONCLUSION

Statins use causes a decrease in total testosterone, not enough to cause a drop below the normal range and also determines increase in FSH levels. No differences were found in LH, Estradiol, SHBG and Free Testosterone analysis

CONFLICT OF INTEREST

None declared.

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Supplementary File 1. Risk of bias analysis Table. Assessed using the The Newcastle-Ottawa Scale (NOS), AXIS tool and the Cochrane tool.

Study ID	Selection				Comparability	Outcome			Total score (out of 9)
	Representativeness of exposed cohort (Maximum:★)	Selection of non- exposed cohort (Maximum:★)	Ascertain ment of exposure (Maximum:★)	Demonstration that outcome of interest was not present at start of study (Maximum:★)	Comparability of cohorts on the basis of the design or analysis (Maximum:★★)	Assessment of outcome (Maximum:★)	Follow Up long enough for outcome occur (Maximum:★)	Adequacy of follow up of cohorts (Maximum:★)	
Purvis, et al. 1992 (37)	★	★	★	★	★	★	-	★	★★★★★★★ (7)
Bernini, et al. 1994 (38)	★	★	★	★	★	★	★	★	★★★★★★★★ (8)
Azzarito, et al. 1996 (39)	★	★	★	★	★	★	★	★	★★★★★★★★ (8)
Segarra, et al. 1996 (40)	★	★	★	★	★	★	★	-	★★★★★★★ (7)
Bernini, et al. 1998 (6)	★	★	★	★	★	★	★	★	★★★★★★★★ (8)
Santini, et al. 2003 (41)	★	★	★	★	★	-	-	★	★★★★★★ (6)
Dogru, et al. 2008 (42)	★	★	★	★	★	-	★	★	★★★★★★★ (7)
Kocum, et al. 2008 (43)	★	★	★	★	★	★	★	★	★★★★★★★★ (8)
Krysiak, et al. 2014 (44)	★	★	★	★	★	★	-	★	★★★★★★★ (7)
Krysiak, et al. 2015 (45)	★	★	★	★	★	★	-	★	★★★★★★★ (7)

Supplementary File 2. GRADE20 table is the summary of evidence.

Author(s):
Question: Does a statin cause a decrease in Testosterone and other hormones in male patients with hypercholesterolenism?
Setting: Patients with Hypercholesterolemia
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statin Use		Relative (95% CI)	Absolute (95% CI)		
Total Testosterone - Cross-sectional studies. Figure 2.I.												
6	observational studies	serious[a]	serious[a]	serious[b]	not serious	publication bias strongly suspected strong association all plausible residual confounding would suggest spurious effect, while no effect was observed[c]	6836	1287	-	MD **55.02 ng/dl higher** (39.4 higher to 70.64 higher)	⨁◯◯◯ Very low	IMPORTANT
Total testosterone - Before and After - Prospective Cohort. Figure 2.II.												
10	observational studies	not serious	not serious	serious[b]	not serious	publication bias strongly suspected[c]	356	356	-	MD **4.01 ng/dl higher** (9.48 lower to 17.5 higher)	⨁◯◯◯ Very low	IMPORTANT
Total testosterone - Before and After - Randomized Clinical Trial. Figure 2.II.												
5	randomised trials	not serious	not serious	serious[b]	not serious	none	289	289	-	MD **13.12 ng/dl higher** (1.16 higher to 25.08 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Total Testosterone - Before and After - All Prospective Comparative Studies. Figure 2.II.												
15	observational studies	not serious	not serious	serious[b]	not serious	none	645	645	-	MD **9.11 ng/dl higher** (0.16 higher to 18.06 higher)	⨁◯◯◯ Very low	CRITICAL
Total Testosterone - Statin X Control - Prospective Cohort. Figure 2.III.												
3	randomised trials	not serious	not serious	serious[b]	serious[d]	publication bias strongly suspected[c]	130	148	-	MD **3.04 ng/dl lower** (60.72 lower to 54.65 higher)	⨁◯◯◯ Very low	CRITICAL
Free Testosterone - Cross-sectional Studies. Figure 2.IV.												
4	observational studies	serious[a]	serious[a]	serious[b]	not serious	none	5411	1096	-	MD **0.6 ng/dl higher** (0.56 higher to 0.64 higher)	⨁◯◯◯ Very low	IMPORTANT
Free Testosterone - Before and After - Prospective Cohort. Figure 2.V.												
2	observational studies	not serious	not serious	serious[b]	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect[c,d]	168	168	-	MD **0.17 ng/dl lower** (0.54 lower to 0.19 higher)	⨁◯◯◯ Very low	IMPORTANT
FSH - Before and After - Prospective Cohort. Figure 2.VI.												
6	observational studies	not serious	not serious	not serious	not serious	none	238	238	-	MD **0.39 IU/L lower** (0.59 lower to 0.19 lower)	⨁⨁◯◯ Low	IMPORTANT
FSH - Before and After - All Prospective Comparative Studies. Figure 2.VI.												
7	observational studies	not serious	not serious	not serious	not serious	none	346	346	-	MD **0.35 IU/L lower** (0.54 lower to 0.15 lower)	⨁⨁◯◯ Low	IMPORTANT
LH - Cross-sectional studies. Figure 3.I.												

REVIEW ARTICLE

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The effectiveness of parasacral transcutaneous electrical nerve stimulation in the treatment of monosymptomatic enuresis in children and adolescents: a systematic review

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ABSTRACT

Background: Parasacral Transcutaneous Electrical Nerve Stimulation (PTENS) is a treatment used in enuresis refractory to first-line treatment. This review aimed to evaluate the effectiveness of PTENS in treating monosymptomatic enuresis (MNE) in children and adolescents.

Methods: The study followed the Preferred Reporting Items for Systematic (PRISMA) guidelines. The search was carried out in the following databases: MEDLINE (via PubMed), Web of Science, SCOPUS, Central Cochrane Library and Physiotherapy Evidence Database (PEDro). The selected studies were randomized clinical trials (RCTs). The "Risk of Bias tool for randomized trials" and the "Risk of Bias VISualization" were used to analyze the risk of bias.

Results: Of the 624 studies selected, four RCTs were eligible. Three included 146 children and adolescents aged between six and 16.3 years and used similar PTENS protocols with a frequency of 10 Hz, pulse duration of 700 µs and 20 minutes three times/week. One study enrolled 52 patients aged seven to 14 years used PTENS at home, with a pulse duration of 200 µs and 20 to 60 minutes twice/day. Risk of bias was observed in three studies due to results' randomization and measurement. Two studies showed a partial response with a reduction in wet nights, one a complete response in 27% of patients, and one showed no improvement.

Conclusion: PTENS reduces wet nights' frequency but does not cure them, except in 27% of patients in one study. Limited RCTs and data heterogeneity are limitations.

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INTRODUCTION

Monosymptomatic enuresis (MNE) is a condition defined by the International Children's Continence Society (ICCS) as isolated intermittent urinary incontinence during sleep in children of five years or above, which occurs once a month for three consecutive months and is not caused by any organic factors. If the child has never achieved urinary continence for more than six months, the condition is defined as primary enuresis, and if a relapse occurs after a dry period of at least six months, it is defined as secondary enuresis. Enuresis is considered infrequent if it occurs less than four times a week and frequent if it occurs four or more times a week (1-4). A recent study showed that 9% of six-year-old children had enuresis, with males being more commonly affected. Of this group, 1.2% were diagnosed with MNE (5).

The exact etiology of enuresis is not yet fully understood. It is considered multifactorial (1,2,6-11). One of the main factors involved in the pathophysiology of enuresis are hereditary factors (1,2, 4-6). Jørgensen et al. (12) revealed 12 protein-coding genes, including PRDM13, S1M1 and EDNRB, which are particularly interesting because they are involved in the three pathophysiological mechanisms of enuresis: excessive production of nocturnal urine (nocturnal polyuria) due to the altered circadian cycle of antidiuretic hormone, disturbances in the function of bladder (reduction in bladder capacity and nocturnal detrusor overactivity) (12, 13) and inability to wake up when you need to urinate (impaired arousal) (14, 15).

In order to diagnose MNE correctly, it is important to conduct a systematic clinical history along with a thorough physical examination (1, 2, 4, 6, 16). To screen for other lower urinary tract symptoms (17-20), psychological and behavioral comorbidities (21), sleep disorders (22), and constipation (23), standardized and validated questionnaires should be used. Additionally, a bladder and bowel diary, dry night diary, and a urinalysis (which includes a urine dipstick to detect glycosuria and leukocytosis) should be ordered (1, 2, 6, 16). If children experience polyuria and polydipsia, it is recommended to test for diabetes insipidus (6). If there is suspicion of neurogenic or anatomical problems in the bladder, additional tests such as urodynamic evaluation may be necessary (16).

Treatment options for MNE include urotherapy, enuresis alarm, and medications such as desmopressin acetate (DDAVP), anticholinergics, and tricyclic antidepressants. A combination of these modalities can also be used (1-4, 6). Currently, the first-line treatments for MNE are considered enuresis alarms and DDAVP (4).

The enuresis alarm is a behavioral or conditioning treatment that requires the participation and motivation of both children and their parents (6), Although it has a success rate of 50 to 70%, it also has a high discontinuation rate (24). However, one of its advantages is the low probability of causing adverse effects (1-4, 6).

DDAVP is a synthetic antidiuretic hormone that reduces urine production during the night (25). Although it is generally safe for long-term use, it can cause water intoxication and hyponatremia, which makes it unsuitable for patients with polydipsia (26). DDAVP has a varying success rate in treating enuretic children. About one-third of patients experience significant improvement; another third reports no change, and the remaining third shows moderate results. However, relapses can occur in up to 70% of cases when the medication is interrupted (25), particularly without structured desmopressin withdrawal, which could help to reduce the risk of relapse (27).

It is estimated that approximately one-third of patients with MNE may require additional treatment after first-line interventions. This can be a challenging situation for pediatricians and urologists (28).

Parasacral transcutaneous electrical nerve stimulation (PTENS) is a treatment modality widely used to manage lower urinary tract dysfunction (LUTD), that failed first-line conservative therapies (29-31). Its mechanism of action in LUTD still needs to be clarified. It is believed that it reorganizes the action or expression of impulses and inhibitory impulses (neurotransmitters or receptors) in the bladder to reverse or recover the organ's function (32, 33). Electric current through the hypogastric nerve activates inhibitory sympathetic neurons and inhibits excitatory parasympathetic neurons (pelvic nerve), promoting central nervous system reor-

ganization and preventing involuntary detrusor muscle contractions (34). Stimulating the sensory afferents S2 and S3 can help regulate involuntary bladder contractions by inhibiting the pontine micturition center. This interruption of excessive detrusor stimulation leads to the restoration of normal micturition reflex. This process, also, causes sensory accommodation by reducing the excitability of ascending sympathetic nerves. (35). Theoretical research suggests that using electrical nerve stimulation during childhood may improve the central and peripheral nervous system's neuroplasticity, leading to potentially better long-term outcomes (36). In addition to its established use in treating overactive bladder, recent randomized clinical trials have demonstrated varying effects of PTENS in treating MNE (29, 37-39). According to Bastos Netto et al. (6) PTENS could be tried in cases where other therapies have failed.

It is essential to understand that children and adolescents with enuresis often have low self-esteem and low quality of life. This medical condition can also negatively impact their academic performance and social life, especially if they are subjected to verbal or physical abuse by their caregivers. Enuresis is typically punished, highlighting the need to educate family members about its involuntary nature and the importance of treatment (40, 41). Thus, finding an effective treatment for children and adolescents with enuresis who do not respond to first-line therapies is crucial. Therefore, this systematic review aims to present the latest literature on the effectiveness of PTENS as a potential treatment option for MNE.

METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement guided this systematic review (42). The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42021269279 (43).

Eligibility criteria

The PICO (Problem or Population, Interventions, Comparison and Outcome or Result) structure was used in the development of the search for an answer to the main question of this review: *Is PTENS effective in treating children and adolescents with MNE?* The acronym PICO in this review stands for:

- P (population or problem): children and adolescents between six and 17 years who have been diagnosed with monosymptomatic enuresis according to ICCS criteria.

- I (intervention): transcutaneous electrical stimulation of the parasacral nerve.

-C (comparison): comparison among children and adolescents who received transcutaneous electrical stimulation of the parasacral nerve and those who did not.

- O (outcome or result): the efficacy of the treatment in reducing the number of wet nights. According to the ICCS criteria, treatment success is categorized into three groups: no-response (<50% symptom reduction), partial response (50 to 99%) and complete response (>100%) (1, 2).

Any articles that involved children or adolescents diagnosed with enuresis but who did not meet ICCS criteria, which used medications that alter the action of the detrusor muscle or external urethral sphincter, which suffered from untreated attention deficit hyperactivity disorder, daytime incontinence, intellectual disability, diabetes mellitus, sickle cell disease, spinal cord injury, spina bifida, radiculopathy, or with urological malformations were excluded from this review.

Literature search strategy

A comprehensive bibliographic search was conducted until September 2023 using the following databases: MEDLINE (via PubMed), Web of Science, SCOPUS, Central Cochrane Library, and Physiotherapy Evidence Database (PEDro). The search terms used were "electrical stimulation", "monosymptomatic enuresis", "bedwetting", "children", and "adolescent". Only Randomized Controlled Trials (RCTs) with no date or language limits were included. Reference checking of selected articles was also conducted to identify additional studies.

Data extraction and storage

Two reviewers independently (MFD and FCCM) examined titles and abstracts to select eligible studies

and filter out duplicates. Afterward, they assessed the studies' titles and summaries to determine the relevant articles. When the reviewers encountered disagreement, they retrieved the full text of the article. Controversies were reconsidered and discussed until a consensus was reached. If controversies persisted, a third reviewer (MMAV) was consulted to make the final inclusion decision. All three reviewers evaluated the full text of the articles that were included in the final selection. To organize the information, a data extraction table was used.

The following data were extracted: study identification (first author, year of publication and country); participants (age, gender, sample size); study design; electrical stimulation variables (therapy type, number of participants in each group, home based PTENS or not, follow up, treatment protocol: pulse frequency, pulse width, number of sessions, frequency and duration of sessions, location of electrode); exclusion of polyuria, refractory to other treatments, key findings, inclusion and exclusion criteria, underwent urotherapy and result evaluation criteria.

All eligible studies were cataloged in an online library system, and those that did not meet the inclusion criteria were excluded, and the reasons for exclusion were documented.

Assessment of risk of bias of individual studies

The analysis of the studies' risk of bias included in this review was carried out using the tools "Risk of Bias tool for randomized trials" (Rob 2.0) (44) and "Risk of Bias VISualization (RoBVIS) (45). RoB 2.0 addresses five specific domains: (1) randomization bias; (2) bias from deviations from intended interventions; (3) bias regarding lack of outcome data; (4) bias in outcome measurement; and (5) bias in outcome selection (44). Two reviewers (EC and EML) utilized the tool independently. Discrepancies were resolved through discussion, with a third author (FCCM) acting as a referee when necessary.

Methodological quality

To assess the methodological quality of clinical trials was used the PEDro scale. It assesses 11 items related to the study internal validity (two to nine) and statistical reporting (10 and 11), except for the first one (eligibility criteria), which is not computed in the total score (46). Scores of this scale range from zero to ten: scores <four indicate poor methodology, between four and seven fair quality, and from seven to ten higher quality (47). The scale was initially applied by two independent reviewers (MFD and FCCM), and in case of any disagreements, a third reviewer (MMAV) was consulted.

RESULTS

Study Selection

A total of 624 studies were selected, with 103 results in MEDLINE (via PubMed), 267 in SCOPUS, 211 in Web of science, 38 in Central Cochrane Library and five in PEDro database. After the first screening, 353 were removed. Then, 100 were excluded based on title, 171 by the summary and eight were eligible to read the full text. One was excluded because of diagnostic criteria monosymptomatic enuresis and electrical stimulation of the posterior tibial nerve and three because other electro stimulation techniques were used. Figure-1 shows the flowchart summarizing the literature search process, following the PRISMA statement (42).

Studies and participants characteristics

This review involved a total of 146 participants with MNE, ranging in age from six to 16.3 years. The intervention group (PTENS) had 92 participants, while the control group (CG) had 54 participants. One study did not have a control group and compared a group of 26 participants using PTENS to another group of 26 participants using transcutaneous interferential electrical stimulation, aged between seven and 14 years (39). Two studies did not have a placebo (37, 39). No statistical difference was found between genders. All studies were published between 2013 and 2023 and were randomized controlled trials (RCTs) (37-39, 48). These studies and participants' characteristics are shown in Table-1.

The study's general characterization is presented in tables to help analyze their methodological quality. Table-2 provides details on the methods used in each study, including inclusion and exclusion criteria and the criteria used to evaluate treatment's effectiveness. Table-3 shows the treatment protocol used by each author,

Figure 1 - Flowchart with the research methodology following PRISMA guidelines.

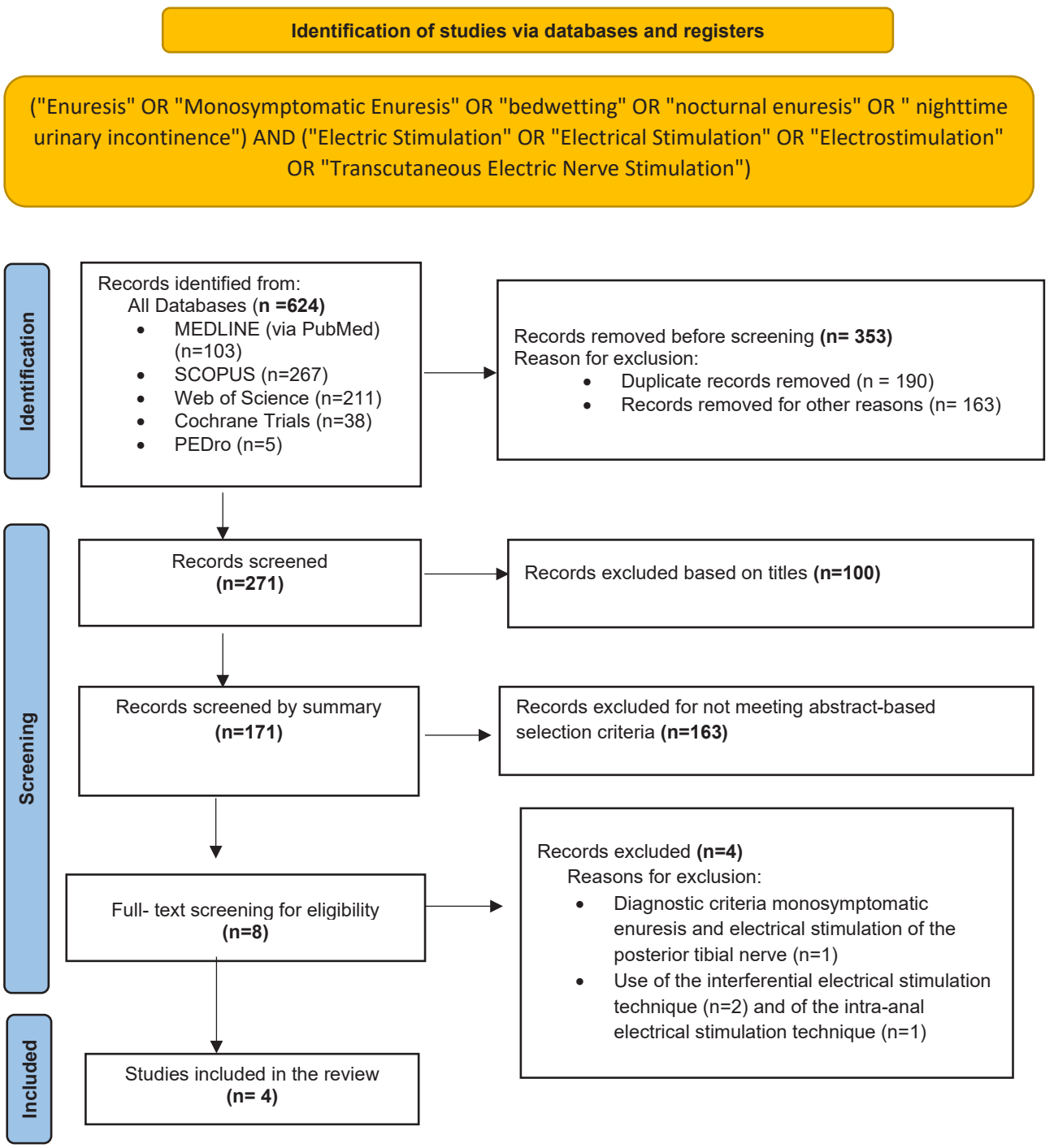


Table 1 - Sociodemographic characteristics of the included studies.

Study	Country	N	Male %	Age years Median interquartile range Mean ± SD	Study design
de Oliveira et al. 2013 (37)	Brazil	45	CG/CI: 50	CG: 9.9 ± 2.7 Range: 6.2-16.3 CI: 9.8 ± 2.9 Range: 6.3-14.1 (p=0.92)	RCT
Jorgensen et al. 2017 (48)	Denmark	47	CG: 74 IG: 88 (p=0.24)	CG: 9.1 ± 2.0 Range: 6-14 CI: 9.8 ± 2.2 Range: 6-14 (p=0.23)	RCT Double-Blind
Abdelhalim & Ibrahim, 2020 (39)	Egypt	52	PTENS G: 61.5 IFC G: 65.4 (p=0.77)	PTENS G: 10.9 ± 2.5 Range: 7-14 IFC G:10.3 ± 2.1 Range: 7-14 (p=0.35)	RCT single-blind
Oliveira et al. 2023 (38)	Brazil	28	CG: 33.3 IG: 37	CG: 8.76 ± 1.91 IG: 9,36 ± 2,52 (p=0.56) Not described median	RCT

SD = standard deviation; RCT = randomized controlled trial; IG = intervention group; CG = control group; PTENS = parasacral transcutaneous nerve stimulation; TIES = transcutaneous interferential electrical stimulation.

including information on follow-up, PTENS parameters such as pulse duration and frequency, number and duration of sessions, electrode location, and main findings.

Protocol and procedures

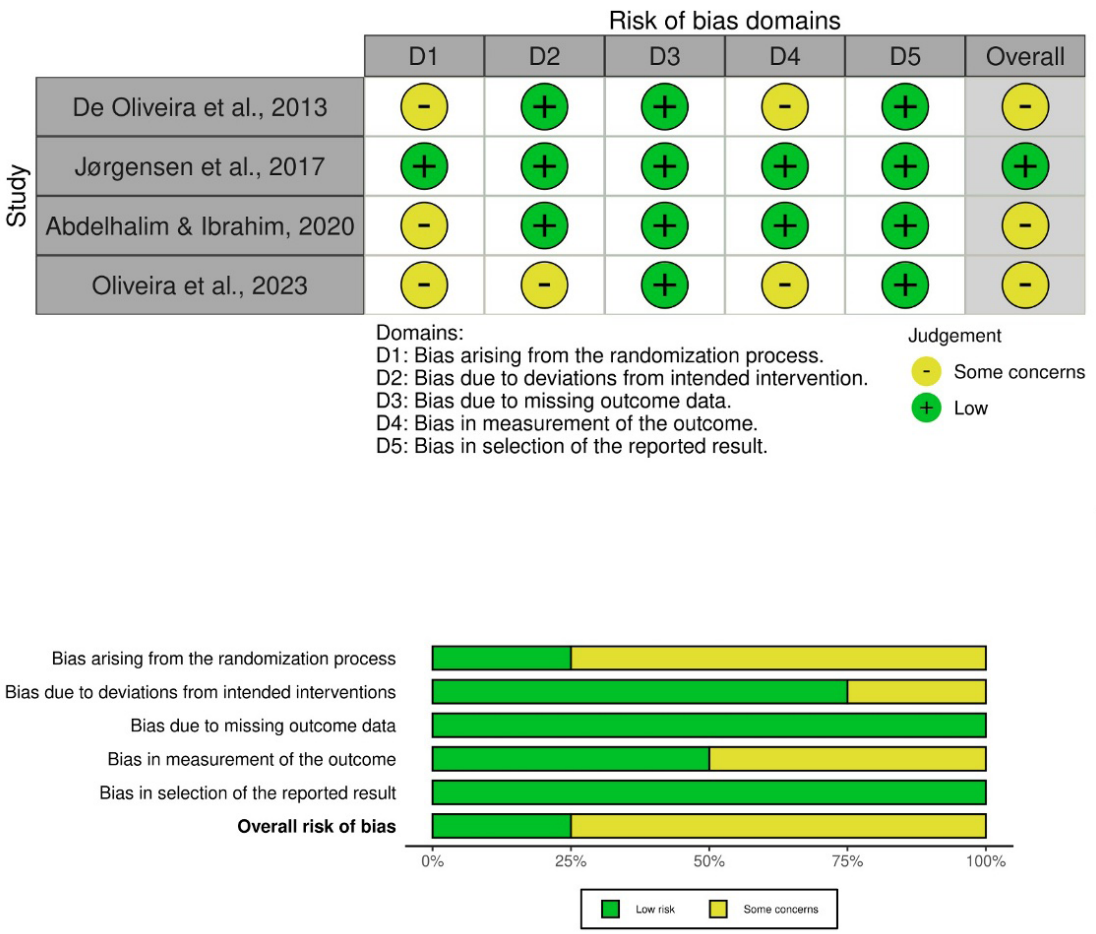
The studies used similar PTENS protocols. All of them used the same electrode location (S2/S3 sacral region) and the same frequency (10Hz) (37-39,48). Three studies used the same pulse duration (700μs), therapy time (20 minutes), and therapy frequency (three times a week) (37-39). Only Jorgensen et al. (48) used home-based PTENS with a pulse duration of 200μs, 60 minutes of application per day and a therapy frequency of twice a day. The total number of sessions varied between ten and 140, and the follow-up between 90 days and six months (Table-3).

Two studies used a minimum age of six years as an inclusion criterion (38, 48), one of five years (37) and the others, of seven years (39). All studies excluded patients with non-monosymptomatic enuresis, secondary enuresis, and neurological disease (37-39, 48). One study also excluded a patient with polyuria (48). More details are described in Table-2.

Risk of bias assessment

The risk of bias summary of the four included studies is shown in Figure-2. One study showed low risk of bias in all domains (48), and the other three showed

Figure 2 - Summary and graph of the risk of bias for the included studies based on the Risk of Bias tool for randomized trials -ROB 2.0.



some concerns, mainly arising from randomization and outcome measurement (37-39).

Methodological quality

The evaluation of methodology's quality is explained in detail in Table-4. Two studies received a score of five on the PEDro scale (37, 38) and one a score of seven (39), showing reasonable quality indicating a limited level of evidence regarding the benefits of PTENS in enuresis. Another study was classified as higher quality, with a score of ten (48). The most common methodological flaws were the absence of allocation concealment, blinding of patients, therapists and evaluators, and intention-to-treat analysis.

Main findings

This review assessed the efficacy of PTENS in MNE based on the number of wet nights, according to ICCS criteria, in four selected RCTs (37-39,48). A single study described a complete response to treatment in 27% and 19.8% of patients immediately and six months after the last session, respectively (39).

In a study conducted by de Oliveira et al. (37), children and adolescents with MNE were randomly assigned to two groups. The first group was treated with a standard urotherapy, while the second group was treated with both standard urotherapy and PTENS. The results showed that the second group (IG) had a significant improvement in wet nights of 61.8%, while the

Table 2 - Description of the methods of the included studies.

	Inclusion criteria	Exclusion criteria	Behavioral therapy	Criteria used for treatment evaluation	N Inicial/ final
de Oliveira, et al. 2013 (37)	Children older than 6 years diagnosed with primary MNE according to ICCS criteria	Children aged less than 6 years, presence of non-MNE or secondary enuresis, history of treatment for enuresis in the 6 months prior to study entry, and presence of urinary tract infection. neurological, psychiatric, or renal disease.	Yes	A decrease of less than 50% on wet nights determined no response, a decrease of 50% to 89% constituted a partial response, and a decrease of more than 89% indicated a response. To calculate the mean rate of improvement on wet nights for CG and IG, the formula %¼ improvement [100 e (wet days after treatment/wet days before treatment)] was used.	45/38
Jorgensen et al. 2017 (48)	Children aged 6 to 14 years diagnosed with primary MNE, with a frequency of at least 3 nights per week and no treatment for nocturnal enuresis 1 week until the start of TENS treatment (2 weeks for enuresis alarm).	Children with nocturnal polyuria (defined as a nighttime urine volume greater than 130% of expected bladder capacity for age), ongoing constipation, and/or fecal incontinence; previous or continuous treatment with PTENS, presence of lower urinary tract infection, neurological or anatomical alterations of the urinary tract, or children undergoing operations on the urinary tract.	Yes	Non-response (less than 50% reduction in wet nights), partial responders (50% to 99% reduction) or complete responders (total dryness).	52/52
Abdelhalim & Ibrahlm, 2020 (39)	Children and adolescents aged 7 to 14 years diagnosed MNE according to the ICCS with a history of three nights of nocturnal enuresis every week without any enuresis treatment for at least 1 month before the beginning of the study.	Children with neurological and/or psychological disorders, diagnosed with non-monosymptomatic or secondary enuresis, congenital anomalies, type I diabetes, urinary tract infection, and chronic constipation.	Yes	Non-response (0–49% wet nights reduced), partial response (50–89% wet nights reduced), good response (90% or more wet nights reduced), and full response (100% wet nights reduced); The percentage of progression % equal to [(number of wet nights pre-treatment) – (number of wet nights post-treatment)/ (number of wet nights pre-treatment] × 100	59/47
Oliveira et al. 2023 (38)	Children older than 5 years diagnosed with primary MNE and not being treated for enuresis or had any treatment in the past 6 months.	Families who showed no interest in participating in the study, those who had difficulty understanding the study objectives, patients with neurological, psychiatric, renal diseases, non-MNE and/or secondary enuresis.	Yes	Not described	72/45

MNE = monosymptomatic nocturnal enuresis; ICCS = International Children's Continence Society; TENS = transcutaneous electrical nerve stimulation; CG = control group; IG = intervention group.

Table 3 - Descriptive summary of parasacral transcutaneous nerve stimulation data from included studies.

Study	Treatment protocol												
	Therapy in IG	Therapy in CG	IG (n)	CG (n)	Home-based PTENS	Follow-up	Pulse Frequency/ Intensity	Pulse width (µs)	Number, frequency, and duration of sessions	Location of electrode	Exclusion of polyuric	Refractory to other treatments	Key findings
de Oliveira et al. 2013 (37)	PTENS	No placebo	27	18	No	6 months	10Hz	700	10 sessions 3/ week 20 min	Sacral S2/S3	No	-	Improvement in MNE frequency was significant better in the EG (61.8%) when compared to CG (37.3%) No patient had complete resolution of symptoms. Combination of PTENS and behavioral therapy decreased more the percentage of wet nights compared to behavioral therapy alone.
Jorgensen et al. 2017 (48)	PTENS	Placebo	24	23	Yes	10 weeks	10Hz. Intensity was the highest tolerable level up to a maximum of 40mA.	200	140 home sessions 2/ day 60min	Sacral S2/S3	Yes	Yes (33)	No effect of PTENS treatment in participants without nocturnal polyuria, on MNE episodes, nocturnal urine production, or bladder reservoir function.
Abdelhalim & Ibrahim, 2020 (39)	PTENS & TIES	No placebo No CG	PTENS: 26 TIES: 26	-	No	6 months	PTENS: 10Hz, with current intensity slowly increased to tolerance. TIES: 4000Hz	700	18 sessions 3/week 20 min	PTENS: Sacral S2/S3 TIES: Bilaterally placed on the symphysis pubic skin and the two other electrodes were crossly placed on the contralateral ischial tuberosity skin area.	No	-	The MNE frequency episodes reduced significantly and had improvement of quality of life in both groups.
Oliveira et al. 2023 (38)	PTENS	Placebo	15	13	No	T1: after 20th session T2: 15 days after treatment T3: 30 days after treatment T4: 60 days after treatment T5: 90 days after treatment	10Hz	700	20 sessions 3/week 20 min	Sacral S2/S3	No	-	No patient had complete resolution of symptoms. The IG had a progressive reduction in the number of dry nights over 90 days of follow-up, while the CG did not maintain the improvement. Combination of PTENS and urotherapy decreased more the percentage of wet nights compared to urotherapy alone.

IG = intervention group; CG = control group; PTENS = parasacral transcutaneous nerve stimulation; TIES = transcutaneous interferential electrical stimulation.

Table 4 - Quality analysis of studies included in the Physiotherapy Evidence Database (PEDro) Scale.

PEDro scale	de Oliveira et al. 2013 (37)	Jorgensen et al. 2017 (48)	Abdelhalim & Ibrahim, 2020 (39)	Oliveira et al. 2023 (38)
1. Eligibility criteria were specified.	Yes	Yes	Yes	Yes
2. Patients were randomly allocated to groups (in a crossover study, they were randomly allocated to groups according to the treatments received)	Yes	Yes	Yes	Yes
3. Allocation concealed	No	Yes	Yes	No
4. Groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	No	Yes
5. Blinding of all patients	No	Yes	No	No
6. Blinding of all therapists who administered the therapy	No	Yes	No	No
7. Blinding of all assessors who measured at least one key outcome	No	Yes	Yes	No
8. Measures of at least one key outcome obtained from more >85% of the patients initially allocated to groups	Yes	Yes	Yes	Yes
9. All patients for whom outcome measures were available received treatment or sham as allocated or, where this was not the case, data for at least one key outcome were subjected to intention-to-treat analysis	No	Yes	Yes	No
10. Results of between-group statistical comparisons were reported for at least one key outcome	Yes	Yes	Yes	Yes
11. Study provided both point measures and measures of variability for at least one key outcome	Yes	Yes	Yes	Yes
Total score	**5**	**10**	**7**	**5**

first group (CG) only had an improvement of 37.3% (p=0.003). However, no patient in either group achieved complete improvement.

Jorgensen et al. (48) compared children randomized in two groups, both were treated with a standard urotherapy. The IG received home-based PTENS therapy, while the CG received sham home-based PTENS therapy. However, there was no reduction in the number of wet nights, nocturnal urine production or bladder reservoir function characteristics.

In a study conducted by Abdelhalim & Ibrahim (39), two different modes of treatment were compared - PTENS and transcutaneous interferential electrical stimulation. The study found that both modes of treatment led to a significant decrease in the number of wet nights and an improvement in the participants' quality of life. However, the group that received transcutaneous interferential electrical stimulation showed greater immediate and short-term improvements sustained over a more extended period than the PTENS group ($p < 0.05$).

According to the latest study conducted by Oliveira et al. (38), both the CG and IG were given standard urotherapy. However, the IG received an additional treatment of PTENS, while the CG received a placebo version of PTENS. Four evaluations were carried out after the intervention, the first, immediately, after the intervention and the last 90 days later. There was a progressive improvement in the number of dry nights in each evaluation, with a significant improvement in IG comparing the pre-treatment values with the values found after 90 days ($p<0.00$).

DISCUSSION

This review aimed to answer whether the PTENS is effective in treating MNE in children and adolescents. Although there are few randomized clinical trials available, this review found that PTENS can effectively reduce the number of wet nights per week, but in most cases, it only shows a partial response. The included studies are heterogeneous, making them unsuitable for meta-analysis. Despite the differences, in all the studies, the children in both groups received urotherapy and used the same electrostimulation frequency parameter (10Hz) (37-39). Only one of the articles used different methods, and the therapy was conducted at home (48). Interestingly, this was the only study that found no improvement in any of the outcomes assessed. This outcome prompts us to consider two reflections. Firstly, the significance of the parameters that were used, and secondly, the quality of the technique that was employed.

PTENS has shown promising results in treating other types of LUTD, such as overactive bladder and non-monosymptomatic enuresis (29, 30, 31). Although there is no agreed-upon definition of the optimal parameters to be used, most of the studies utilize the same parameters as those used by de Oliveira et al. (37), Abdelhalim & Ibrahim (39), and Oliveira et al. (38). Furthermore, the technical quality of the intervention carried out by a trained professional is undoubtedly better when compared to the technique of a lay person. In this case, appropriate positioning of electrodes and adjusting the current amplitude to the maximum sensory threshold can improve the therapeutic response. However, Jørgensen et al. (48) did not fully address these two requirements in the study.

Although the exact PTENS' mechanism of action is still unclear, a study conducted by Netto et al. (49) has shown increased connectivity between the anterior cingulate cortex and the dorsolateral prefrontal cortex. This leads to a balance of sympathetic and parasympathetic stimuli in the bladder, promoting central nervous system reorganization and preventing involuntary detrusor muscle contractions, as demonstrated by Lindstrom et al. (50). Considering that one of the tripods in the pathophysiology of enuresis is detrusor hyperactivity, it is expected that PTENS will have a positive effect on at least this causal factor. In a recent meta-analysis, several treatments for overactive bladder in children were compared for their effectiveness and safety. The study found that PTENS was the best therapeutic option for improving maximum urinary volume, followed by urotherapy when compared to antimuscarinics. (51) It is known that as bladder capacity increases, it becomes possible to store more urine, which may be enough to accommodate urine production during sleep without the need to urinate.

It is still being determined whether standard urotherapy should be the first line of treatment for MNE (52). However, it is established that it can be used to treat other types of LUTD. Its effectiveness seems to be related to the greater intensity of treatment (53). In this review, studies that performed PTENS in person had a greater opportunity to reinforce standard urotherapy with frequent contact with the professional, which could be considered a confounding factor.

Two studies have demonstrated that symptoms gradually improve over the course of treatment (37, 38). The first study, conducted by de Oliveira et al. (37), involved only ten sessions, while the second study (38) involved 20 sessions. Both studies found that patients responded positively to treatment. We were unable to find any other clinical trial that investigated the relationship between the number of sessions and the gradual improvement of MNE. However, Veiga et al. (54) conducted a survey to evaluate the effectiveness of PTENS in overactive bladder per session. They observed that improvement occurred gradually, with more significant improvement after the 13th session. The improvement curve continued to increase until the end of the treatment at the 20th session. It was suggested that if treatment continued beyond the 20th session, an increased number of patients would have showed improvement.

A recent systematic review showed that using PTENS to treat enuresis is of no benefit. However, it is worth highlighting that this review included studies with patients who had non-monosymptomatic enuresis (55). In contrast, our review focused only on patients with monosymptomatic enuresis and found that PTENS can effectively reduce the number of wet nights. However, only one of the RTCs (39) showed complete remission in 27% of patients. We believe that the effectiveness of the treatment depends on the parameters used and the correct treatment technique applied by the professional. Effective treatment of enuresis is crucial due to its prevalence and impact on the quality of life of children and their families. (4, 40, 56). Although first-line therapies are well established, they are often ineffective and have high discontinuation rates (4, 24, 25). Therefore, it is essential to have robust studies that prove the effectiveness of alternative treatments such as PTENS.

It's worth noting that there are certain limitations to this review. Firstly, we only included a few studies due to our strict inclusion criteria, which involved complying with the ICCS guidelines and selecting only randomized controlled trials. Another limitation was the relatively small sample sizes of the studies. Additionally, due to the heterogeneous nature of the data, it was not possible to conduct a meta-analysis.

CONCLUSION

According to the review, PTENS can reduce the occurrence of wet nights in children and adolescents with MNE. However, it is not a complete cure for the condition, except for one study that reported a 27% cure rate among patients. To determine the most effective protocol for this treatment, more high-quality research is needed. Comprehensive evaluation of its effectiveness will require larger samples and more sessions.

ABBREVIATIONS

BVS = Biblioteca virtual em saúde
CG = Control group
DDAVP = Desmopressin acetate
ICCS = International Children´s Continence Society
IG = Intervention group
LUTD = Lower urinary tract dysfunction
MNE = Monosymptomatic enuresis
PEDro = Physiotherapy Evidence Database
PICO = Problem or Population, Interventions, Comparison and Outcome
PRISMA = Preferred Reporting Items for Systematic
PROSPERO = International Prospective Register of Systematic Reviews and Meta-Analyses
PTENS = Parasacral transcutaneous electrical nerve stimulation
ROB2 = Risk-of-bias in randomized trials
ROBVIS = Risk-of-bias visualization

RTCs = Randomized controlled trials
TIES = Transcutaneous interferential electrical stimulation

COMPLIANCE WITH ETHICAL STANDARDS

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CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Postoperative antibiotic prophylaxis for percutaneous nephrolithotomy and risk of infection: a systematic review and meta-analysis

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ABSTRACT

Purpose: The aim of this study is to perform a high-quality meta-analysis using only randomized controlled trials (RCT) to better define the role of postoperative antibiotics in patients undergoing percutaneous nephrolithotomy (PCNL).

Materials and Methods: A literature search for RCTs in EMBASE, PubMed, and Web of Science up to May 2023 was conducted following the PICO framework: Population—adult patients who underwent PCNL; Intervention—postoperative antibiotic prophylaxis until nephrostomy tube withdrawal; Control—single dose of antibiotic during the induction of anesthesia; and Outcome—systemic inflammatory response syndrome (SIRS) or sepsis and fever after PCNL. The protocol was registered on the PROSPERO database (CRD42022361579). We calculated odds ratios (OR) and 95% confidence intervals (CI). A random-effects model was employed, and the alpha risk was defined as < 0.05.

Results: Seven articles, encompassing a total of 629 patients, were included in the analysis. The outcome of SIRS or sepsis was extracted from six of the included studies, while the outcome of postoperative fever was extracted from four studies. The analysis revealed no statistical association between the use of postoperative antibiotic prophylaxis until nephrostomy tube withdrawal and the occurrence of SIRS/sepsis (OR 1.236, 95% CI 0.731 – 2.089, p=0.429) or fever (OR 2.049, 95% CI 0.790 – 5.316, p=0.140).

Conclusion: Our findings suggest that there is no benefit associated with the use of postoperative antibiotic prophylaxis until nephrostomy tube withdrawal in patients undergoing percutaneous nephrolithotomy (PCNL). We recommend that antibiotic prophylaxis should be administered only until the induction of anesthesia in PCNL.

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INTRODUCTION

Currently, percutaneous nephrolithotomy (PCNL) stands as the gold standard treatment for kidney stones larger than 20 mm (1). However, infectious complications in PCNL pose a significant life-threatening concern. Fever is estimated to occur in up to 18% of patients, systemic inflammatory response syndrome (SIRS) in up to 35%, and sepsis in up to 6% (2-5). The use of antimicrobials in the perioperative period is a topic of ongoing discussion among specialists. There is currently no consensus regarding the optimal regimen and timing for administering antibiotics to these patients (1).

Although there is currently no evidence supporting the benefit of prophylaxis extended beyond 24 hours or until the removal of catheters, it is noteworthy that many urologists continue to use postoperative antibiotics until nephrostomy tube withdrawal (6-8). Urological guidelines explicitly state that there is no added benefit beyond single-dose prophylaxis (1). However, this statement is grounded in limited randomized controlled trials (RCTs). Our hypothesis posits that a meta-analysis could contribute a higher level of evidence on this subject, aiding urologists in adopting the best available practices. Presently, there is no meta-analysis that selects articles with a substantial number of patients to provide evidence against the prescription of antimicrobials until tube and nephrostomy removal. The practice of antibiotic maintenance remains prevalent in prescriptions worldwide. The objective of this study is to conduct a high-quality meta-analysis utilizing only RCTs to define the role of postoperative antibiotics in patients undergoing PCNL.

MATERIALS AND METHODS

Identification and Eligibility of Trials

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (9). We exclusively included RCTs that compared a single dose of antibiotic during the induction of anesthesia with postoperative antibiotic prophylaxis until nephrostomy tube withdrawal in patients undergoing PCNL. Articles were retrieved from the EMBASE, PubMed, and Web of Science databases up to May 2023. Exclusion criteria encompassed observational and retrospective studies, case reports, case-control studies, letters to the editor, editorials, congress abstracts, and studies involving patients under 18 years old. The meta-analysis protocol was duly registered on the PROSPERO database on October 1, 2022 (CRD42022361579).

Development of Prospective Meta-analysis Protocol

The PICO (Population, Intervention, Control, and Outcome) framework was established prior to data collection, as follows:

- Population: Adult patients (> 18 years old) who underwent PCNL.
- Intervention: Postoperative antibiotic prophylaxis until nephrostomy tube withdrawal.
- Control: Single dose of antibiotic administered during the induction of anesthesia.
- Outcome: SIRS or sepsis, and fever after PCNL.

Outcomes and Comparisons

The primary outcome measure for this study was SIRS or sepsis after PCNL, with a comparison between a single dose of antibiotic during the induction of anesthesia and postoperative antibiotic prophylaxis until nephrostomy tube withdrawal. The secondary outcome was the occurrence of fever after PCNL. The definition of SIRS or sepsis was based on the criteria specified in each individual study (10, 11).

Assessment of risk of bias in included studies

The assessment of risk of bias was conducted independently by two investigators, and any discrepancies were resolved through agreement. The risk of bias for each RCT was evaluated using version 2 of the Cochrane Risk of Bias Assessment Tool (RoB 2). RoB 2 is organized into domains of bias, encompassing trial design, conduct, and reporting of results, and is classified as unclear, low, or high risk (12).

Data Analyses

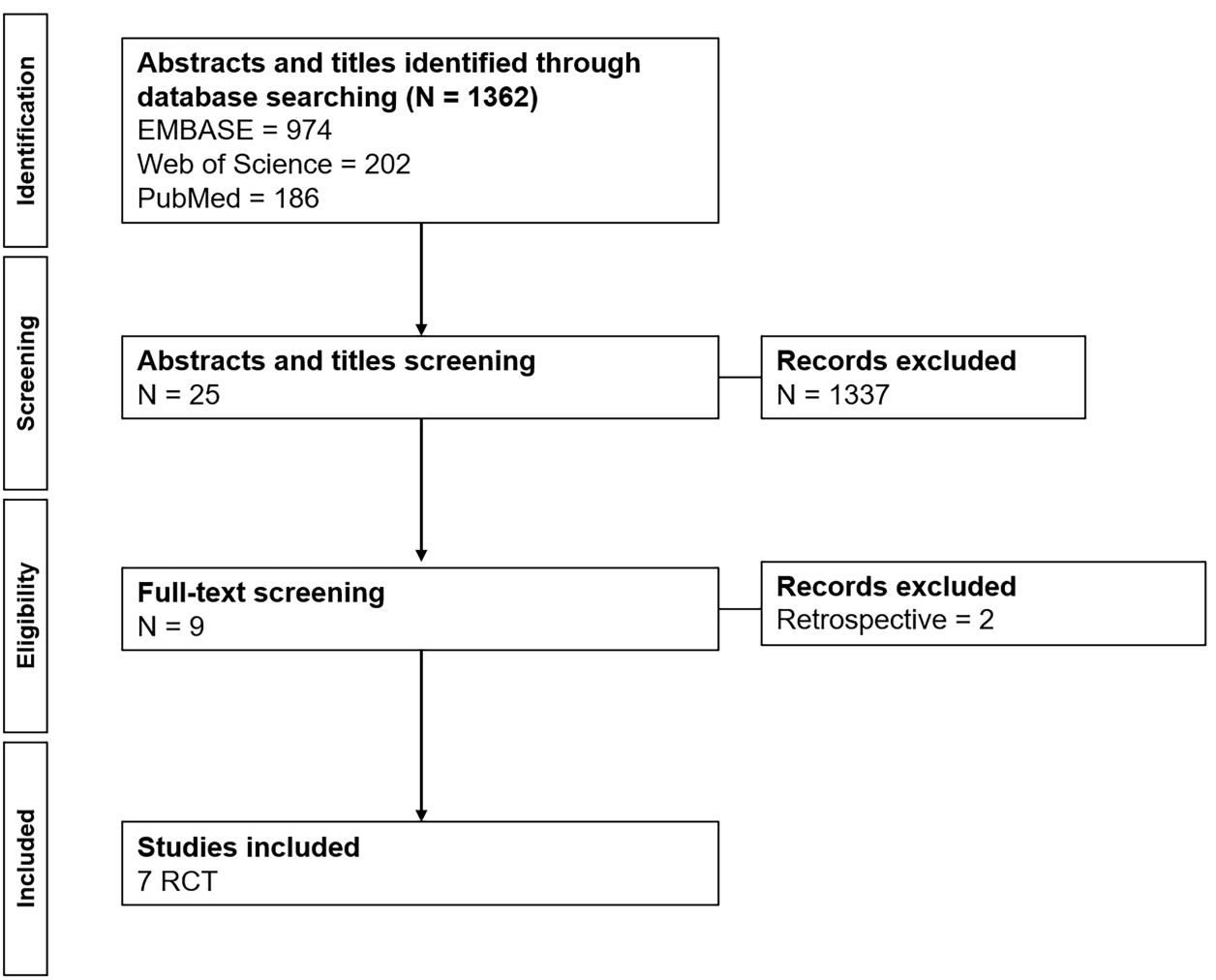
All analyses were conducted using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). The primary outcome was extracted from six out of the seven included studies, while the secondary outcome was extracted from four out of the seven included studies. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each study to assess differences among them. Heterogeneity was evaluated using the Chi-squared test and I2. A random-effects model was applied. The alpha risk was defined as < 0.05.

RESULTS

Search results and selection process

In May 2023, a search strategy for "percutaneous nephrolithotomy" and "antibiotic" was executed on EMBASE (974 results), PubMed (197 results), and Web of Science (202 results) platforms, yielding a total of 1362 publications, as illustrated in Figure-1. Screening of abstracts and titles was performed, resulting in the exclusion of all studies that were not RCTs. Following full-text screening, seven RCTs were ultimately chosen, and two retrospective studies were excluded from the final selection. Consequently,

Figure 1 – PRISMA flowchart.



the final set comprised seven RCTs, involving a total of 629 patients.

Risk of bias

All studies demonstrated low risk regarding reporting bias but were not clear about selection, performance, and detection bias according to RoB 2 criteria (Figure-2).

Specifically, Demirtas 2012 was deemed high risk in selection bias because "patients were divided into two groups according to prophylactic antibiotic," and Seyrek 2012 was considered unclear because "patients were randomized into two groups according to the type of antibiotic used" (13, 14).

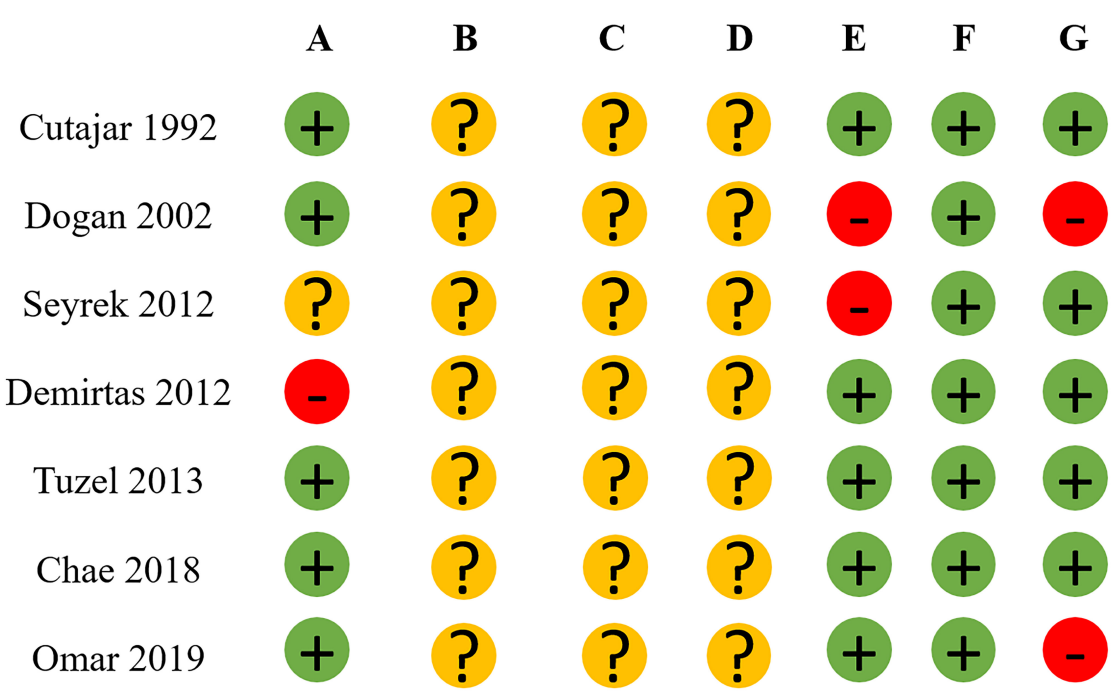
Regarding attrition bias, Dogan 2002 and Seyrek 2012 were categorized as high risk because "urine and blood culture were taken only from febrile patients" and "after randomization, 7 patients were excluded because of purulent urine from the access needle," respectively (14, 15).

In terms of other bias, Dogan 2002 reported a "high rate of resistance to fluoroquinolones in isolated bacteria," and Omar et al. 2019 used two different antibiotics (15, 16).

Characteristics of included studies

Cutajar 1992 conducted one of the pioneering studies comparing antimicrobial regimens in patients undergoing PCNL. In this early investigation, 70 patients undergoing the procedure were divided into two groups: one receiving a single dose of cefuroxime or norfloxacin during the induction of anesthesia and six additional doses after surgery. The study found no significant difference between the groups in terms of outcomes related to sepsis, bacteriuria, and bacteremia (17).

Figure 2 – Risk of bias of randomized controlled trials.



A) Random sequence generation (selection bias); B) Allocation concealment (selection bias); C) Blinding of participants and personnel (performance bias); D) Blinding of outcome assessment (detection bias); E) Incomplete outcome data (attrition bias); F) Selective reporting (reporting bias); G) Other bias.

Dogan 2002 conducted a comparative study involving 81 patients undergoing PCNL, comparing a single dose of antibiotic during the induction of anesthesia with postoperative antibiotic prophylaxis until nephrostomy tube withdrawal. The study found no significant difference between the groups concerning bacteriuria, bacteremia, positive stone cultures, and postoperative fever. Notably, the factors associated with postoperative fever were a duration of surgery ≥ 102 minutes (p = 0.011) and the use of at least 23 L of irrigation fluid (p = 0.028) (15).

Seyrek et al. 2012 conducted a RCT involving 191 patients to assess the impact of postoperative antibiotic therapy in patients undergoing PCNL. The population was divided into two large groups based on the chosen antimicrobial (ampicillin-sulbactam and cefuroxime), and these groups were further divided into subgroups receiving single-dose prophylaxis, an additional dose 12 hours after prophylaxis, and prophylactic dose until nephrostomy tube removal. The analysis of the SIRS outcome showed no significant difference between groups (p = 0.44). The authors concluded that a single-dose administration is sufficient to prevent infectious complications (14).

Demirtas et al. 2012 conducted a study on 90 patients undergoing PCNL who were administered either ciprofloxacin or ceftriaxone. The patients were further divided into subgroups based on the drug dosage: a single dose during the induction of anesthesia, antibiotic until 12 hours after surgery, and antibiotic until nephrostomy removal. The study concluded that there was no significant difference in SIRS outcomes with respect to the use of antimicrobials (p = 0.52). Additionally, the study demonstrated no statistical association between the positivity of stone culture, renal pelvis urine culture, and postoperative urine culture in the development of SIRS in the population (13, 15).

Tuzel et al. 2013 compared 36 patients using ceftriaxone during the anesthetic induction of PCNL with 37 patients using third-generation oral cephalosporin until the removal of the nephrostomy tube. The study found no difference between the groups when evaluating outcomes such as fever (p = 0.52), positive culture of the renal pelvis (p = 0.32), stone (p = 0.47), and urine culture on the day of nephrostomy removal (p = 0.54). The conclusion drawn was that a single-dose regimen could be recommended for patients undergoing PCNL (18).

Chae et al. 2018 conducted a study involving 40 patients randomized into two groups: the first group received 2g of ceftriaxone 30 minutes before the procedure, and the second group received the same drug preoperatively plus oral cefdopoxime proxetil for three days. The study found no significant difference in postoperative fever > 38.0 ºC (p = 0.3), positive stone culture (p = 0.8), and SIRS (p = 1.0), demonstrating no superiority in extended postoperative antibiotic prophylaxis (19).

Omar et al. 2019 randomized 84 patients into two groups to evaluate a single dose of ciprofloxacin versus cefotaxime during anesthetic induction and 12 hours after the procedure. The incidence of postoperative fever was higher in the group that received cefotaxime (p = 0.002). However, there was no significant difference between the groups regarding the outcomes of length of hospital stay (p = 0.7), positive stone culture (p = 0.6), and positive urine pelvic culture (p = 0.4). The conclusion drawn was that the single-dose ciprofloxacin regimen was more effective for patients undergoing PCNL (16). Table-1 summarizes the studies included in this meta-analysis.

Outcomes

The outcome of SIRS/sepsis was extracted from six of the included studies, while the postoperative fever outcome was extracted from four studies. Figure-3 displays funnel plots, and Forest plots in Figure-4 illustrate that there was no statistical association between the use of postoperative antibiotic prophylaxis and the occurrence of SIRS/sepsis (OR 1.236, 95% CI 0.731 – 2.089, p=0.429) and postoperative fever (OR 2.049, 95% CI 0.790 – 5.316, p=0.140).

DISCUSSION

This meta-analysis provides evidence suggesting that there is no reduction in the incidence of

Table 1 - Baseline characteristics of included randomized controlled trials

Study	Country	Design	Inclusion criteria	Definition of SIRS or Sepsis	Procedure	Patients, n
Cutajar 1992 (17)	Malta	RCT	Patients undergoing PCNL	Bacteremia was defined as the presence of bacteria in the blood (not necessarily associated with urinary tract infection) and septicemia was diagnosed when the patient developed pyrexia and rigors.	Norfloxacin before PCNL and post-operatively for a total of 6 doses vs. A single intravenous dose of cefuroxime given before PCNL	35 vs. 35
Dogan 2002 (15)	Turkey	RCT	Patients who had sterile urine preoperatively and a large stone burden or stones resistant to SWL	NA	Ofloxacin per day until removal of the nephrostomy catheter vs. A single dose of ofloxacin intravenously during induction of anesthesia	38 vs. 43
Demirtas et al. 2012 (13)	Turkey	RCT	Patients undergoing PCNL	SIRS was defined as two or more of these criteria: white blood cell count < 4,000 or >12,000, heart rate >100 per minute, fever <36°C or >38°C, respiratory rate >20 per minute. Urosepsis was defined as bacteriuria or bacteremia with SIRS positive criteria.	The first subgroup had daily dose antibiotic (ciprofloxacin or ceftriaxone) continued after the first preoperative dose antibiotic and until nephrostomy tube was extracted. The second subgroup was administered a preoperative single dose (ciprofloxacin or ceftriaxone); the postoperative was discontinued following the one given in the 12th hour. vs. A single dose of antibiotics (ciprofloxacin or ceftriaxone), rather than postoperative dose.	60 vs. 30

Seyrek et al. 2012 (14)	Turkey	RCT	Patients undergoing PCNL	SIRS was defined as two or more of these criteria: white blood cell count < 4,000 or >12,000, heart rate >100 per minute, fever <36°C or >38°C, respiratory rate >20 per minute.	Sulbactam-ampicillin 30 minutes before surgery, and then every 6 hours until removal of the nephrostomy tube; sulbactam-ampicillin 30 minutes before and 12 hours after surgery; cefuroxime 30 minutes before and 12 hours after surgery; or cefuroxime 30 minutes before surgery, and then every 8 hours until removal of the nephrostomy tube. vs. Sulbactam-ampicillin 30 minutes before surgery or cefuroxime 30 minutes before surgery	128 vs. 63
Tuzel et al. 2013 (18)	Turkey	RCT	Patients with renal stones > 2 cm and with preoperative sterile urine who underwent PCNL	NA	Ceftriaxone plus an oral third-generation cephalosporin until nephrostomy catheter withdrawal. vs. A single dose of ceftriaxone during induction of anesthesia 30 minutes before the operation	37 vs. 36
Chae et al. 2018 (19)	Korea	RCT	Patients undergoing PCNL	SIRS was defined as two or more of these criteria: white blood cell count < 4,000 or >12,000, heart rate >100 per minute, fever <36°C or >38°C, respiratory rate >20 per minute.	Ceftriaxone preoperatively and additional oral cefpodoxime proxetil for three days vs. A single dose of ceftriaxone 30 minutes before the PCNL	20 vs. 20
Omar et al. 2019 (16)	Egypt	RCT	Patients undergoing PCNL	NA	Cefotaxime divided into 2 doses, 30 minutes before induction of anesthesia and 12 hours later vs. A single dose of ciprofloxacin	43 vs. 41

SIRS = systemic inflammatory response syndrome; PCNL = Percutaneous Nephrolithotomy; SWL = Shock Wave Lithotripsy; RCT = randomized controlled trials; NA = not available.

Figure 3 – Funnel plot – (A) RCTs included in the meta-analysis for the risk of SIRS or sepsis; (B) RCTs included in the meta-analysis for the risk of fever.

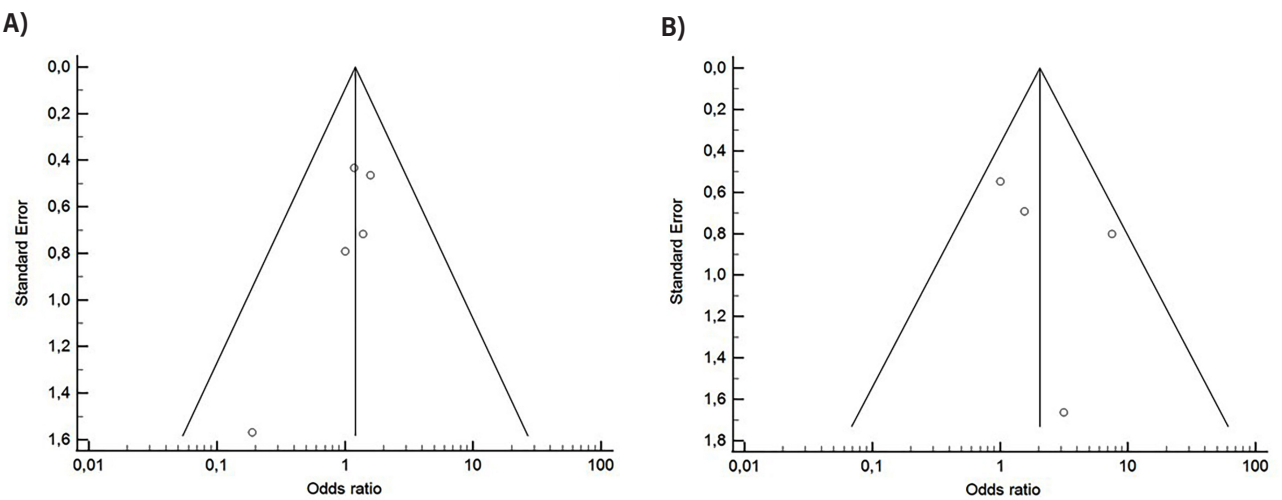
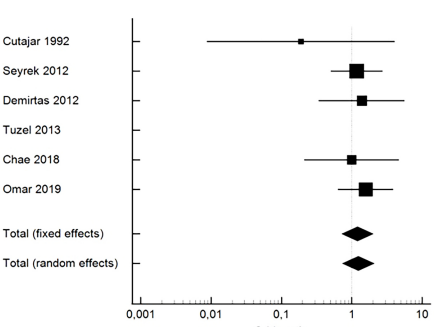


Figure 4 – Forest plot – (A) SIRS or sepsis in control vs. intervention; (B) fever in control vs. intervention.

A)

	Control		Intervention		Weight (random events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Cutajar 1992	2	35	0	35	2.91%	0.189 (0.008 – 4.077)
Seyrek 2012	9	63	21	128	38.4%	1.178 (0.505 – 2.746)
Demirtas 2012	3	30	8	60	13.9%	1.385 (0.339 – 5.649)
Tuzel 2013	0	36	0	37	-	-
Chae 2018	4	20	4	20	11.5%	1.000 (0.212 – 4.709)
Omar 2019	12	41	17	43	33.3%	1.580 (0.637 - 3.922)
Total	30	225	50	323	100%	1.236 (0.731 – 2.089)*

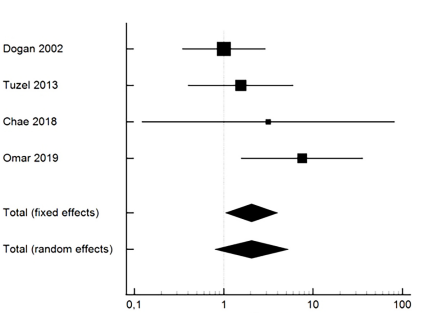
* p = 0.429; Test for heterogeneity: Chi2 = 1.8364, DF = 4, p = 0.7658, I2 = 0% (0.0 – 57.36).



B)

	Control		Intervention		Weight (random events)	Odds Ratio (95% CI)
Study	**Events**	**Total**	**Events**	**Total**		
Dogan 2002	9	43	8	38	38.2%	1.007 (0.345 – 2.941)
Tuzel 2013	4	36	6	37	29.6%	1.548 (0.398 – 6.022)
Chae 2018	0	20	1	20	7.7%	3.154 (0.121 – 82.170)
Omar 2019	2	41	12	43	24.6%	7.548 (1.571 – 36.265)
Total	15	140	27	138	100%	2.049 (0.790 – 5.316)*

* p = 0.140; Test for heterogeneity: Chi2 = 4.5682, DF = 3, p = 0.2063, I2 = 34.33% (0.0 – 76.97).



SIRS/sepsis or fever when patients receive antibiotics for an extended period beyond the induction of anesthesia in PCNL procedures. The RCTs included in this meta-analysis compared patients who received postoperative antibiotic prophylaxis until nephrostomy tube withdrawal to those who received a single dose of antibiotic during the induction of anesthesia.

In the context of PCNL, infection is a concerning complication, leading to prolonged hospital stays and posing life-threatening risks (3). Recognized risk factors for infection after PCNL include a prior positive urine culture, the presence of a nephrostomy tube or double J catheter, longer operative time, larger stones, and diabetes (2, 3, 20-22). It's important to note that the majority of RCTs included in this meta-analysis excluded patients with a history of urinary tract infection weeks prior to PCNL and other known risk factors such as immunocompromised status and the presence of an indwelling catheter (13-19). As a result, the findings of this meta-analysis are applicable primarily to patients without some of the major risk factors for infection after PCNL.

Currently, there is a consensus among Infectious Diseases societies that there is no need to continue antibiotics for prophylactic purposes in the postoperative period, even in the presence of drains, with a level of IA evidence, as it does not reduce the incidence of infectious complications (7, 23). The indiscriminate use of antimicrobials beyond the appropriate time can lead to the selection of multidrug-resistant bacteria, creating a threatening scenario in terms of reducing therapeutic treatment options. The practice of Antimicrobial Stewardship (AMS) emerges as a necessary option in the surgical scenario, especially in Urology. AMS involves a set of practices to optimize the prescription of antibiotics when necessary, reducing patient exposure to the selection of multidrug-resistant microorganisms, improving the safety of medical care, and also reducing costs to the health service. Despite this general orientation, it is estimated that antimicrobial prescription errors occur in up to 68% of urological infections (8, 24). Therefore, more specific studies in the field of Urology are necessary to convince urologists to prescribe antibiotics according to the current best practices.

Recent meta-analyses on the topic have combined patients in different scenarios, including both pre- and postoperative use of antibiotics to prevent infection in patients undergoing PCNL. Additionally, these analyses have included different study designs, combining RCTs with retrospective studies in the same meta-analysis. This approach makes it challenging to analyze different populations within the same study (25).

In contrast, studies focusing exclusively on the preoperative scenario have indicated that seven days of oral antibiotics before PCNL can reduce the incidence of SIRS/sepsis, as well as the positivity of intraoperative urine culture and stone culture (26). It's important to note that many, but not all, of the patients included in these studies had some infectious risk factors, such as larger stone size, positive preoperative urine culture, dilated pelvicalyceal system, or the presence of an indwelling ureteral stent or nephrostomy tube (26). However, to the best of our knowledge, this is the first meta-analysis exclusively focusing on studies that compared patients receiving postoperative antibiotic prophylaxis until nephrostomy tube withdrawal with those receiving a single dose of antibiotic during the induction of anesthesia.

This meta-analysis has enhanced the level of evidence by exclusively selecting RCTs for the study population, thereby minimizing potential biases. Additionally, the intervention population focused solely on patients receiving postoperative antibiotics, eliminating confounding factors from other perioperative periods. However, it is essential to acknowledge some limitations in this meta-analysis. Key variables, such as the choice of antibiotic, the patient's risk for infection, and other clinical factors that may influence infectious outcomes, were not analyzed. Additionally, although none of the RCTs explicitly mentioned mini PCNL, a recent meta-analysis comparing mini PCNL to standard PCNL suggested no significant difference in infection complications between the two procedures (27). All PCNL procedures included in

this meta-analysis were performed with patients in the prone position. While studies comparing prone to supine positions have demonstrated no significant difference in infection complications (28-30), this aspect should still be considered.

The meta-analysis findings underscore the importance of adopting a drug-sparing strategy, especially in the current pharmacological landscape where few new antimicrobials are anticipated. This approach becomes crucial to minimize unnecessary exposure of patients to the potential side effects of antibiotics. Furthermore, it plays a pivotal role in preventing the selection of multidrug-resistant microorganisms, for which therapeutic options are limited. In light of these findings, it is recommended that postoperative prophylactic antibiotics should not be administered to patients undergoing PCNL. This recommendation aligns with the goal of optimizing antimicrobial use, reducing the risk of antibiotic-related complications, and contributing to the broader strategy of antimicrobial stewardship.

CONCLUSIONS

We conclude that there is no benefit regarding the use of postoperative antibiotic prophylaxis until nephrostomy tube withdrawal in patients undergoing PCNL. Antibiotic prophylaxis should be administered until induction of anesthesia of PCNL..

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Kidney collecting system anatomy applied to endourology - a narrative review

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ABSTRACT

Objective: To evaluate the surgical anatomy of the kidney collecting system through a narrative review of the literature, highlighting its importance during diagnosis and its approach during surgical procedures for the treatment of renal stones.

Material and Methods: We carried out a review about the anatomy of the kidney collecting system. We analyzed papers published in the past 40 years in the databases Pubmed, Embase and Scielo, and we included only papers in English and excluded case reports, editorials and opinions of specialists.

Results: Renal collecting system could be divided in four groups: A1 – kidney midzone (KM), drained by minor calyx that are dependent on the superior or the inferior caliceal groups; A2 – KM drained by crossed calyx, one draining into the superior caliceal group and another draining into the inferior caliceal group; B1 – KM drained by a major caliceal group independent of both the superior and inferior groups; and B2 – KM drained by minor calyx entering directly into the renal pelvis.

Some details and anatomic variations of the collecting system are related to clinical and radiological aspects, particularly perpendicular calyces, interpyelocalyx space, position of calyces in relation to renal border, classification of the renal collecting system, infundibular diameter and the angle between the lower infundibulum and renal pelvis.

Conclusion: The knowledge of intra-renal collecting system divisions and variations as the angle between the renal pelvis and lower infundibula, position of the calices in relationship with renal edge and the diameter and position of the calyces are important for the planning of minimally invasive renal surgeries.

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INTRODUCTION

The incidence of nephrolithiasis has increased in developed and underdeveloped countries, comprehending 10 to 15% on the population (1). In the USA, prevalence of renal stones has increased 37% (2). Recurrence is 15% in one year, 50% in five years and 80% in 25 years, after the first incidence of renal colic (1). In Brazil, hospitalization index related to renal lithiasis was 2:3000 patients per month in 1996. In 2006, this number increased to 6:7000 per month (3). It is estimated that 50% of patients with stone disease with symptoms of obstruction of urinary system will need to be submitted to surgical intervention (4).

Current treatments for renal lithiasis include Shock Wave Lithotripsy (SWL), percutaneous nephrolithotripsy (PNL), and flexible retrograde ureterorenoscopy (FUR) (5, 6). All these procedures to be performed depend on a good knowledge of intra-renal anatomy. The anatomical variations of the angles between the renal pelvis and infundibulum (IPA), the number and diameter of the calices as well the complexity of the lower pole drainage system affect the success rates for each chosen treatment (7-9).

The lower pole stones are of special interest in endourological procedures. The percentage of complete elimination of fragments from the upper pole, middle calix, renal pelvis, and lower pole are 78%, 76%, 84%, and 58%, respectively after SWL (10). Besides the gravity-dependent factor, which would make difficult the elimination of stone fragments, the lower pole collecting system anatomy is important for the retention of fragments after endourological surgeries (11). Nevertheless, the negative effects of lower IPA, infundibular length, and width are critical for SWL (12). Besides gravity-dependent position of lower pole calices, these anatomical features might influence fragment clearance after SWL for lower pole lithiasis (11, 12).

Knowledge of the renal collecting system anatomy and radiological analysis of urinary system is necessary for the performance of renal punctures during percutaneous surgeries and the management of the ureteroscope and access to the calyces during FUR and consequently to the success of the treatment of intra-renal calculi (13-17). Despite the method of choice for treating lower pole nephrolithiasis, it is important to know if the method used for studying the lower pole caliceal anatomy is precise. This knowledge is very important for planning the percutaneous access, for flexible ureterorenoscopy of the lower pole calices, and also for indicating and predicting the success of SWL for treating lower pole lithiasis.

Correlation between the type of collecting system and technical difficulties that may be found in a particular anatomic group may indicate the probable result of the surgery in special of lower pole calculi.

The aim of the present work is to evaluate the surgical anatomy of the kidney collecting system through a narrative review of the literature, highlighting its importance during diagnosis and its approach during surgical procedures for the treatment of renal stones.

MATERIAL AND METHODS

In this study we carried out a review of the anatomy of the renal collecting system. We analyzed papers published in the past 40 years in the database Pubmed, Embase and Scielo, using the key expressions "Anatomy"; "Kidney Anatomy"; "Shock Wave lithotripsy", "Percutaneous nephrolithotripsy", "Retrograde ureterorenoscopy", "MRI"; "CT"; "Endourology"; and "Endourologic Surgery". We found several papers in these database and we included only papers in English and excluded case reports, editorials and opinions of specialists.

We also studied five renal endocasts of collecting system using the injection corrosion technique with polyester resin (18). In order to perform the injection, we used the following method: for each 100 mL of resin, we added 10 mL of styrene monomer and 2 to 5 mL of catalyzing agent, and the dye (we standardized the following colors: yellow for the collecting system, red for arteries and blue for veins). Following the resin hardening, we initiated the process of corrosion in order to remove all organic material and confection of the mold (Figure-1). After injection, the material was dipped in hydrochloric,

sulfuric or muriatic acids for 24 hours. After this time, the mold was removed from the recipient, cleaned and dried for analysis (18, 19).

Figure 1 – Final aspect of a three-dimensional polyester resin collecting system endocast. We can observe that in this technique the distribution of minor and major calices and the relationships between the renal pelvis and infundibulum is very easy to analyze.

RESULTS

Anatomy of the renal collecting system

Minor calyces drain the renal papillae, and their number are variable: 70% of kidneys present 7 to 9 minor calyces (20). A minor calyx may be simple (when drains one papillae) or compound (when drains two or three papillae). Calyces in the polar regions of the kidney frequently are compound, particularly those located in the superior pole. Minor calyces may directly drain to an infundibulum or get together, forming major calyces that subsequently will drain to the infundibulum; finally, those infundibula, considered primary divisions of the pyelocaliceal system drain to the renal pelvis (19, 20).

Many authors claim that there is only one caliceal infundibulum draining each renal pole (21, 22). However, in a previous study of Sampaio (18, 19), it was shown that in 56.8% of kidneys the lower pole was drained by more than one infundibulum (3 to 7) distributed into two rows: anterior and posterior. In 43.2%, the lower pole was drained by one only infundibulum located in the middle line, that received two or three adhered papillae. The presence of multiple calyces may difficult the drainage, and consequently lower the possibility to eliminate fragments after endourological procedures when compared to a unique calix infundibulum that receives adhered calyces (18, 19).

A recent morphometric study in human fixed corps showed that the accurate knowledge of normal and anatomical variations of pelvicalyceal system is mandatory for urologists as well as radiologists. The intra-renal pelvis was narrow and had funnel shaped appearance in 48.5% of the cases, and the extra-renal pelvis was dilated as balloon shaped in 43 of the specimens. In 20.9% the renal pelvis was partially intra- and extra-renal located. Bilateral symmetry was found in only 27.1% of collecting systems. The length of lower infundibulum was more than 22 mm in 9.7% of cases which directly affects the stone clearance rate during open and endoscopic surgeries on pelvicalyceal system (23).

Knowledge of calyceal pattern is also important for donor selection. Regional anatomy is assessed in detail to decide the precise surgical method, which will avoid donor complication, and to ensure good recipient graft function. A detailed description of calyceal pattern will be of great significance in renal transplantation and also for other urological procedures (24).

A recent systematic review shows the importance of the renal collecting system anatomy applied to endourological procedures. This paper shows that retrograde intrarenal surgery is an effective treatment option for the management of lower pole stones. Infundibular pelvic angle (IPA) seems to be the most important predictor for stone free results. Pelvicalyceal anatomy in conjunction with stone size and hardness seem to dictate the success of retrograde intra-renal surgery for lower pole stones and decisions on the type of surgical interventions (25). The pelvicalyceal anatomical system (PCS) plays a role in both upper calyceal stone formation and in the success of the endoscopic combined intrarenal surgery (ECIRS) procedure (26).

Some details and anatomic variations of the collecting system are clinical and radiologically important, particularly perpendicular calyces, interpyelocaliceal space, position of calyces in relation to the renal edge, the classification of the renal collecting system, the infundibular diameter and the angle between the inferior infundibulum and the renal pelvis (18, 19, 27, 28).

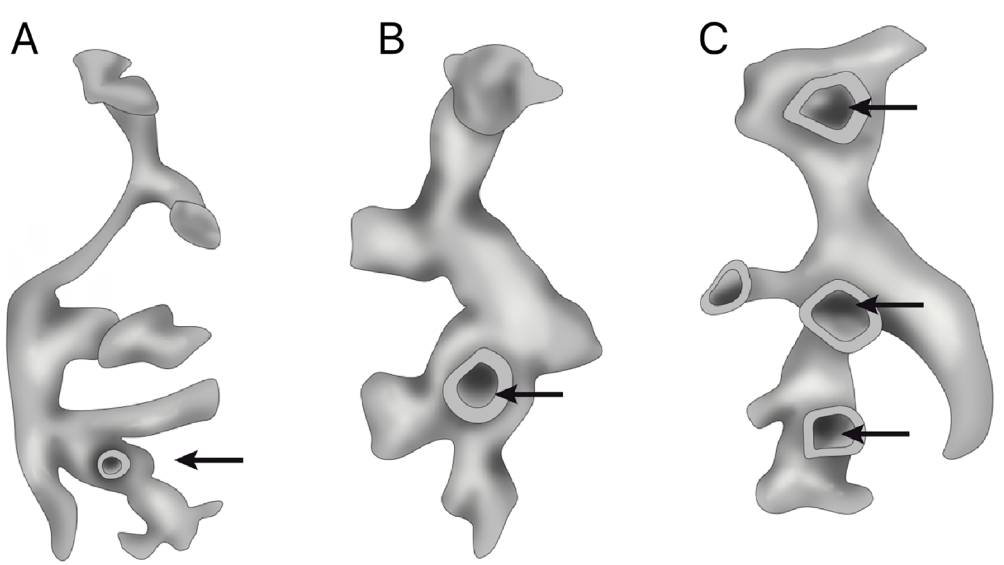
PRESENCE OF MINOR PERPENDICULAR CALYCES

The presence of perpendicular smaller calyces is observed in 11.4% of kidneys when the renal collecting system is studied (18, 19, 27, 28). Perpendicular calyces drain to the renal pelvis or to a major calyx, in general with diameter smaller than 4 mm. Perpendicular calyces are important since they can be overlayed to other structures that difficult radiological visualization and the access during endourological procedures (Figure-2).

INTERPIELOCALYCEAL REGION

Another important anatomical aspect of the renal collecting system is the presence of crossed calyces in the mid-renal zone, present in about 17.2% of kidneys (18, 19, 27, 28). When present, one of the calyces drains to the superior group of calyces and the other drains to the lower calyceal group. Medially,

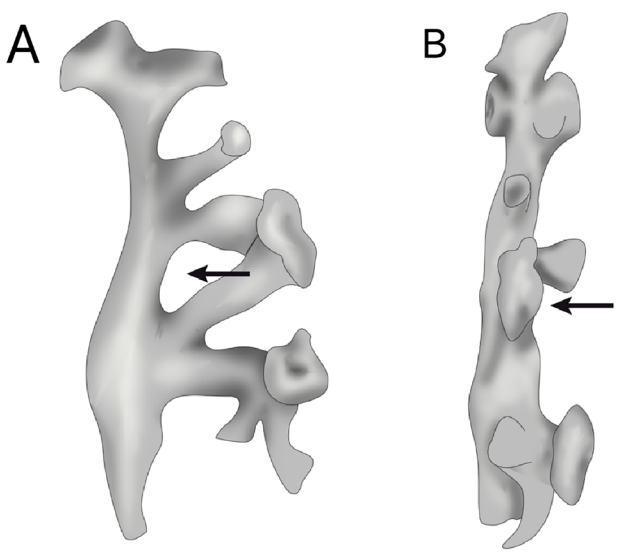
Figure 2 – Perpendicular calyces. We can observe in the 3 figures examples of minor calices perpendicular to major infundibulum.



A) Schematic drawing showing a small minor calyx perpendicular to lower pole infundibulum (arrowhead); B) Schematic drawing showing a large minor calyx perpendicular to lower pole infundibula (arrowhead) and C) Schematic drawing showing 3 minor calices perpendicular to upper, medium and lower pole infundibulum.

the renal pelvis and the laterally crossed calyces demarcate the region called interpielocalyceal region. This space may present several forms: lozenge (most common), long and narrow, small and round, depending on the size of the calyces (Figure-3). When crossed calyces exist in the mid renal zone, the calyx that drains to the inferior group is anterior in 87.5% of kidneys. This spatial arrangement is important to endourological maneuvers (18, 19, 27, 28).

Figure 3 – Inter pielo-calyceal region.



A) Schematic drawing showing the presence of a calyx draining to the superior calyx group and another draining to the lower group. Renal pelvis medially and crossed calyces laterally determine the region called inter-pyelocaliceal region (arrowhead); B) Schematic drawing showing that the calyx that drains to the inferior calyx group (arrowhead) is anterior in most kidneys.

CALYCES POSITION IN RELATION TO EDGE OF THE KIDNEY

The position of the calyces in relation to the kidney edge is also important when we review the anatomy of the renal collecting system (27-29). In 27.8% of kidneys the anterior calyces are more lateral (peripheral) than the posterior calyces. In 19.3% the posterior calyces are more lateral than the anterior. In most kidneys (52.9%) the anterior and posterior calyces are overlapped or arranged alternately. Since the local of choice of access of the collecting system is through a posterior calyx during percutaneous nephrolithotripsy, it is important to determine which calyces are anterior and which are posterior. There is a great anatomic variation of the position of calyces in relation to the renal edge. The use of computed tomography with reconstruction is of great importance to the surgical planning.

Classification of the renal collecting system

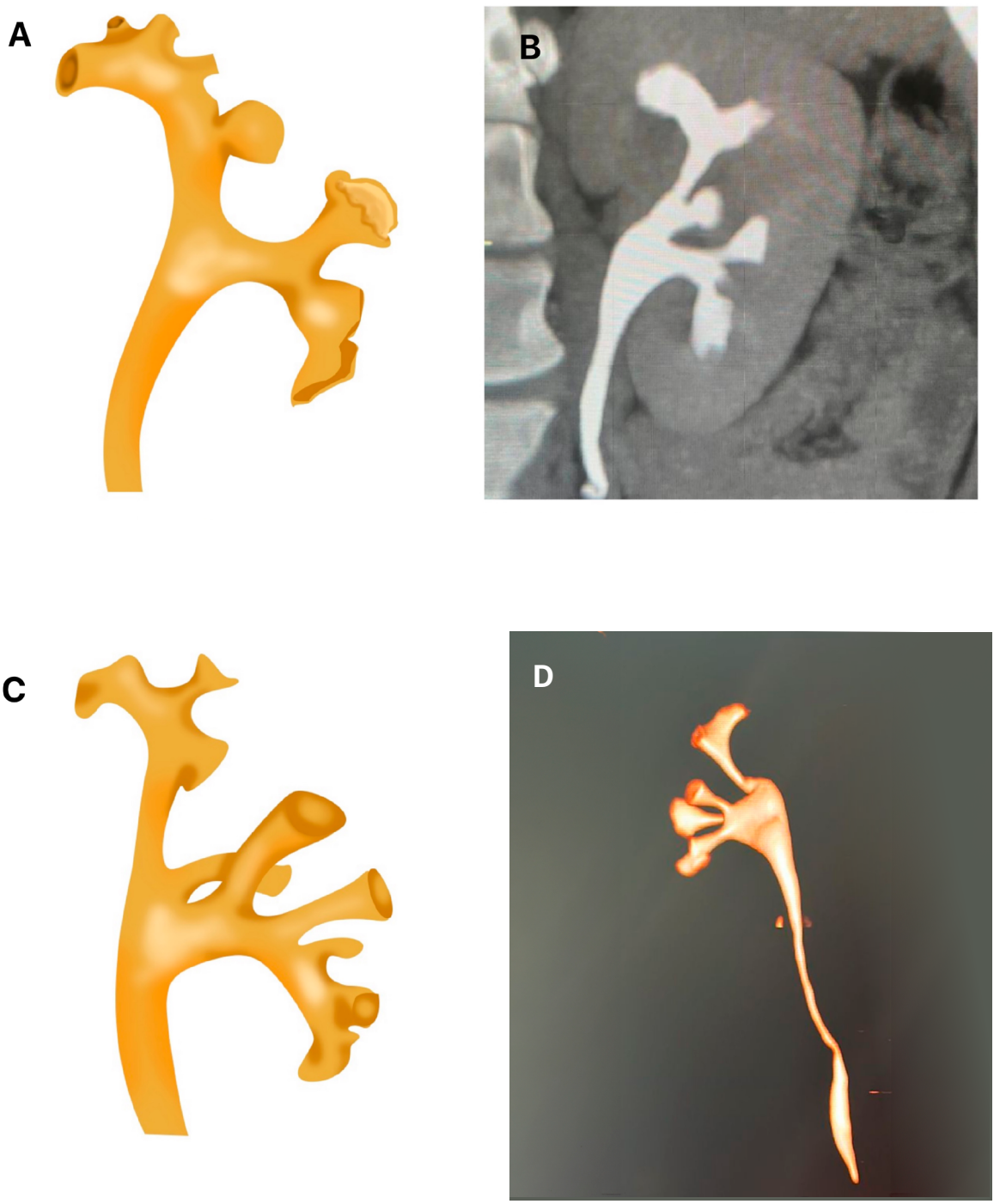
The analysis of the renal collecting system proposed by Sampaio is well accepted in the clinical field and is easily identified in the image methods (18, 19).

The intrarenal collecting system is divided in two major groups (with two intermediate variations in each major group). This division is based on the calyceal drainage of the superior pole, inferior pole, and mid-renal zone (hilar) (19). We will describe the anatomy of these two groups, named Groups A and B.

Group A: It comprises pyelocaliceal systems that present two main calyceal groups (superior and inferior) dividing primarily the renal pelvis, and the drainage of the mid-renal zone depends on these two major calyceal groups (62%) (Figure-4). This group comprehends two different types (variations) of the pyelocaliceal system: types A-I and A-II. A-I type (around 45% of kidneys): the mid-renal zone is drained by minor calyces that are dependent on the superior or inferior calyceal groups, or both, simultaneously (Figure-5). Type A-II (around 17% of kidneys): the mid-renal zone is drained by crossed calyces; one drains to the superior calyceal group and the other to the inferior group, simultaneously (Figure-4).

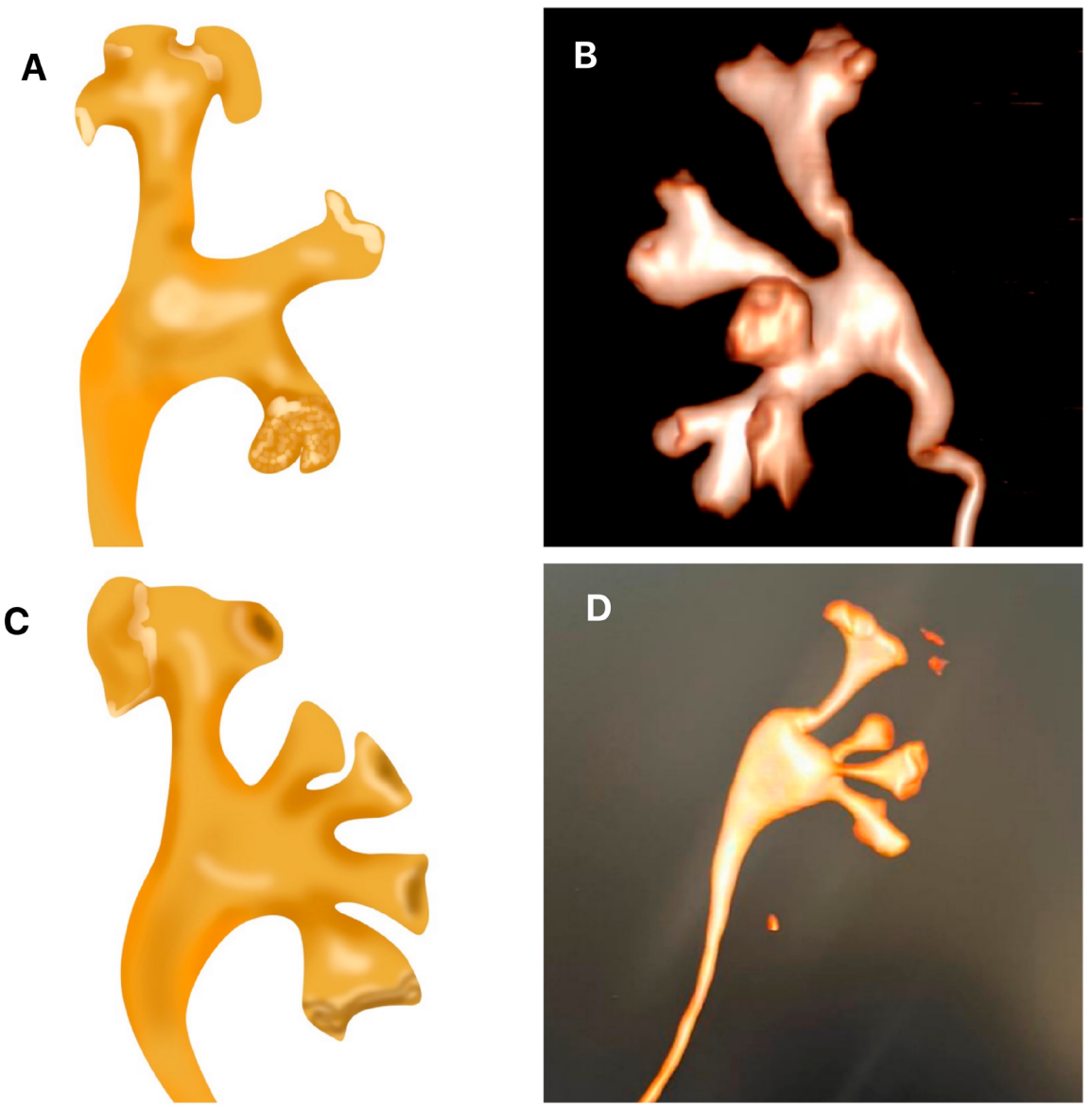
Group B: It comprises by pyelocaliceal systems that drain the mid-renal zone independently of the superior and inferior groups (38%) (Figure-4). This group also includes two different types (variations) of the pyelocaliceal system: type B-I (21.5%) and type B-II (16.4%). Type B-I: the mid-renal region is drained by a major calyceal group, independently of the superior and inferior calyceal groups (Figure-4). Type B-II: the mid-renal zone is drained by minor calyces (one o four) that penetrate directly into the renal pelvis. These minor calyces are independent of the superior and inferior groups.

Figure 4 – Renal collecting system classification - Group A: In this group, mid renal zone drainage depends on the superior and inferior calyx groups.



A) Schematic drawing of a collecting system of group A1 – Mid renal zone is drained by minor calyces that are dependent of the superior calyx group or the inferior calyx group. B) The drawing shows a computer tomography of a patient of group A1; C) Schematic drawing of a collecting system of group A2 – Mid renal zone is drained by crossed calyces, one of them drains to the superior calyx group and the other to the inferior group, simultaneously, and D) the figure shows a computer tomography of a patient of group A2.

Figure 5 – The figure shows the classification of renal collecting system of Group B: In this group, calyx drainage of mid renal zone is not dependent on the superior or the inferior calyceal group.



A) Schematic drawing of a collecting system of group B1 – Mid renal zone is drained by a major calyceal group, that is not dependent of the superior and inferior groups; B) The figure represents a reconstruction of a computer tomography of a patient of Group B1; C) Schematic drawing of a collecting system of group B2 – mid renal zone is drained by minor calyces (one to four) that penetrate directly into the renal pelvis. The minor calyxes are not dependent on the superior and inferior groups and D) the figure represents the reconstruction of a computer tomography of a patient of Group B2.

It is easy to evaluate several important parameters utilized during renal stones surgeries when this classification is used. These parameters include: the frequency of each collecting system type, the number and spatial orientation of calyx, the angle between the lower infundibulum and renal pelvis (LIP), the angle between the lower infundibulum and the inferior minor calyx (LIICA), the inferior infundibular width and length and perpendicular calyx frequency (18, 19). Although this pyelocaliceal classification includes all morphological types of renal calyces and pelvis, it is important for the urologist to keep in mind

that the anatomy of the renal collecting system is widely variable.

A recent study proposed a variation of the classification of the renal collecting system including 5 types of renal pelvis: Type A - a single pelvis without bifurcated branch and subclassified into three subtypes according to the cross- sectional area of renal pelvis: Type A1 - If the cross-sectional area ratio of the pelvis to the UPJ is lower than 4 times, the pelvis is considered to be type A1, which is a slim-line pelvis morphology, Type A2 - formed by a typical funnel shaped pelvis and the cross-sectional area of the pelvis is about 4–16 times larger than that of the UPJ, and this subtype is the most frequently observed standard morphology; and Type A3 - subtype that included a broad pelvis morphology forming a large box shaped pelvis with the cross-sectional area ratio of the pelvis to the UPJ greater than 16 times. A divided pelvis with bifurcated branches is seen as Type B and subclassified into two subtypes: Type B1 with the wide and flat lower calyx infundibulum, and Type B2 with the narrow and steep lower calyx infundibulum (30). However, in our opinion, this division proposed by these authors includes some alterations that already are considered by Sampaio (18, 19).

An interesting study shows the importance of the Sampaio's classification in endourological procedures. The anatomical architecture is a prominent factor in the outcomes of flexible ureteroscopy (FURS) (31). Total stone-free rate (SFR) during the first postoperative month evaluation using non-contrast computerized tomography was 63.6%. The evaluation of the SFR in all subgroup of cases (based on Sampaio classification) showed that SFR was significantly lower in subgroup A2 (30.4%), and significantly higher in subgroup B2. The comparative analysis of the operative length showed that the shortest was observed in Type B1 subgroup cases, and the longest (84.7 ± 25.7 min) in the Type A2 subgroup cases. Even though this length was found to be relatively higher in Type A2 subgroup cases than the others, this difference was not statistically significant. Fluoroscopy time was noted to be shortest in B1 subgroup and longest in A2 subgroup with a statistically significant difference. The calyceal structure of the kidney affects the SFR; therefore, a detailed classification of pelvicalyceal system could improve the outcome, decrease the rate of auxiliary procedures, and prevent complications (31).

INFUNDIBULAR DIAMETER

The infundibular diameter of the inferior calyces is also important during surgical procedures to treat renal stones. Around 60% of kidneys show inferior infundibular diameter equal or greater than 4 mm and in 40% the inferior calyces present at least one infundibulum with a diameter smaller than 4 mm. Smaller infundibula (smaller than 4 mm) may difficult the passage of fragments following SWL and URL (32-25). On the other side, one single infundibulum with a proper diameter (higher than 4 mm) will facilitate the elimination of these fragments (35, 36).

The presence of multiple calyces may difficult the treatment of renal stones located at the lower pole (35, 36). One interesting previous study showed that the lower pole was drained by 4 or more calyces in 49.41%, with a greater prevalence in Group A kidneys, according to the Sampaio's classification (33, 34). In that same study the only group with no difference of the number of anterior, posterior or lateral calyces is group A2 kidneys, demonstrating that there is a larger number of anterior and posterior calyces in relation to the other studied groups (37).

ANGLE BETWEEN THE INFERIOR INFUNDIBULUM AND RENAL PELVIS

The angle of the inferior infundibulum and the renal pelvis is paramount on the drainage of the lower pole. Patients with that angle greater than 90º will drain better, and consequently, eliminate residual fragments easier than those with an angle smaller than 90o (32, 33). When the patient lies in the orthostatic position, the kidneys drained by infundibula with angles larger than 90o will present a reasonable drainage (33 ,34). When these anatomical details are considered in patients with lower pole stones (inferior calyces), the radiological study before surgery

must be obtained previously in order to determine the correct anatomy of the lower pole collecting system (34). The use of computed tomography or magnetic resonance with tridimensional reconstruction may help determine the exact spatial distribution of the calyces (38).

Based on these images, the urologist may discriminate patients with an unfavorable gravitational position of the lower calyces, and other anatomical variations (multiple calyces, infundibula with a diameter lower than 4 mm, and infundibular angle equal or smaller than 90o) that may difficult the elimination of fragments and the surgical access during percutaneous renal surgery or URL (32-35, 37).

For the evaluation of the angle, two lines are traced. The first unites the central axle of the superior ureter with the central axle of the uretero-pyelic junction. In order to draw the second line, we must consider in which calyx the stone is located. If the stone is located in a calyx whose neck accompanies the axle of the inferior major infundibulum, the second line is drawn through the central axle of this infundibulum. However, if the stone is located in a minor calyx whose infundibulum (calyx neck) does not accompany the central axle of the inferior major infundibulum, the second line is drawn through the central axle of the infundibulum of the calyx in which the stone is located (37, 39, 40).

LIP is one of the most important factors for successful FUR (flexible ureteroscope) results, although there is controversy about the limit considered unfavorable, varying from <30° to <90°, depending on the study (33-36). According to Elbahnasy (12) the LIP> 70° is considered a favorable factor to eliminate calculi from the lower pole. Size and volume of calices are also limiting factors for FUR success, regardless of location (41). Long infundibular length (> 3cm) and narrow width (< 5mm) lead to lower FUR success rates (41).

It has been shown that patients with a long infundibulum and with an acute infundibulum-pelvic angle are more susceptible to a second surgical procedure, however without a higher incidence of complications (36). The presence of these anatomic characteristics will difficult the ureteroscope access and the elimination of calculi. It was speculated that these previous limitations in patients with unfavorable angles could have been associated with the use of older ureterorenoscopes (8, 9 ,11). New equipment are more easily to maneuver and present a better vision in relation to the old ones, improving the results of the surgeon and of the surgery itself (42).

Elbahnasy (12) considered the following favorable factors for the elimination of calculi at the renal inferior pole: infundibulum-pelvic angle > 70o, infundibulum length ≤ 3 mm and infundibulum width > 5 mm. On the opposite, angle < 70o, infundibulum length > 3 mm and infundibulum width ≤ 5 mm are unfavorable factors. Sampaio (27, 28) standardized different values as restrictive aspects for the elimination of calculi of the lower pole: angle < 90o, and infundibulum width < 4 mm. When both angle determination methods are compared, it is realized that in the Sampaio's method the media of angle is 20,21o (17,87o to 22,74o), bigger that when the Elbahnasy method is used, precisely as the parameter values determined by those methods (12, 27, 28, 37, 40).

Previous studies have shown that angles smaller than 45o (8) and smaller than 30o (38) are unfavorable for the success of FUR. Marroig (40) did not observe the presence of angles smaller than 60º at the pyelograms and in 39% of the kidneys the angles measured 61 to 90o, and in 95% of them the collecting systems were of group B. The collecting system of group B showed a smaller IPA (median 92.71o at group B1 and 80.94o at group B2) than the collecting systems of the group A (median of 113,8o in group A1 and 116,8o in group A2). The difference was statistically significant (p=0.0002) (40).

Most unfavorable angles were observed in group B kidneys, regardless the used method for measure. The collecting systems of the group B kidneys show calyces entering directly at the mid renal zone or through an infundibulum (37, 40). Therefore, the inferior calyces are distributed more inferiorly, closing the IPA, resulting in a factor that difficult the elimination of fragments and the ureteral access (36). However, although in the presence of an unfavorable

angle, more than 85% of inferior calyces were accessed by the ureteroscope in group B kidneys, similarly of what was observed in the collecting systems of group A1 (87.50%). The lower success rate was observed in group A2 (63.64%), whose IPA usually was greater than 90o (37, 40).

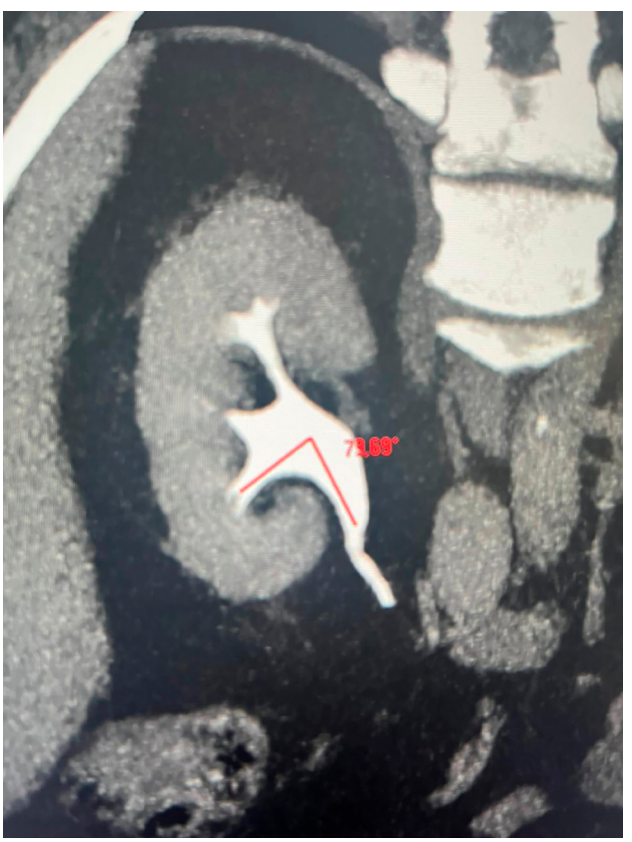
This predominance of angles greater that 90o in group A2 kidneys could explain the presence of minor calyx that extends superiorly, originating from the inferior collecting system, pulling all collecting system cranially, and whose IPA is the greatest among all groups (116.8o). The group with the higher number of kidneys with angles between 61 and 90o was group B (37, 40). These observations make us wonder if the IPA is an important factor for the treatment of renal calculi using SWL and for the elimination of fragments (8, 12, 43); but necessarily is not a difficult factor for the introduction of the ureteroscope, when we consider an IPA > 60o.

The ureteroscope may reach the inferior infundibulum easily, but the angle of the device must be observed in order to access the minor calyces. Group A2 kidneys present the higher percentage of number of major calyces. They show the more closed IPA angles caudally and present the bigger angles directed superiorly, obliging the ureteroscope to follow a sinuous path in order to reach the more superior calyces of the lower pole (37, 40). This observation by itself could justify the lower accessibility of the ureteroscope in group A2 kidneys. In relation to the inferior infundibulum width, A2 group kidneys showed the higher values compared to other groups.

Jessen et al. (36) showed that a narrow infundibulum does not affect the success of the ureteroscope treatment, in accordance to the results of the present paper: the ureteroscope access was less efficient in this group, and when the width was a difficult factor for the assessment, it would be expected that the width was the lowest among groups. Therefore, in those studies, infundibular width was not considered a difficult factor related to the success of the ureteroscope treatment (37, 40) (Figure-6).

When we analyze the infundibular length, the measures of group A2 kidneys pointed to lower accessibility of the ureteroscope in this group, however without statistical significance in this sample; the longest infundibular length observed in the molds was present in group A2 (3.09 cm ±0,45 cm) (37,40). Geavlete et al. (8) have already demonstrated that 3 cm of limit of length of infundibulum is a determinant factor for the success of ureteroscopy. Fabregas Arzoz (35) established the limit of 2.2 cm as the length to predict a free stone rate after SWL, similar to the value (2.32 cm) pointed by Jessen et al. (36) that predicted the free stone rate after FUR.

Figure 6 – The figure shows a reconstruction of a computer tomography representing the anatomy of the renal collecting system. It shows an example of measurement of the angle between the lower infundibulum and renal pelvis (red line).



Flexible ureteroscopy has become an essential tool in the arsenal of modern urologists for the treatment of renal lithiasis. Technological advances have made this procedure safe, and efficient, and

provided excellent results in the benefit-safety ratio. Some characteristics of the intrarenal anatomy as the infundibulum pelvic angle and infundibular length must be considered before any procedure (44).

Image exams for planning of renal surgery

In some cases of nephrolithiasis, mainly in the lower pole, the surgical treatment of urinary lithiasis remains a theme of debate (4, 45-47). Tridimensional tomographic reconstruction of the collecting system allows for the previous anatomic knowledge before endoscopic surgeries (45-47). It allows for better decision making of the surgical technique to be employed. With the use of tomographic reconstruction, it is possible to evaluate several anatomic parameters, such as the number of major and minor calyces, their diameters, the angle between calyces and pelvis and between calyces and infundibula, and the position of calyces.

The measurement of angles and length and width of calyces at the preoperative period allows for the use of a lower caliber laser fiber in order to access a calyx with a bigger angulation although these thinner fibers have a lower power of fragmentation. Or the use of a fiber with greater caliber in calyces with anatomic parameters favorable to the introduction of the ureteroscope; these larger fibers support a higher intensity of the laser bean and consequently allows for a faster and more effective fragmentation of calculi (48). The knowledge of the anatomy may also help choose the most proper place for the renal puncture or for the indication of SWL. Knowledge of the anatomy of the renal collecting system and its variants is very important for the surgical planning and interpretation of these exams (40). This is particularly true in lower renal pole calculi. Previous studies proposed that the angle formed between the lower infundibulum and the renal pelvis (i.e., lower infundibulum–pelvic angle [IPA]), the lower infundibulum diameter (ID), and the number of lower pole calyces (i.e., caliceal distribution [CD]) would be the most important factors. The success rate of the treatment of calculi located in the lower pole of the kidney, regardless of the method used, is directly related to the anatomical parameters of this region (37, 40).

A recent study with 145 patients with complex renal calculi treated by FUR showed worse success (83%) when calculi were located in the lower pole (49) due to anatomic factors that difficulted the ureteroscope access, leading to a lower stone free rate (50).

The 3D-HCT is a commonly used examination in the investigation of many renal pathologies such as lithiasis, tumors, vascular anomalies and also in the study of vascular anatomy in renal donors (51-54). The 3D-HCT is much more precise to study calculus location, tumors, and vessels and the lower pole spatial anatomy.

CONCLUSIONS

The spatial anatomy of renal collecting system is of utmost importance during endourologic procedures. The knowledge of intra-renal collecting system divisions and variations as the angle between the renal pelvis and lower infundibula, position of the calyces in relation to the renal edge and the diameter and position of the calices are of great importance for the planning of minimally invasive renal surgeries.

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CONFLICT OF INTEREST

None declared.

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Identify risk factors for perioperative outcomes in Intracorporeal Urinary Diversion and Extracorporeal Urinary Diversion with Robotic Cystectomy

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ABSTRACT

Introduction: The increasing adoption of robotic-assisted cystectomy with intracorporeal urinary diversion (ICUD), despite its complexity, prompts a detailed comparison with extracorporeal urinary diversion (ECUD). Our study at a single institution investigates perioperative outcomes and identifies risk factors impacting the success of these surgical approaches.

Methods: In this retrospective analysis, 174 patients who underwent robotic-assisted cystectomy at the University of Louisville from June 2016 to August 2021 were reviewed. The cohort was divided into two groups based on the urinary diversion method: 30 patients underwent ECUD and 144 underwent ICUD. Data on demographics, complication rates, length of hospital stay, and readmission rates were meticulously collected and analyzed.

Results: Operative times were comparable between the ICUD and ECUD groups. However, the ICUD group had a significantly lower intraoperative transfusion rate (0.5 vs. 1.0, p=0.02) and shorter hospital stay (7.8 vs. 12.3 days, p<0.001). Factors such as male sex, smoking history, diabetes mellitus, intravesical therapy, higher ASA, and ACCI scores were associated with increased Clavien-Dindo Grade 3 or higher complications. Age over 70 was the sole factor linked to a higher 90-day readmission rate, with no specific characteristics influencing the 30-day rate.

Conclusion: Robotic cystectomy with ICUD results in shorter hospitalizations and lower intraoperative transfusion rates compared to ECUD, without differences in operative time, high-grade postoperative complications, or readmission rates. These findings can inform clinical decision-making, highlighting ICUD as a potentially more favorable option in appropriate settings.

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INTRODUCTION

Bladder cancer is the fourth most common cancer in men in the United States and as such, creates a substantial financial burden at both the individual and the national level. Radical cystectomy with urinary diversion remains the standard surgical approach for non-metastatic muscle-invasive bladder cancer (MIBC) as well as for certain cases of high-risk non-muscle invasive bladder cancer (NMIBC) (1). On the other hand, simple cystectomy was used in certain refractory diseases of radiation cystitis, neurogenic bladder, interstitial cystitis, or incontinence in addition to urinary diversion. Initially, open cystectomy with extracorporeal diversion was the preferred surgical approach. Since the advent of robotic-assisted procedures, however, studies have set out to compare the safety, efficacy, and perioperative and oncologic outcomes of open vs. robotic-assisted laparoscopic cystectomy(2-7). Recently, multiple RCT trials compared open cystectomy vs. robotic cystectomy with intracorporeal urinary diversion were published (7-10). Different urinary diversions have been reported to be performed in either intracorporeal or extracorporeal fashion (11). A topic that has been less closely examined is the comparison of intracorporeal urinary diversion (ICUD) vs. extracorporeal urinary diversion (ECUD) following robotic-assisted laparoscopic cystectomy with different types of urinary diversion.

Despite several studies comparing perioperative outcomes between ICUD and ECUD, most are large database studies with unclear results. We hypothesized that patients with intracorporeal urinary diversion (ICUD) may potentially have a faster bowel recovery time. To address this issue, we present our study from a single institution and aim to use the perioperative outcomes including perioperative blood loss, transfusion, operative times, postoperative complications rates, and 30-day and 90-day readmission rates to identify the demographic feature or operative techniques that may influence the outcome.

MATERIALS AND METHODS

Study Design

This retrospective study, approved by the Human Subjects Office/Institutional Review Board (IRB) at the University of Louisville (IRB number 20.0406), involved 174 patients who underwent robotic-assisted cystectomy at the University of Louisville Hospital between May 2016 and July 2021.

Inclusion criteria were as follows: patients who underwent planned robotic total cystectomy with urinary diversion, with or without concurrent procedures. Patients were excluded if they underwent partial cystectomy, had anesthetic contraindications to robotic surgery, or lacked demographic information or postoperative follow-up data.

Baseline demographics included the patient's age, gender, BMI, smoking status, bladder cancer status, history of diabetes mellitus, type of urinary diversion (ileal conduit, neobladder, or Indiana pouch), method of urinary diversion (intracorporeal or extracorporeal), ECOG status, ASA, ACCI score, neoadjuvant chemotherapy status, intravesical treatment status, and history of pelvic radiation.

Patients were divided into two groups based on the method of urinary diversion employed: the ECUD group and the ICUD group. The study classified 30 patients into the ECUD group and 144 into the ICUD group. The primary outcome measured was complications of Clavien-Dindo Grade III or above. Secondary outcomes focused on 30-day and 90-day readmission rates. All the patients in our study were initiated with ERAS protocol and were encouraged to start a liquid diet and ambulation post-operative day one. No narcotic was regularly prescribed postoperatively. The detailed protocol was described in the supplementary documentary 2 in APPENDIX.

The study also considered other perioperative outcomes, including operative time, postoperative ileus, day of initiating per oral intake (PO), length of stay, urine leak, and bowel leak. Postoperative ileus was defined as postoperative vomiting paired with radiographic evidence of ileus that necessitated nasogastric tube (NG tube) placement. The day of initiating PO was defined as the day when the patient started a solid diet post-surgery. For the study's integrity, patients lacking 90-day follow-up information were excluded from the research.

Procedure

All surgeries involved in this study were performed by the same surgeon using the Da Vinci Robot

Xi system and encompassed both radical and simple robotic cystectomy procedures. An extended bilateral pelvic lymph node dissection was carried out on all patients undergoing radical cystectomy. This dissection included perivesical, external iliac, common iliac, obturator, and presacral lymph nodes.

While the operations adhered to a standard template, variations were made as necessary for specific cases. Given that the ileal conduit was the most frequently used method of urinary diversion in this cohort, a detailed template of the robotic cystectomy and both intracorporeal and extracorporeal ileal conduit creation is provided in supplementary document 1 in APPENDIX for reference. Different techniques were reported to reconstruct neobladder, and we used a Studer/Wiklund technique in our orthotopic neobladder reconstruction (12, 13). The robotic intracorporeal continent cutaneous urinary diversion (Indiana pouch) was performed in a similar fashion as previously reported (14).

Statistical Analysis

We used the chi-square test to compare the association between category variables. Student's t-test was used to analyze the association between continuous variables in patients' demographics. All P values were two-tailed with differences considered significant at values of $P<0.05$. Statistical analysis was performed with MedCalc software (version 18.2.1; MedCalc, Mariakerke, Belgium).

RESULTS

Patients' baseline demographics between the ECUD group and the ICUD group

In total, 174 patients were enrolled in this study, with 30 assigned to the ECUD group and 144 to the ICUD group. As detailed in z, no significant differences were found between the two subgroups in terms of age, gender, BMI, preoperative diagnosis, smoking status, diabetes mellitus status, neoadjuvant chemotherapy, intravesical treatment, baseline ECOG scores, ASA scores, and ACCI scores.

The choice of urinary diversion method correlated with the type of urinary diversion. Specifically, 66.7% (16/24) of patients with an Indiana pouch underwent extracorporeal surgery, while all 42 patients with a neobladder underwent the procedure intracorporeally. Furthermore, a larger proportion of patients in the extracorporeal subgroup had received pelvic radiotherapy before the surgery compared to the ICUD group (23.3% vs. 7.6%, $p = 0.010$).

Comparison of the perioperative outcomes between ECUD and ICUD subgroups

As detailed in Table-1, there was no statistically significant difference in operative time between the ECUD and ICUD groups. The median operative time for the ECUD group was 303.5 minutes, compared to 287.0 minutes for the ICUD group. However, patients who underwent ECUD required more transfusions on average than those in the ICUD group (1.0 vs. 0.5, $p=0.020$).

Additionally, patients in the ICUD group initiated a diet earlier than those in the ECUD subgroup (median day 4 vs. 5.5, $p=0.029$). They also had an earlier recovery for both flatus (median day 4 vs. 3) and bowel movement (median day 5 vs. 4). The average length of hospital stay was longer for patients in the ECUD group than in the ICUD group (12.3 vs. 7.8 days, $p<0.001$), with a median stay of 9 days for ECUD patients compared to 7 days for those in the ICUD group.

The association between Clavien-Dino Grade 3 above complications and patient characteristics

In this study, 29.8% of patients experienced Clavien-Dindo Grade 3 or higher complications. In the ECUD subgroup, 13 out of 40 patients (43.3%) were diagnosed with Clavien-Dindo Grade 3 or above complications, while 39 out of 144 patients (27%) in the ICUD group experienced the same. However, no statistical difference was found regarding the risk of high-grade complications between these two groups.

Upon further analysis to identify potential risk factors for high-grade complications, it was found that the male gender exhibited a higher risk compared to the female, with an odds ratio (OR) of 2.330 ($p=0.041$). Patients who underwent other types of urinary diver-

Table 1 - Patient demographics and perioperative outcomes of the UofL cohort between ECUD and ICUD.

	All patients (%)	ECUD (%)	ICUD (%)	*P*
Gender[1]				0.114
Female	49 (28.2)	12 (6.9)	37 (21.3)	
Male	125 (71.8)	18 (10.3)	107 (61.5)	
Age [2]	66 (58-74)	62 (57-75)	66 (58.5-73.5)	0.710
BMI [2]	29.3 (24.5-34.5)	27.5 (22.8-31.8)	29.6 (25.1-35.1)	0.552
Diversion type[1]				**<0.001**
Ileal Conduit	103 (59.2)	13 (7.5)	90 (51.7)	
Indiana Pouch	24 (13.8)	16 (9.2)	8 (4.6)	
Neobladder	42 (24.1)	0	42 (24.1)	
Others	5 (2.9)	1 (0.6)	4 (2.3)	
Preoperative diagnosis[1]				0.670
Bladder cancer	134 (77.0)	24 (13.8)	110 (63.2)	
Others	40 (23.0)	6 (3.4)	34 (19.5)	
Cystectomy types				0.565
Simple cystectomy	34 (19.5)	7 (4.0)	27 (13.2)	
Radical cystectomy	140 (80.5)	23 (13.2)	117 (67.2)	
Smoking status[1]				0.196
Never	38 (21.8)	10 (5.7)	28 (16.1)	
Former smoker	78 (44.8)	10 (5.7)	68 (39.1)	
Current smoker	58 (33.3)	10 (5.7)	48 (27.6)	
Diabetes Mellitus[1]				0.523
No	119 (68.4)	22 (12.6)	97 (55.7)	
Yes	55 (31.6)	8 (4.6)	47 (27.0)	
Neoadjuvant Chemotherapy[1]				0.102
No	117 (67.2)	24 (13.8)	93 (53.4)	
Yes	57 (32.8)	6 (3.4)	51 (29.3)	
Intravesical treatment[1]				0.189
No	140 (80.5)	25 (14.4)	115 (66.1)	
Yes	34 (19.5)	5 (2.9)	29 (16.7)	
Pelvic Radiotherapy[1]				**0.010**
No	156 (89.7)	23 (13.2)	133 (76.4)	
Yes	18 (10.3)	7 (4.0)	11 (6.3)	

ECOG [1]				0.726
0	115 (66.1)	19 (10.9)	96 (55.2)	
≥1	59 (33.9)	11(6.3)	48 (27.6)	
ASA [1]				0.718
≤3	153 (87.9)	25 (14.4)	128 (73.6)	
≥4	21 (12.1)	5 (2.9)	16 (9.2)	
ACCI [1]				0.207
≤6	129 (74.1)	25 (14.4)	104 (59.8)	
≥7	45 (25.9)	5 (2.9)	40 (23.0)	
Operative time (minutes)				0.743
Mean±SD	303.2±81.4	307.5±79.3	294.0±76.3	
Median (25%-75%)	302 (241-349)	303 (248-358)	287 (242-341)	
Intraoperative Transfusion (unit)				**0.020**
Mean±SD	0.7±1.7	1.0±1.6	0.5±1.2	
Median (25%-75%)	0 (0-0)	0 (0-2)	0 (0-0)	
Postoperative Transfusion (unit)				**<0.001**
Mean±SD	0.6±1.2	1.2±1.7	0.4±1.0	
Median (25%-75%)	0 (0-0)	0 (0-2)	0 (0-0)	
Length of Stay (days)				**<0.001**
Mean±SD	9.5±8.0	12.3±8.7	7.8±5.3	
Median (25%-75%)	7 (5-9)	9 (7-16)	7 (5-9)	
Days initiating PO				**0.029**
Mean±SD	4.9 ± 4.3	6.1±3.0	4.7±2.7	
Median (25%-75%)	5 (3-7)	5.5 (4-7)	4(3-7)	
Days to Flatus				**0.002**
Mean±SD	3.5 ± 1.8	4.4±3.0	3.3 ± 1.5	
Median (25%-75%)	3 (2-4)	4 (3-5)	3 (2-4)	
Days to bowel movement				**0.003**
Mean±SD	4.2±2.0	5.2±2.8	4.0±1.7	
Median (25%-75%)	4(3-5)	5 (3-6)	4(3-5)	
Clavien Dinno Grade 3 or above complication				0.077
Yes	52 (29.9)	13 (9.8)	105 (60.3)	
No	122 (70.1)	17 (7.5)	39 (22.4)	

ASA = American Society of Anesthesiology score; ACCI = Age-adjusted Charlson Comorbidity Index scores; ECUD = extracorporeal urinary diversion; ECOG = Eastern Cooperative Oncology Group performance status; ICUD = intracorporeal urinary diversion; SD = standard deviation;
[1] chi-square test was used for categorized variables
[2] t independent test was used for continuous variables, Median (25%-75%)

sion (including percutaneous ureterostomy, ureterosigmoidostomy, and colon conduit) were more likely to be associated with high-grade complications compared to those who had an ileal conduit, with an OR of 11.259 (p=0.033). Other factors associated with Clavien-Dindo Grade 3 or higher complications were a history of smoking, previous intravesical treatment, high ASA score, and high ACCI score, as shown in Table-2. A separate subgroup analysis was performed regarding the pelvic radiation risk in different cystectomy types (simple vs. radical) patient populations. In this subgroup analysis, pelvic radiotherapy was significantly correlated to higher Clavien-Dinno 3 risk with OR 5.4 (1.1-26.9, p =0.039) in the radical cystectomy subgroup while pelvic radiation is not statistically significantly associated with higher Clavien-Dinno 3 complication risk (p=0.141) in the simple cystectomy subgroup.

Then, we performed multivariable analysis with logistic regression including all the factors that were previously statistically significant. Interestingly, only smoking history and diabetes were found to be associated with high Clavien-Dinno 3 complication risk (p =0.034 and p = 0.025, respectively).

The association between 30-day and 90-day readmission and patient characteristics

Of the 174 patients in the study, 46 (26.4%) required readmission within 30 days, and 59 (33.9%) were readmitted within 90 days. In the ECUD group, 26.6% of patients were readmitted within 30 days, comparable to the 26.3% in the ICUD group. Regarding 90-day readmission, 40% of patients in the ECUD group were readmitted, compared to 32.6% in the ICUD group.

An association analysis of 30-day readmission risk with patient characteristics is presented in Table-S1. No significant correlations were found between 30-day readmission and factors like patient gender, age, BMI, method of diversion, type of diversion, cystectomy types, preoperative diagnosis, smoking status, diabetes mellitus, neoadjuvant chemotherapy, intravesical treatment, pelvic radiation therapy, ECOG score, ASA score, and ACCI score. A similar analysis was conducted for 90-day readmission risk. It was found that patients aged less than 70 years had a lower risk of 90-day readmission, with an odds ratio of 0.490 (p=0.037), suggesting that younger age is a protective factor against 90-day readmission.

DISCUSSION

The debate surrounding the advantages of ICUD versus ECUD has been ongoing since the emergence of robotic surgery. However, years later, there is still a scarcity of data and conflicting results regarding the perioperative outcomes of these two surgical procedures. In this study, we aimed to scrutinize the perioperative outcomes in patients who underwent ICUD and ECUD after robotic-assisted cystectomy. All operations were performed by a single surgeon at our institution, helping to provide further insight into this complex issue.

In our research, we found that ICUD was the preferred procedure, outnumbering ECUD. This outcome was not surprising considering that patient randomization was not part of our study design. Despite this, preoperative patient demographics, including average BMI, gender, and median age at the time of the procedure, showed no significant difference between the two groups. This suggests that specific patient characteristics did not notably influence the choice of one surgical method over the other. However, patients with a history of pelvic radiotherapy and those who underwent Indiana Pouch creation were more likely to have ECUD, perhaps due to the increased technical difficulties associated with performing ICUD in these groups. These findings from our single-institution study align with previous research investigating this topic at an international level (15-17). Mazzone et al. reported that ICUD in highly comorbid patients has a lower risk of postoperative complications rate compared to ECUD (18). However, in this study, we found no significant difference between the two procedures. Both ICUD and ECUD groups displayed comparable rates of high-grade Clavien-Dindo complications (defined as Clavien-Dindo Grade 3 or higher), as well as 30 or 90-day readmission rates.

Conclusions regarding perioperative transfusion rates have varied in previous studies, with some indicating no difference between the two methods of urinary diversion, while others suggest a reduced need

Table 2 - Patient characteristics and association with Clavien-Dino Grade 3 above complications.

Characteristics	OR (95% CI)	P
Univariable		
Gender (Male vs. Female[1])	2.330 (1.035-5.249)	0.041
Age (≥70 vs. <70 [1])	1.044 (0.539-2.025)	0.898
BMI		
30-40 vs. <30 [1]	1.080 (0.540-2.159)	0.827
≥40 vs. <30 [1]	1.692 (0.547-5.230)	0.360
Method of Diversion (ICUD vs. ECUD[1])	0.485 (0.216-1.092)	0.080
Diversion type		
Indiana Pouch vs. Ileal conduit[1]	2.010 (0.799-5.058)	0.138
Neobladder vs. Ileal conduit[1]	0.998 (0.441-2.259)	0.997
Others [2] vs. Ileal conduit [1]	11.259 (1.205-105.225)	**0.033**
Preoperative diagnosis (Others vs. Bladder cancer [1])	0.511 (0.217-1.202)	0.124
Radical cystectomy vs. Simple cystectomy [1]	0.916 (0.409-2.054)	0.832
Smoking status		
Former smoker vs. Never smoker [1]	2.768 (1.082-7.075)	**0.033**
Current smoker vs. Never smoker [1]	1.545 (0.563-4.237)	0.398
Diabetes Mellitus (Yes vs. No [1])	2.516 (1.274-4.970)	**0.008**
Neoadjuvant Chemotherapy (Yes vs. No [1])	0.513 (0.244-1.078)	0.078
Intravesical treatment (Yes vs. No [1])	2.198 (1.013-4.767)	**0.046**
Pelvic Radiation therapy (Yes vs. No [1])	2.036 (0.754-5.497)	0.160
ECOG (≥1 vs. 0 [1])	0.816 (0.407-1.638)	0.568
ASA (≥4 vs. ≤3[1])	3.005 (1.187-7.601)	**0.020**
ACCI (≥7 vs. ≤6[1])	2.126 (1.043-4.330)	**0.037**
Multivariable		
Gender (Male vs. Female[1])	1.685 (0.717-3.959)	0.230
Diversion type		
Indiana Pouch vs. Ileal conduit [1]	1.435 (0.448-4.594)	0.542
Neobladder vs. Ileal conduit [1]	0.853 (0.340-2.138)	0.734
Others [2] vs. Ileal conduit [1]	2.695 (0.168-43.215)	0.483
Smoking status		
Former smoker vs. Never smoker [1]	3.354 (1.094-10.285)	**0.034**
Current smoker vs. Never smoker [1]	2.354 (0.733-7.558)	0.150
Diabetes Mellitus (Yes vs. No [1])	2.327 (1.111-4.858)	**0.025**
Intravesical treatment (Yes vs. No [1])	1.893 (0.776-4.616)	0.160
ASA (≥4 vs. ≤3 [1])	1.719 (0.552-5.355)	0.345
ACCI (≥7 vs. ≤6 [1])	1.585 (0.687-3.657)	0.280

ASA = American Society of Anesthesiology score; ACCI = Age-adjusted Charlson Comorbidity Index scores; ECUD = extracorporeal urinary diversion; ECOG = Eastern Cooperative Oncology Group performance status; ICUD = intracorporeal urinary diversion; SD = standard deviation;
[1] calculated as a reference
[2] Including percutaneous ureterostomy, ureterosigmoidostomy, colon conduit, etc

for intraoperative transfusion in patients undergoing ICUD (15,16, 19, 20). Our research also found a decreased requirement for intraoperative transfusion in the ICUD group, with rates at 0.5 compared to 1.0 for the ECUD group. This finding bears significant relevance considering its implications on a patient's disease course. Increased perioperative transfusions following radical cystectomy have been associated with a higher risk of both cancer recurrence and mortality (21,22).

A principal concern related to the use of ICUD is the potential increase in operative time, attributed to the technical challenges posed by a fully intracorporeal procedure (23-26). Prolonged operative time becomes especially problematic for patients undergoing any robotic surgery, as the requisite use of CO2 for insufflation may be challenging for certain patients with pre-existing cardiopulmonary comorbidities. Moreover, extended usage may lead to acidosis. Given these considerations, it's noteworthy that we found no substantial difference in operative time between ICUD (294.0 min) and ECUD (301.5 min). This aligns with prior studies demonstrating that as surgeons gain more experience performing robotic procedures, operative times reduce, potentially rivaling those of open procedures (27-29).

The significant operational costs of a robotic surgical system have often been cited as a drawback to adopting robotic surgical approaches, with the direct and indirect costs of a robotic procedure estimated to be around $4250 (30). Although the surgery was commonly performed in the Da Vinci platform, ICUD was also reported to be done in different systems (31). However, we observed that patients undergoing ICUD initiated oral intake sooner, consequently leading to a shorter hospital stay. Thus, a portion of these costs may be counterbalanced in patients undergoing ICUD, as reduced length of stay can decrease direct costs for both patients and healthcare systems (29, 30). Our findings demonstrate a shorter hospital stay in the ICUD group, with an average of 7.8 days versus 12.3 days in the ECUD group. The potential cost savings implicit in this difference are significant for both the hospital system and patients. Given sufficient patient volume, these savings could even offset the costs of purchasing and maintaining robotic systems over time.

Our study, being retrospective, has inherent selection biases. Additionally, the distribution of patients undergoing ICUD compared to ECUD was uneven, owing to the non-randomized nature of this investigation. It's also important to note that the consistency in operative time between ICUD and ECUD observed in this study may not be universally applicable, given that the procedures were performed by a single surgeon experienced in robotic techniques. This study mainly focuses on the perioperative outcome instead of long-term complications, late complications are not uncommon in this population including ureteral ileal stenosis, chronic kidney disease, and urinary tract infection (32). Future studies can be designed to focus on the long-term complication outcomes. Also, both simple cystectomy and radical cystectomy were included which can potentially increase confounding factors of the study given different disease nature and lack of lymph nodes dissection in simple cystectomy subgroup. While one could argue that our results have limited generalizability, considering they're based on outcomes from a single institution and surgeon, our approach also bypasses the decreased specificity often resulting from larger database studies, which is a strength of our work. A multicenter retrospective study with a propensity score match could potentially decrease the selection bias (33). Further randomized studies are indeed necessary to clarify these findings and fill the existing data gap on this topic. Additionally, an analysis of cost versus savings between the two surgical approaches could shed more light on the cost benefits to both patients and hospital systems resulting from a reduced length of stay.

Our results indicate that with a proficient robotic surgeon, the operative time – often considered a limiting factor in executing this procedure – doesn't differ significantly between ICUD and ECUD. Additionally, we observed that the hospital stay was substantially shortened, and the transfusion rate improved in the ICUD group compared to the ECUD group. Despite these differences, we found no significant variance between the two groups in terms of postoperative complication rates or readmission rates. These findings may suggest that the intracorporeal approach to urinary diversion can provide certain advantages without increasing postop-

erative complications or readmission rates, particularly when performed by a surgeon well-versed in robotic procedures.

COMPLIANCE WITH ETHICAL STANDARDS

The Human Subjects Office/Institutional Review Board (IRB) reviewed our study. This retrospective study, approved by the Human Subjects Office/Institutional Review Board (IRB) at the University of Louisville (IRB number 20.0406),

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CONFLICT OF INTEREST

None declared.

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APPENDIX:

Table S1. Patient characteristics and association with 30-days and 90-days readmission rate

Characteristics	30-days readmission		90-days readmission	
	OR (95% CI)	P	OR (95% CI)	P
Gender (Male vs. Female [1])	0.993 (0.469-2.099)	0.986	0.952 (0.475-1.909)	0.891
Age (<70vs. ≥70 [1])	0.663 (0.326-1.347)	0.256	0.490 (0.250-0.960)	0.037
BMI				
30-40 vs. <30 [1]	1.643 (0.804-3.361)	0.173	1.713 (0.879-3.337)	0.113
≥40 vs. <30 [1]	1.800 (0.551-5.871)	0.329	1.692 (0.547-5.229)	0.361
Method of Diversion (ICUD vs. ECUD [1])	1.272 (0.383-4.228)	0.693	0.726 (0.323-1.632)	0.439
Diversion type				
Indiana Pouch vs. Ileal conduit [1]	1.355 (0.503-3.654)	0.548	1.822 (0.727-4.565)	0.200
Neobladder vs. Ileal conduit [1]	1.475 (0.664-3.277)	0.339	1.735 (0.818-3.677)	0.150
Others vs. Ileal conduit [1]	2.194 (0.346-13.909)	0.404	3.827 (0.607-24.101)	0.152
Preoperative diagnosis (Others vs. Bladder cancer [1])	1.313 (0.571-3.022)	0.521	1.471 (0.675-3.206)	0.331
Smoking status				
Former smoker vs. Never smoker[1]	1.968 (0.760-5.093)	0.162	1.534 (0.664-3.540)	0.316
Current smoker vs. Never smoker[1]	1.545 (0.563-4.237)	0.398	1.104 (0.451-2.703)	0.827
Diabetes Mellitus (Yes vs. No[1])	1.581 (0.781-3.199)	0.202	1.477 (0.760-2.871)	0.249
Neoadjuvant Chemotherapy (Yes vs. No[1])	0.990 (0.483-2.032)	0.979	0.855 (0.435-1.681)	0.650
Intravesical treatment (Yes vs. No[1])	0.826 (0.344-1.982)	0.668	0.773 (0.342-1.748)	0.537
Pelvic Radiation therapy (Yes vs. No[1])	1.450 (0.510-4.118)	0.485	1.647 (0.613-4.424)	0.322
ECOG (0 vs. ≥1[1])	0.608 (0.287-1.287)	0.194	0.550 (0.274-1.103)	0.092
ASA (≥4 vs. ≤3[1])	1.862 (0.717-4.835)	0.201	1.929 (0.768-4.847)	0.162
ACCI (≥7 vs. ≤6[1])	1.580 (0.754-3.312)	0.225	1.431 (0.709-2.888)	0.317

ECUD = extracorporeal urinary diversion; ICUD = intracorporeal urinary diversion; SD = standard deviation
[1] calculated as a reference

Supplementary Document 1. Technique Description of Robotic Cystectomy with Intracorporeal Ileal Conduit Creation and Extracorporeal Ileal Conduit Creation in Male

Robotic cystectomy with Intracorporeal ileal conduit creation (Male)

1. the patient was placed in low lithotomy position with all pressure points padded.
2. A paramedian left upper quadrant 12 mm trocar was placed by modified Hasson Technique. Pneumoperitoneum was then established. Four additional 8 mm robotic trocars were placed for triangulation to the bladder/cecum. A left lateral 5 mm trocar placed for assistant. The Davinci XI robot was then docked in a typical sterile fashion.
3. The sigmoid colon was reflected out of the pelvis and the left ureter was identified in the retroperitoneum. This was dissected to the vesical hiatus and clipped distally with a 10 mm hemo-lok clip, and proximally with a 10 mm hemo-lok with a Vicryl tag. The right ureter was handled in similar manner after identification in the retroperitoneum.
4. We then made an incision in the pouch of Douglas and developed the space between the rectum and the bladder/prostate.
5. Incision was made lateral to the right medial umbilical ligament and the space of Retzius was developed. This was extended to the right vas which was used as a handle. The right superior vesical artery was clipped with a 10 mm Hemo-lok and divided with a Davinci vessel sealer.
6. The posterior bladder pedicle was divided with a vessel sealer to the apical prostate. The left space of Retzius was developed in a similar manner. The left side bladder pedicle handled in a similar manner.
7. Once this was accomplished the medial and median umbilical ligaments were divided and the space of Retzius was completely developed.
8. The bladder was retracted out of the pelvis and the puboprostatic ligaments were identified and exposed. These were divided and the dorsal vein divided with cautery and vessel sealer. The apical urethra was divided sharply and the urethra was closed with a 3-0 Vicryl to prevent spillage.
9. The terminal ileum was identified and divided in 20 cm proximal to the Ileocecal valve, and again 15 cm proximal to this incision for the future ileal conduit using a Echelon 60 mm stapler.
10. The mesenteric pedicle was developed with the vessel sealer.
11. A side to side ileo-ileostomy was then performed using the Echelon 60 mm stapler.
12. The enterotomy was closed in 2 layers with 3-0 PDS.
13. Bilateral ureteral anastomosis carried out in a two layer fashion using 3-0 Vicryl to anastomose adventitia to the seromuscular layer of the pouch.
14. Mucosal anastomosis after wide spatulation of the ureter with 4-0 Monocryl.
15. Prior to closure of the ureter 7F bander ureteral stents placed and secured into the conduit using 3-0 Chromic through the stent. Stents brought through the stomal end.
16. The Pelvis was then irrigated and suctioned out
17. A 19 round Blake drain was placed in the pelvis through a 8 mm trocar
18. Stoma matured in the previously marked RLQ space with 2-0 Vicryl in a standard Brooke Fashion.
19. The Hasson trocar was then extended and the specimen extracted.
20. Fascia was closed using interrupted figure of eight 1 PDS sutures. The Hasson trocar was closed using a figure of eight 0 PDS.
21. Skin closed with 4-0 Monocryl.
22. The port incisions were closed with 4-0 Monocryl. The patient had a 19 round Blake drains placed through the left side 8 mm trocar.

Extracorporeal ileal conduit creation (Male)
Following the step 8 from Robotic cystectomy with Intracorporeal ileal conduit creation (Male)

1. We then identified the patient's cecum and terminal ileum. A segment of terminal ileum approximately 15 cm from the ileocecal valve was marked using a 3-0 Vicryl stitch.
2. At this portion of the procedure, we then converted to an open procedure along the midline. On the proximal side of the ileum we isolated a 15 cm segment for use as the ileal conduit using the previous mark.
3. Bilateral ureteral anastomosis carried out in a two layer fashion using 3-0 Vicryl to anastomose adventitia to the seromuscular layer of the pouch.
4. Mucosal anastomosis after wide spatulation of the ureter with 4-0 Monocryl.
5. Prior to closure of the ureter 7F bander ureteral stents placed and secured into the conduit using 3-0 Chromic through the stent. Stents brought through the stomal end.
6. The Pelvis was then irrigated and suctioned out.
7. The stoma matured in the LUQ in a typical brook fashion.
8. A 19 round Blake drain was placed in the pelvis through the 8 mm trocar.
9. The Hasson trocar was closed using a figure of eight 0 Vicryl. Skin closed with 4-0 Monocryl. The port incisions were closed with 4-0 Monocryl.
10. The midline was closed with interrupted 0 PDS figure of eight sutures, and skin in the midline closed with staples.

Supplementary Document 2. Postoperatively ERAS protocol in robotic cystectomy patients. Robotic cystectomy with Intracorporeal ileal conduit creation (Male)

Following an unremarkable intraoperative event, our patients adhered to an Enhanced Recovery After Surgery (ERAS) protocol, emphasizing a faster recovery with reduced complications.
Postoperatively, all patients were transferred to a specialized urology floor. The recovery process began on the night of the surgery, with patients being encouraged to sit in a chair and consume hard candy along with small sips of clear liquid. . Of note, nasogastric tube was not routinely placed. Pain management was a critical component of our protocol. We employed a combination of IV Toradol, oral ibuprofen, and epidural anesthetics, deliberately avoiding oral or IV narcotics to mitigate potential side effects and enhance recovery.
Dietary progression was carefully monitored, with patients starting on a clear liquid diet from the first postoperative day. Advancement to a soft solid diet was contingent on evidence of returning bowel function, indicated by flatus or bowel movement. This gradual dietary transition played a significant role in patient comfort and bowel recovery.
Additionally, we placed a strong emphasis on early mobilization. Patients were encouraged to ambulate aggressively starting from postoperative day 1. This early physical activity is a cornerstone of ERAS and has been shown to significantly contribute to reducing postoperative complications and hastening recovery.
All patients were started DVT prophylaxis before intubation and immediately after surgery unless concerned for bleeding postoperatively. We don't routinely continue antibiotics postoperatively.

ORIGINAL ARTICLE

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Use of ChatGPT in Urology and its Relevance in Clinical Practice: Is it useful?

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ABSTRACT

Purpouse: One of the many artificial intelligence based tools that has gained popularity is the Chat-Generative Pre-Trained Transformer (ChatGPT). Due to its popularity, incorrect information provided by ChatGPT will have an impact on patient misinformation. Furthermore, it may cause misconduct as ChatGPT can mislead physicians on the decision-making pathway. Therefore, the aim of this study is to evaluate the accuracy and reproducibility of ChatGPT answers regarding urological diagnoses.

Materials and Methods: ChatGPT 3.5 version was used. The questions asked for the program involved Primary Megaureter (pMU), Enuresis and Vesicoureteral Reflux (VUR). There were three queries for each topic. The queries were inserted twice, and both responses were recorded to examine the reproducibility of ChatGPT's answers. Afterwards, both answers were combined. Finally, those rwere evaluated qualitatively by a board of three specialists. A descriptive analysis was performed.

Results and Conclusion: ChatGPT simulated general knowledge on the researched topics. Regarding Enuresis, the provided definition was partially correct, as the generic response allowed for misinterpretation. For VUR, the response was considered appropriate. For pMU it was partially correct, lacking essential aspects of its definition such as the diameter of the dilatation of the ureter. Unnecessary exams were suggested, for Enuresis and pMU. Regarding the treatment of the conditions mentioned, it specified treatments for Enuresis that are ineffective, such as bladder training. Therefore, ChatGPT responses present a combination of accurate information, but also incomplete, ambiguous and, occasionally, misleading details.

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INTRODUCTION

One of the many AI-based tools that has gained popularity is the Chat-Generative Pre-Trained Transformer (ChatGPT) (1, 2).

Today, ChatGPT is used thoroughly, as a "Search Engine", by patients and physicians, seeking adjuvant information and knowledge about their disease (2-4). However, due to its popularity, and its massive media coverage, incorrect and misleading information provided by ChatGPT will have a profound impact, leading patients and physicians to misinformation (3, 4). Furthermore, it may cause misdiagnosis and mistreatment as ChatGPT can lead the physician to the wrong path on the decision-making chart (3-6).

Consequently, it is essential to evaluate and assess its accuracy and consistency regarding urological queries. The aim of this study is to evaluate and investigate the reliability of ChatGPT 3.5 in terms of concept description, as well as usefulness for decision-making in clinical practice regarding urology.

METHODS

ChatGPT 3.5 version from March 14 was used. The questions asked for the LLM program involved three urological conditions, Primary Megaureter (pMU), Enuresis and Vesicoureteral Reflux (VUR), that were chosen due to a certain ambiguity regarding its diagnosis and treatment.

Regarding the number of questions prompt to ChatGPT, there were 3 queries for each of the topics mentioned above adding up to 9. All the questions provided to ChatGPT are summarized on Table-1.

Each question was entered as a separate, independent prompt using the "New Chat" function and an anonymous window to minimize bias. The suffix "in a two-page long answer" was used to assure that ChatGPT would provide a similar length answer to every query. The queries were inserted into ChatGPT twice, at the same time, and both responses were recorded to examine the reproducibility of ChatGPT's answers.

Afterwards, both questions were combined, forming a single answer. Subsequently, those responses were evaluated qualitatively by a board of three specialists, considered thought leaders in the field (AK, LB and UB), each providing a report regarding the accuracy of ChatGPT.

Descriptive analyses were performed. ChatGPT answers were categorized in three types, according to its relevance in clinical practice and patient's information (Table-1).

A table (Table-1) with ChatGPT's type of answer was generated.

RESULTS

The information contained in the ChatGPT responses was analyzed by urologists who are experts in the field and have extensive clinical experience in the respective pathologies.

ENURESIS

The ChatGPT defines enuresis as "medical term that refers to the involuntary discharge of urine, usually during sleep, in a person who is beyond the age of toilet training. It is commonly known as bedwetting". However, by definition, enuresis always and not usually occurs during sleep. The usage of the term "usually" in the previous explanation introduces ambiguity and imprecision.

When ChatGPT is asked about the diagnosis of enuresis, it replies that it can be done through "clinical history, physical examination and complementary tests". Regarding the clinical history, the specialist highlighted that crucial aspects were omitted during the anamnesis, including the evaluation of daytime urinary symptoms, and psychological abnormalities, which are essential for making an accurate diagnosis.

The evaluation of the lumbosacral region, which is essential for patients with urinary symptoms, should be highlighted, as it was not mentioned by ChatGPT. Furthermore, the possible presence of bladder prolapse or enlarged prostate should not be included.

Table 1 - Questions to ChatGPT according to pathology and its level of response.

PATHOLOGY	QUESTION	CHATGPT'S TYPE OF ANSWER
ENURESIS	What is the definition of Enuresis?	Type 2
	How to diagnose Enuresis in a two-page long answer?	Type 1
	How to treat Enuresis in a two-page long answer?	Type 1
VESICOURETERAL REFLUX	What is the definition of Vesicoureteral reflux?	Type 3
	What are the indications for endoscopic injection treatment for Vesicoureteral reflux in a two-page long answer?	Type 1
	What are the results for endoscopic injection treatment for Vesicoureteral reflux, in a two-page long answer?	Type 2
PRIMARY MEGAURETER	What is the definition of Primary Megaureter?	Type 2
	How to diagnose Primary Megaureter in a two-page long answer?	Type 1
	How to treat Primary Megaureter in a two-page long answer?	Type 1

Subtitle:
Type 1 - Misleading/Negative Impact to Care.
Type 2 - Helpful to lay person but lacking in substance.
Type 3 - Useful information for patients and treating healthcare providers.

We found the following errors and inconsistencies regarding complementary tests: in relation to ultrasonography, the evaluation of the post void residual is not mentioned and there is no indication of performing a urodynamic study for the diagnosis of enuresis, as well as blood tests. Magnetic resonance imaging would only be indicated in very particular situations. In addition, there is no citation of the voiding diary and nocturnal calendar, which are essential tools.

ChatGPT's answer in regard to treatment contains inaccurate information regarding the effectiveness of bladder training for treating enuresis. The statement suggesting that bladder training involves encouraging the patient to hold urine for progressively longer periods and gradually increasing the time between urinations is incorrect.

Regarding treatment, we found some inconsistency and some missed information. Bladder training does not work for monosymptomatic enuresis.

It does not mention the dose, duration of treatment and the main side effect of the medications, that is, hyponatremia for desmopressin and cardiotoxicity for imipramine; nothing is said about the success rate of the alarm. ChatGPT provided satisfactory comments on urotherapy, however, it falls short in terms of medication guidance and incomplete information about the alarm method. The lack of details on medication usage, main side effects, success rate, and duration of use hampers the ability to make informed decisions based on the description of enuresis treatment provided by ChatGPT.

VESICOURETERAL REFLUX

We have no comment on the definition of this condition provided by ChatGPT, indicating that no inconsistencies were found in the answer.

On the other hand, the response regarding the indication of endoscopic treatment of VUR presented some incomplete and even wrong information. Deflux is FDA approved for grades II-IV and also for duplex ureters that are not mentioned in the text.

For patients with high surgical risk, ChatGPT says that endoscopic injection therapy may be indicated for patients who are at high risk for surgical complications. This information is false, as the procedures are performed under anesthesia in an operating room. Thus, high surgical risk patients are at the same anesthetic risk.

ChatGPT also mentions the treatment of reflux associated with voiding dysfunction. This statement is false because endoscopic injection does not correct lower urinary tract disfunction *per se*. It can be used in this situation, but it does not correct the filling and emptying changes and may result in a lower success rate than children without lower urinary tract disfunction.

When inquired about the outcomes of endoscopic injection for the treatment of reflux, ChatGPT provides a list of points, as outlined below.

Initially, the answer generated talks about preventing recurrent urinary tract infections. It was not considered the experience with more than 5 years of follow-up is 94% of clinical success (7).

Regarding the improvement of kidney function, we found in the answer the explanation that "VUR can cause damage and scarring in the kidneys". Preservation of kidney function is difficult to define, as most grades 1-3 have normal function, so they achieve preserved kidney function. Furthermore, when high success rates are cited in the excerpt, the long-term data is missing.

The answer also includes information about low complication rates, and ChatGPT mentions the possibility of ureteral perforation. We are not aware about this specific complication.

PRIMARY MEGAURETER

Concerning the definition of this condition, ChatGPT has been created in lay-term and imprecise language, avoiding using medical terms such as "ureter". Furthermore, any definition of Primary Megaureter (pMU) must include the dilatation of the ureter, which is exactly what defines this condition, a discussion that ChatGPT does not mention.

In addition, ChatGPT doesn't mention any cutoff point of ureteral dilatation, which is greater than 7mm measured behind the bladder on ultrasonographic transverse view. ChatGPT also continuous to be unspecific as it does not classify pMU in refluxing, obstructive or refluxing obstructive megaureter. The AI platform mentions that megaureter is typically diagnosed in childhood, however most cases are diagnosed antenatally.

Regarding the diagnosis of pMU ChatGPT level of accuracy is low, with generic and incorrect statements. ChatGPT doesn't mention the subtypes that may need a Lasix renal scan (MAG3 or DTPA), a VCUG to rule out VUR or even other tests such as MRU. However, most cases are diagnosed prenatally, therefore physical exam is not required. It also says that the physician needs to palpate the bladder, however, once the problem occurs above the bladder level, bladder is not distended in pMU, showing that ChatGPT gave an incorrect statement.

ChatGPT also says that imaging studies, such as ultrasound is needed; however, its answer is very

simplistic, doesn't mentioning the minimal diameter of the ureter, where it should be measured, the grades of hydronephrosis and other aspects that impacts the medical decision. ChatGPT also recommends doing Voiding cystourethrogram (VCUG), once, according to ChatGPT, it can identify VUR. However, VUR is not a complication of pMU, it is considered one of the three types of megaureter, showing a mistake. Renal scan is mentioned by ChatGPT correctly, but it doesn't mention its major importance: provide information about the drainage of the urinary system which is essential in cases of pMU. ChatGPT also says that urine culture is necessary, but doesn't show the indications of the exam, that's only needed if the child develops a UTI, not being necessary for every patient with pMU. It implied that most patients should have a urine test done as part of the diagnostic work up, which is incorrect. Tests such as renal functional such as glomerular filtration rate (GFR) are also mentioned; however, most children will not need these tests, as the condition is unilateral. The major mistake of ChatGPT is that it doesn't mention the prenatal diagnosis, once there is no way to suspect that a baby has pMU, and most patients are born asymptomatic.

About the treatment options, ChatGPT says correct sentences, such as, it depends on the severity of the condition and any associated complications, the age and overall health of the patients, and that the goals of treatment are to prevent infections, protect kidney function and relieve symptoms if present. However, it doesn't mention the watchful waiting on antibiotics, once evidence has shown that there is a role for antibiotic prophylaxis in patients with pMU, reducing the rate of UTI.

Regarding endoscopic surgery, ChatGPT states that it corrects the dilatation of the ureter, which is not correct. It is the opposite once it corrects the narrow distal segment of the ureter by stretching it with a balloon or a stent. ChatGPT also states that laparoscopic surgery results in less pain and faster recovery rates; however, this has not been shown in cases of tapered ureteral reimplantation. No comparative studies have been done with those pathologies, not been possible to state a sentence like that. It also says that nephrectomy is indicated in some cases that the affected kidney isn't functioning properly or causing complications; however, it is extremely unlikely to have a kidney completely damaged due to pMU.

DISCUSSION

According to Evidence Based Medicine medical decisions should be based on the latest medical research evidence to provide the most appropriated treatment and diagnosis plan for the patient (6). AI has the potential to bring several benefits in medical knowledge, such as improving clinical decision-making and contributing to education, once by making direct questions, ChatGPT gives almost instant answers based on high level evidence.

However, there are concerns related to excessive confidence in technology and ethical issues in its use. At this time, ChatGPT lacks genuine clinical experience and judgment, and may provide wrong information. Urology is a field of medicine with complex pathologies that doesn't necessarily have direct answers and unique diagnosis or types of treatment, making the clinician's experience indispensable. ChatGPT performs well in less complex questions; however, its performance decreases as the complexity of medical decisions increases. It demonstrates knowledge equivalent to a third-year medical student, as shown on Aidan Gilson et al study, based on its performance in United States Medical Licensing Examination® responses (8).

Numerous cardiology and oncology approaches have demonstrated the utility of AI, particularly in identifying and classifying disease phenotypes and improving predictive outcome models by incorporating unstructured data (9-12). Using AI to identify inhaler techniques in electronic health records for asthma care, a study suggests it may be possible to eliminate the expensive manual chart review required for guideline-conformant documentation in asthma care by employing a machine learning strategy (9). However, to the best of our knowledge, no study has evaluated the impact of ChatGPT on

medical decision-making in Urology, regarding those three specific diagnoses. This could lead to a greater efficacy of medical information for the patient, a higher rate of treatment adherence, and a reduction in treatment costs, as well as the secondary effects of incorrectly treating prevalent diseases, such as the ones we analyzed.

In our study, we analyzed the quality of the information provided by ChatGPT in responses on relevant topics in urology. ChatGPT provided wrong answers to important topics, such as, the definition of enuresis, which was partially correct. It gave generic responses that did not align with reality. Concerning the evaluation and diagnosis, ChatGPT omitted crucial aspects of anamnesis, which is an essential part of clinical evaluation and defines decision-making.

After analyzing the response regarding enuresis, we identified unnecessary diagnostic exams being suggested, including urodynamic studies and magnetic resonance imaging.

Regarding the endoscopic treatment of vesicoureteral reflux, we had a response that could confuse the reader regarding the method's efficacy. This is due to the lack of citation of results found in relevant published studies on the subject, as well as suggesting outcomes that are not realistic, such as the resolution of urinary symptoms (13-15). This error in treatment is repeated in the response about enuresis, which mentions ineffective treatments such as bladder training.

Our findings concur with those of Katharina Jeblick et al., who examined the use of ChatGPT in radiology reports. They found both accurate and incorrect statements, which were categorized into four error categories: misinterpretation of medical terms, imprecise language, hallucination, strange language, and grammatical errors (16). While we did find accurate information, given ChatGPT's broad background, the language models employed lack specialized medical understanding and knowledge, resulting in imprecise responses that occasionally contain phrases from previous interactions (17, 18).

Therefore, ChatGPT is a tool that can facilitate public access to information. However, these technologies must be upgraded to enhance the comprehension of medical questions and facilitate clinical decision-making by providing more specific answers and fewer generic texts.

CONCLUSIONS

ChatGPT responses contain a mosaic of accurate and pertinent information; however, the majority of its responses contain broad, insufficient, and misleading information. In the face of the experts' feedback and evaluations, it is not recommended to base clinical and therapeutic decisions solely on ChatGPT's knowledge. It is important to disseminate this information to non-expert professionals and patients, given that ChatGPT has received significant media attention and is widely accessible to the public. In this way, we seek to protect users from harm.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Smoking characteristics and years since quitting smoking of US adults diagnosed with lung and bladder cancer: A national health and nutrition examination survey analysis

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ABSTRACT

Purpose: Smoking is a recognized risk factor for bladder BC and lung cancer LC. We investigated the enduring risk of BC after smoking cessation using U.S. national survey data. Our analysis focused on comparing characteristics of LC and BC patients, emphasizing smoking status and the latency period from smoking cessation to cancer diagnosis in former smokers.
Materials and Methods: We analyzed data from the National Health and Examination Survey (2003-2016), identifying adults with LC or BC history. Smoking status (never, active, former) and the interval between quitting smoking and cancer diagnosis for former smokers were assessed. We reported descriptive statistics using frequencies and percentages for categorical variables and median with interquartile ranges (IQR) for continuous variables.
Results: Among LC patients, 8.9% never smoked, 18.9% active smokers, and 72.2% former smokers. Former smokers had a median interval of 8 years (IQR 2-12) between quitting and LC diagnosis, with 88.3% quitting within 0-19 years before diagnosis. For BC patients, 26.8% never smoked, 22.4% were active smokers, and 50.8% former smokers. Former smokers had a median interval of 21 years (IQR 14-33) between quitting and BC diagnosis, with 49.3% quitting within 0-19 years before diagnosis.
Conclusions: BC patients exhibit a prolonged latency period between smoking cessation and cancer diagnosis compared to LC patients. Despite smoking status evaluation in microhematuria, current risk stratification models for urothelial cancer do not incorporate it. Our findings emphasize the significance of long-term post-smoking cessation surveillance and advocate for integrating smoking history into future risk stratification guidelines.

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INTRODUCTION

Bladder cancer (BC) is the most common smoking-related genitourinary cancer (1, 2). The duration and intensity of tobacco exposure has a strong relationship with BC incidence and potentially disease stage at presentation. Active smokers have been identified as the individuals at greatest risk of developing BC, with a two to four-fold higher risk than never smokers (2-5). Since 2005, in the US and worldwide, the prevalence of former smokers has grown to exceed active smokers, potentially due to effective anti-smoking campaigns (6, 7).

It is not currently known how the risk of developing BC changes over time among those that quit smoking. By way of comparison, it has been shown that the risk of developing lung cancer (LC) is greatly reduced 15 years after quitting smoking. Accordingly, the US Preventive Services Task Force (USPSTF), former smokers aged 50-80 years no longer need thoracic CT scans after this point (8). There is comparatively less data about how the risk of BC changes after quitting smoking. Still, there is evidence that the risk of BC might persist up to several decades (9-12). Thus, we hypothesized that the risk of BC might persist over several decades even after quitting smoking. In this setting, we sought to assess differences in the smoking status and the interval from quitting smoking to cancer diagnosis among a national sample of men and women with a personal history of LC and BC.

MATERIALS AND METHODS

Data source

The National Health and Nutrition Examination Survey (NHANES) is a major National Center for Health Statistics program designed to assess adults' and children's health and nutritional status in the US by combining interviews and physical examinations. This nationally representative cross-sectional survey is conducted in two-year cycles, and data are available to the public on the National Center for Health Statistics website (13). The survey uses a complex, multi-stage, stratified sampling frame design to ensure that the sample is representative of the US civilian, non-institutionalized population of all ages. The sample is updated every two years to maintain representativeness. Data are collected during an in-home interview and in a mobile examination center. In the in-home interview, the family and sample person questionnaires are administered by trained interviewers in English or Spanish using the Computer-Assisted Personal Interview (CAPI) system. The overall response rate is approximately 60-70%, varying across demographic groups and survey cycles. All the data are then reviewed and edited to guarantee completeness and consistency of answers, and the resulting data are weighted to address non-response bias (14, 15). We obtained institutional review board approval (IRB Number: 2015P000341) for the use of de-identified administrative data.

For this study, we retrospectively queried NHANES to collect data from successive survey cycles conducted between 2003 and 2016. Specifically, we focused on extracting data from the "Questionnaire data", "Medical conditions" and "Smoking-Cigarette Use" sections, derived from the in-home interview of the survey. It is pertinent to note that NHANES data following 2016 were not included in the analyses because weighting variables changed in the year cohorts after 2016.

The modification in weighting variables after 2016 may have unintentionally given the false impression of a temporal shift that did not truly occur. Consequently, the chosen timeframe, encompassing the years 2003 to 2016, was judiciously selected to standardize the analytical framework. This temporal constraint ensures uniformity in variable utilization and weighting procedures throughout the considered period.

Study subjects

We included individuals aged 20 and older who completed the in-home interview. Our cohort included individuals who answered "Yes" to the question "Ever told you had cancer or malignancy" and who answered, "Lung cancer" or "Bladder cancer" at least once to the three questions "What kind of cancer" (MCQ230a – MCQ230b – MCQ230c). Since the survey only captured information on each participant's age at the first BC or LC event, we included only the first reported event in our analyses. Therefore, if a participant reported multiple BC or LC cancer events, we only considered the first event for our analyses.

Among those with a personal history of LC or BC, we designated as never smokers those individuals who answered "no" to the question "Smoked at least 100 cigarettes in life" and "Not at all" to the question "Do you now smoke cigarettes". We designated as active smokers those individuals who answered "yes" to the question "Smoked at least 100 cigarettes in life" and "yes" to the question "Do you now smoke cigarettes". Finally, we designated as former smokers those individuals who answered "yes" to the question "Smoked at least 100 cigarettes in life" and "not at all" to the question "Do you now smoke cigarettes". This classification of never, active, and former smokers among individuals with a personal history of LC or BC is based on a conventional approach commonly employed to categorize smoking status in epidemiological research (16).

For former smokers, we derived the years since quitting smoking at the time of the survey using the following two questions: "how long since quit smoking cigarettes" and "Unit of measure (day/week/month/year)". To account for the inconsistent grouping of long-term quitters in different survey cycles, individuals who stopped smoking more than 50 years ago were assigned 50 years since quitting smoking. The variable "years since quitting smoking" was then categorized into the following groups: ≤9, 10-19, 20-29, 30-39, 40-49, and ≥ 50. In this way, we could provide granular information regarding LC and BC events distribution across different years since quitting smoking categories.

Finally, to determine the duration between smoking cessation and LC or BC diagnosis, we utilized the variables "age at bladder cancer diagnosis", "age at lung cancer diagnosis", "age at interview", and "years since quitting smoking". First, we plotted the distribution of LC and BC events according to the years that elapsed between smoking cessation and LC or BC diagnosis. Therefore, we categorized the years elapsed into 10-year intervals: ≤9, 10-19, 20-29, 30-39, 40-49, and ≥ 50 years.

To estimate the number of pack-years smoked, the years of smoking cigarettes exposure were derived using the variables "age started smoking cigarettes regularly" and "age last smoked cigarettes regularly". The "number of cigarettes smoked during the entire life" was approximated using the "number of cigarettes smoked per day when quit" and the years of smoking cigarettes exposure. The "number of cigarettes smoked during the entire life" was then converted into pack-years smoked by dividing it by 20 (the mean number of cigarettes per pack). Finally, the number of pack-years was categorized into 0.1-20 ("light smokers"), 20.1-40 ("moderate smokers"), and 40.1 or above packs-year ("heavy smokers") (17).

Statistical Analysis

Since data was used from the in-home interview, the sample "interview weight variable" (wtint2yr) was used to weigh the data. A proper weighting procedure was followed to construct the correct weight variable for combined NHANES Survey Cycles as indicated on the NHANES website (11). The following variables were used to define strata (sdmvstra), and cluster (sdmvpsu). We reported descriptive statistics using frequencies and percentages for categorical variables, and median with interquartile ranges (IQR) for continuous variables, accounting for the complex survey (weights, strata, and cluster). All statistical analyses were performed using STATA (Stata/SE 17.0 for Mac [Apple Silicon] Revision 13 Oct 2022, Copyright 1985-2021 StataCorp LLC), and two-sided P values < 0.05 were considered statistically significant.

RESULTS

Cohort and baseline characteristics

We identified 39,221 individuals older than 19 who completed NHANES surveys between 2003 and 2016, corresponding to a Weighted National Estimate (WNE) of 219,596,787 individuals. Among those, 953,386 (WNE) individuals reported a history of LC and BC. Overall, 53.6% (WNE of 510,975 individuals) of our sample reported a personal history of LC, whereas 46.4% (WNE of 442,411 individuals) reported a history of BC. For patients with LC, the median age at diagnosis was 62 (IQR 55 – 69), and the median age at the time of the survey was 67 (IQR 63 – 74). For patients with BC, the median age at diagnosis was 55 (IQR 55 – 75), and the median age at the time of the survey was 76 (IQR 66 – 80). Further demographic details are shown in Table-1.

Table 1 - Patient baseline characteristics according to lung or bladder cancer diagnosis.

	Lung cancer	Bladder cancer	Total	p-value
	N=99 **N*=510,975**	**N=98** **N*=442,411**	**N=197** **N*=953,386**	
Gender				**0.061**
Male	57 (57.6%) *260,476 (51.0%)	69 (70.4%) *286,677 (64.8%)	126 (64.0%) *547,153 (57.4%)	
Female	42 (42.4%) *250,499 (49.0%)	29 (29.6%) *155,734 (35.2%)	71 (36.0%) *406,233 (42.6%)	
Age at the time of the survey				**0.055**
20-39	2 (2.0%) *14,116 (2.8%)	2 (2.0%) *7,698 (1.7%)	4 (2.0%) *21,814 (2.3%)	
40-59	18 (18.2%) *109,641 (21.5%)	6 (6.1%) *43,572 (9.8%)	24 (12.2%) *153,213 (16.1%)	
60-79	53 (53.5%) *295,784 (57.9%)	54 (55.1%) *262,771 (59.4%)	107 (54.3%) *558,556 (58.6%)	
≥ 80	26 (26.3%) *91,433 (17.9%)	36 (36.7%) *128,370 (29.0%)	62 (31.5%) *219,803 (23.1%)	
Smoking status at the time of the survey				**0.002**
Never Smokers	10 (10.1%) *45,265 (8.9%)	28 (28.6%) *118,436 (26.8%)	38 (19.3%) *163,701 (17.2%)	
ACTIVE Smokers	17 (17.2%) *96,640 (18.9%)	19 (19.4%) *99,065 (22.4%)	36 (18.3%) *195,705 (20.5%)	
Former Smokers	72 (72.7%) *369,070 (72.2%)	51 (52.0%) *224,910 (50.8%)	123 (62.4%) *593,980 (62.3%)	
Age at lung cancer diagnosis				
20-39	2 (2.0%) *14,116 (2.8%)	/	2 (2.0%) *14,116 (2.8%)	
40-59	26 (26.5%) *159,408 (32.1%)	/	26 (26.5%) *159,408 (32.1%)	
60-79	60 (61.2%) *294,613 (59.3%)	/	60 (61.2%) *294,613 (59.3%)	
≥ 80	10 (10.2%) *28,927 (5.8%)	/	10 (10.2%) *28,927 (5.8%)	

Age at bladder cancer diagnosis				
20-39	/	1 (1.0%) *4,118 (0.9%)	1 (1.0%) *4,118 (0.9%)	
40-59	/	29 (30.2%) *155,148 (35.5%)	29 (30.2%) *155,148 (35.5%)	
60-79	/	47 (49.0%) *215,624 (49.3%)	47 (49.0%) *215,624 (49.3%)	
≥ 80	/	19 (19.8%) *62,711 (14.3%)	19 (19.8%) *62,711 (14.3%)	
Age when quit smoking				**<0.001**
< 20	1 (1.4%) *4,526 (1.2%)	1 (2.0%) *7,728 (3.5%)	2 (1.7%) *12,254 (2.1%)	
20-39	6 (8.5%) *35,449 (9.7%)	11 (22.0%) *54,481 (24.8%)	17 (14.0%) *89,931 (15.3%)	
40-59	26 (36.6%) *141,439 (38.5%)	29 (58.0%) *130,600 (59.4%)	55 (45.5%) *272,039 (46.3%)	
60-79	38 (53.5%) *185,694 (50.6%)	9 (18.0%) *27,216 (12.3%)	47 (38.8%) *212,910 (36.3%)	
Years since quitting smoking at the time of the survey				**<0.001**
0-9	34 (47.2%) *169,278 (45.9%)	7 (14.0%) *18,679 (8.5%)	41 (33.6%) *187,956 (31.9%)	
10-19	22 (30.6%) *134,889 (36.5%)	5 (10.0%) *22,068 (10.0%)	27 (22.1%) *156,957 (26.6%)	
20-29	7 (9.7%) *36,317 (9.8%)	12 (24.0%) *61,632 (28.0%)	19 (15.6%) *97,950 (16.6%)	
30-39	5 (6.9%) *16,398 (4.4%)	14 (28.0%) *51,366 (23.3%)	19 (15.6%) *67,763 (11.5%)	
40-49	4 (5.6%) *12,188 (3.3%)	7 (14.0%) *42,743 (19.4%)	11 (9.0%) *54,931 (9.3%)	
≥ 50	0 (0.0%) *0 (0.0%)	5 (10.0%) *23,537 (10.7%)	5 (4.1%) *23,537 (4.0%)	
Number of pack-years smoked				**0.050**
0/20 pack-years	13 (20.0%) *69,221 (21.2%)	19 (40.4%) *94,944 (44.9%)	32 (28.6%) *164,215 (30.5%)	
20.1/40 pack-years	13 (20.0%) *72,689 (22.2%)	9 (19.1%) *34,766 (16.4%)	22 (19.6%) *107,455 (19.9%)	
> 40 pack-years	39 (60.0%) *185,027 (56.6%)	19 (40.4%) *82,022(38.7%)	58 (51.8%) *267,049 (49.6%)	

Data are presented as n (%).
*= weighted national estimates

Smoking status and Pack Year History

Among survey respondents with a history of LC, 8.9% were never smokers, 18.9% were active smokers, and 72.2% were former smokers at the time of the survey. Among survey respondents with a history of BC, 26.8% were never smokers, 22.4% were active smokers, and 50.8% were former smokers at the time of the survey. Table-2a illustrates the smoking status at the time of cancer diagnosis and at the time of the survey for LC and BC survivors. Among our cohort of LC or BC patients who were former smokers 30.5% of them had a light smoking history (< 20 pack-years), 19.9% had a medium smoking history (20-40 pack-years), and 49.6% of them had a heavy smoking history (> 40 pack-years).

Years From Quitting to Diagnosis Among Former Smokers

A total of 88.3% of former smokers with a history of LC were diagnosed 0-19 years after quitting, with the majority (66.0%) being diagnosed 0-9 years after quitting. The median interval from quitting smoking to LC diagnosis was 8 years (IQR 2-12). In contrast, 49.3 % of former smokers with a history of BC were diagnosed 0-19 years after quitting. The median interval from quitting smoking to BC diagnosis was 21 years (IQR 14-33). Table-2b and Figure-1 illustrate the distribution of LC or BC events affecting the population of former smokers after quitting smoking, looking at the years elapsed from quitting smoking to

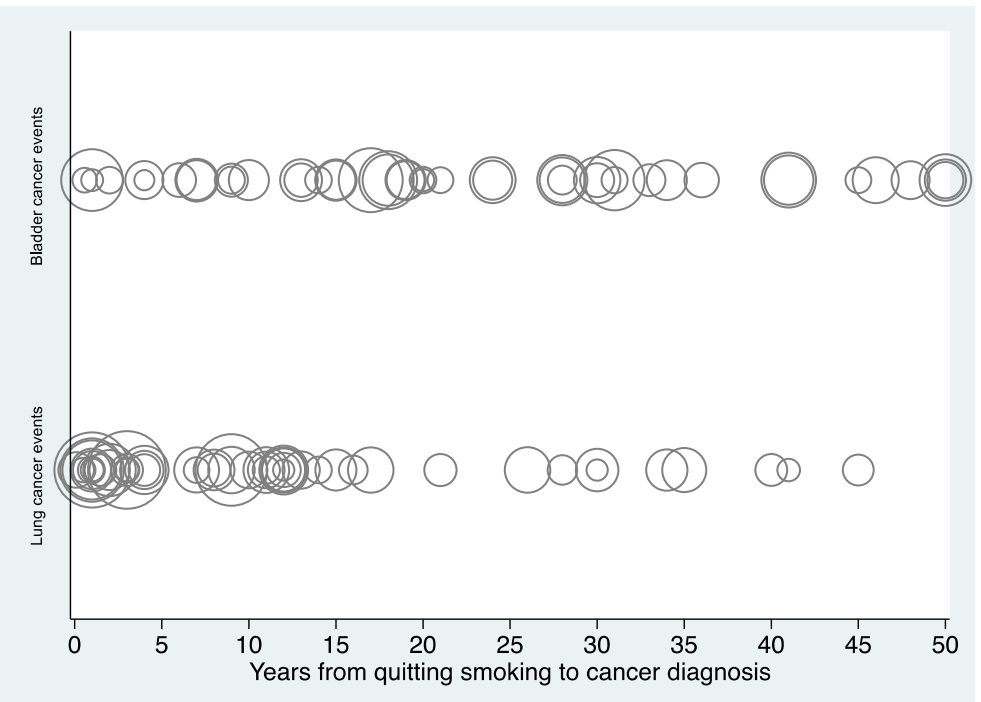
Table 2a. Frequencies of smoking status attitude at the time of cancer diagnosis and at the time of the survey for Lung cancer survivors and Bladder cancer survivors. Data are captured in the National Health and Nutrition Examination Survey from 2003 to 2016 and they are presented as weighted national estimates (%).

Smoking Status	Lung Cancer Survivors (%)		Bladder Cancer Survivors (%)	
	Diagnosis	**Survey**	**Diagnosis**	**Survey**
Never Smokers	8.9	8.9	26.8	26.8
Active Smokers	24.8	72.2	2.9	50.8
Former Smokers	24.8	18.9	2.9	22.4

Table 2b. Distribution of Lung or Bladder cancer events affecting the population of former smokers after quitting smoking, stratified according to the latency period to cancer diagnosis. The time elapsed between smoking cessation and Lung or Bladder cancer diagnosis is stratified into 10-year categories. Data are captured in the National Health and Nutrition Examination Survey from 2003 to 2016 and they are presented as weighted national estimates (%).

Years Since Quitting Smoking	Lung Cancer Events (%)	Bladder Cancer Events (%)
0-9 years	67.0	20.0
10-19 years	21.2	29.3
20-29 years	3.8	14.5
30-39 years	5.7	15.4
40-49 years	2.3	13.1
50 years	0	7.7

Figure 1 - Distribution of lung or bladder cancer events affecting the population of former smokers after quitting smoking according to the years elapsed between quitting smoking and (A) Lung cancer diagnosis, and (B) Bladder cancer diagnosis, captured in the National Health and Nutrition Examination Survey from 2003 to 2016. The plot depicts the relationship between the time elapsed since smoking cessation, presented as a continuous variable, and lung or bladder cancer diagnosis. Circle-hollow markers are used to represent individual cases, with the size of the markers that is proportional to the number of lung or bladder cancer events reported at each time point.



Data are presented as weighted national estimates.

LC or BC diagnosis as a categorical and continuous variable, respectively.

DISCUSSION

This study describes the self-reported smoking status and interval from quitting smoking to diagnosis among a sample of US adults with LC or BC. Whereas most former smokers with LC reported a short duration between quitting smoking and diagnosis (median of 8 years [IQR 2-12]), former smokers with a history of BC reported a much longer (>2.5x) interval between quitting and diagnosis (median interval of 21 years [IQR 14-33]).

While this study did not prospectively follow former smokers (it is subject to survivor bias and cannot prospectively estimate the risk at each year after quitting smoking), the findings illustrate the typical interval between quitting and diagnosis among a sample of survey respondents with LC and BC. Among respondents with BC, a comparatively large portion are diagnosed several decades after quitting smoking with an average interval of over 20 years from quitting to diagnosis. This contrasts with LC: among

survey respondents with LC, most had quit less than 10 years before diagnosis. This is consistent with existing research showing a large LC risk reduction 15 years after quitting and supports consensus recommendations that LC screening can be curtailed post-quitting (18-20).

In contrast, the findings in BC support current American Urological Association guidelines that incorporate smoking history and pack-years into risk stratification for possible urothelial cancer in patients with microhematuria, with no reduction in risk categorization based on years since quitting smoking (21-23).

Biological evidence supports a prolonged latency between smoking cessation and BC diagnosis. Bladder cancer can be caused by various factors, including lifetime exposure to toxins like aromatic amines, pioglitazone medication, aristolochic acid in dietary supplements, and arsenic in drinking water, all of which can damage DNA. Cell growth, invasion, and metastasis require the acquisition of specific properties, including uncontrolled growth and cellular mobility mediated by EGF and EGFRs, modulation of cell adhesion molecules, and overproduction of angiogenic factors. As with colorectal cancer, BC pathogenesis involves a buildup of stereotyped phenotypic and molecular alterations leading to progression from adenoma to carcinoma, which can result in a prolonged latency between the genetic origins of the disease and the onset of clinically detectable symptoms. As a consequence, the disease primarily affects older adults due to the cumulative impact of long-term exposure to carcinogens and procarcinogens as well as deficient DNA repair mechanisms in this population, uncertain immune mechanisms, and local factors such as urinary retention that collectively contribute to increased disease risk (24, 25).

Furthermore, the number of former smokers is constantly increasing. As previously pointed out, it exceeded that of active smokers in the early 2000s (7). Looking at BC statistics in the US from 2005, a reduction from 19.9 (in 2005) to 16.8 (in 2019) of BC observed events rate per 100,000 persons is reported (15, 20). Seisen et al. already underlined that assuming quitting smoking leads to an immediate and progressive reduction in BC risk, the large variations in tobacco smoking prevalence only partially explain the incidence trends for BC in the US population over the past half-century. Therefore, they addressed occupational and environmental exposures and genetic predispositions as the possible explanatory of this persistence of high BC incidence (26). Our finding that large portions of BC patients are diagnosed several decades after quitting smoking suggests that the relationship between smoking and BC risk may be more complex and long-lasting.

Our study has several limitations. Firstly, recall bias may have affected the accuracy of self-reported data on medical conditions and smoking habits. Secondly, we only focused on smoking habits as a risk factor for BC and LC, excluding other known risk factors such as occupational and environmental exposure, genetic background, and infective pathogens. Additionally, our findings are based on the self-reported data of former smokers with a history of LC or BC, and only those who survived long enough to fill out the survey post-diagnosis were included. If data on those who died were available, the time from quitting smoking until cancer diagnosis could be shorter in both groups. This may affect the interpretation of our results. Furthermore, BC is typically diagnosed at an older median age than LC and has a higher survival rate. This may lead to bias in the sample, over-representing those with BC and a longer latency period. Lastly, due to differences in data collection across NHANES cycles, some approximations were made in reporting certain variables in the analysis.

Despite limitations, our study highlights an extended latency period post-smoking cessation and BC diagnosis, particularly in contrast to the analogous interval observed for lung cancer in former smokers. Our study supports ongoing BC risk even many years after quitting smoking.

CONCLUSIONS

These results highlight the typical smoking history of individuals with lung and bladder cancer responding to a large national survey of US adults. Although there are potential sources for bias with any retrospective survey-based research, large portions of survey respondents with bladder cancer were diagnosed several decades after quitting smoking,

with an average of nearly 25 years between quitting and diagnosis. This finding supports current guidelines and risk stratification models, which incorporate smoking history as a bladder cancer risk factors even many years after quitting.

COMPLIANCE WITH ETHICAL STANDARDS

This study received institutional review board approval (IRB Number: 2015P000341) for the use of de-identified administrative data.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The landscape of biomedical research funding in Brazil: a current overview

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ABSTRACT

Objective: The objective of this narrative review is to discuss the current state of research funding in Brazil.

Materials and Methods: This study is based on the most recent edition of the course Funding for Research and Innovation in the University of Sao Paulo School of Medicine which was a three-day course with 12 hours of instruction. The course brought together leading experts in the field to comprehensively discuss the current state of research funding in Brazil. Each speaker provided a presentation on a specific topic related to research funding. After the workshop, speakers assembled relevant topics in this manuscript.

Results: collaborative research is critical for securing research funding. It optimizes proposal competitiveness, amplifies societal impact, and manages risks effectively. As such, fostering and supporting these collaborations is paramount for both researchers and funding agencies. To maintain the highest integrity in research, investigators involved in these collaborations must disclose any relationships that could potentially influence the outcomes or interpretation of their projects.

Conclusions: In Brazil, the mainstay of research funding stems from public entities, with agencies such as CNPq, CAPES, and state bodies like FAPESP, FAPERJ, FAPEMIG and others at the forefront. Concurrently, industry funding offers viable pathways, especially through industry-sponsored studies, investigator-led projects, and collaborative initiatives. The Brazilian funding landscape is further enriched by innovative platforms, including crowdfunding and the contributions of institutions like the Serrapilheira Institute. Internationally, esteemed organizations such as the National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation stand out as potential funders.

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INTRODUCTION

IScience funding is important to develop knowledge, technology, and foster innovation. Although it is universally accepted that it is essential to invest in biomedical research, funding in this field differs considerably among countries.

Total global investment in biomedical and health research was estimated at US$240 billion in 2009, equivalent to approximately US$300 billion in 2023 (1). Governments have been the main source for biomedical research funding throughout the World. The health gains arising from biomedical research are easy to demonstrate as they lead to new ways to prevent, diagnose, and treat illnesses, as seen in the recent development of effective vaccines and treatments for COVID-19. Moreover, biomedical research prepare world-class scientists and has the potential to bolster the economy and reduce the burden of illness (2, 3).

Funding is critical to maintaining research labs and active researchers, who often rely on research grants for their salaries or stipends. The NIH (National Institutes of Health – United States' medical research agency) is the largest public funder of biomedical research in the World, providing research grants that support more than 300,000 researchers at more than 2,500 institutions in the United States. Other very important national agencies that fund biomedical research are the European Research Council (European Union), the Medical Research Council (United Kingdom), the Deutsche Forschungsgemeinschaft (Germany) and the National Natural Science Foundation of China.

In Brazil, research funding is provided through different systems and institutions, which are directly or indirectly linked to Brazilian ministries or federal agencies, such as the National Council for Scientific and Technological Development (CNPQ – Brazil), Coordination for the Improvement of Higher Education Personnel (CAPES), Financier of Studies and Projects (FINEP) and National Fund for Scientific and Technological Development (4). In addition, several state Foundations for Research Support provide funding, like FAPESP (Sao Paulo Research Foundation), Rio de Janeiro State Research Foundation (FAPERJ) and Minas Gerais State Research Foundation (FAPEMIG) (5, 6).

Significant constraints in research funding have been observed in many countries in the past few years and Brazil has been affected significantly (4, 5, 7). Because government research funding is limited, finding sources other than the government has become a top priority of several research groups (8-16).

The objective of this narrative review is to discuss the current state of research funding in Brazil.

MATERIALS AND METHODS

Since many researchers and postgraduate students in the early phase of their careers do not have a proper understanding of the importance as well as of the process and opportunities for obtaining funding for scientific research in Brazil, we have developed a discipline entitled "Funding for Research and Innovation" in the University of Sao Paulo School of Medicine. This narrative review is based on the most recent edition of the course, which was a three-day course with 12 hours of instruction that was held in São Paulo, Brazil, in November 2022. The course brought together leading experts in the field to comprehensively discuss the current state of research funding in Brazil. Each speaker provided a presentation on a specific topic related to research funding. After the workshop, speakers assembled relevant topics in this manuscript.

The discipline focus on biomedical research funding in Brazil and our audience consists of postgraduation students (Master's or Doctoral students) from different backgrounds and with different levels of experience in biomedical research. The program was developed to address the domains: (1) Importance of funding in biomedical research, (2) Elements of a remarkable research project, (3) Opportunities with public funding Agencies for biomedical research in Brazil, (4) Industry funding for biomedical research, (5) Other funding opportunities; (6) Fundable items in a research project and (7) Step by step submission of a research project to a government funding institution. The instructional methods consist of alternating lectures and discussions as detailed in Table-1.

Table 1 - Course programme.

Day	Time	Activity - Topic	Instructional method
1	08:00-08:15	Welcome and Introduction	
1	08:15-09:00	Fundraising Essentials: Understanding value, Ethics and financial Implications	Lecture and Q&A*
1	09:00-09:45	Navigating the CNPQ** Landscape: Opportunities & Unique Aspects	Lecture and Q&A
1	09:45-10:00	Break	Health
1	10:00-10:45	The Reviewer's perspective: Mastering Grant Success Elements and Priorities	Lecture and Q&A
1	10:45-11:30	A Guide to Grant Applications: Strategies to optimizing Success	Lecture and group discussions
1	11:30-12:00	Efficient Resource Management in sponsored Clinical Studies	Lecture and Q&A
2	**08:00-08:15**	**Opening of Day 2**	
2	08:15-09:00	The Role of the Private Sector and Philanthropy in Modern Research Funding	Lecture and Q&A
2	09:00-09:45	Innovative Research Funding: The Pivotal Role of FAPESP	Lecture and Q&A
2	09:45-10:00	Break	Health
2	10:00-10:40	Ensuring Quality: Addressing Bias in Funded Research and its Publication Impact	Journal club and group discussions
2	10:40-11:20	Crowdfunding: A Modern Frontier for Scientific Research Funding	Lecture and Q&A
2	11:20-12:00	Driving Innovation: A Look at Butantan's Financial model	Lecture and Q&A
3	**08:00-08:15**	**Opening of Day 3**	
3	08:15-09:00	Research at the University of São Paulo: Current funding profile and perspectives	Lecture and Q&A
3	09:00-09:45	The Pharmaceutical Industry's Role in funding Modern Research	Lecture and Q&A
3	09:45-10:00	Break	Health
3	10:00-10:30	The Editor's perspective: Perceptions of Industry-Funded Research in Indexed Journals	Lecture and group discussions
3	10:30-11:15	Research at Hospital Israelita Albert Einstein: Opportunities and challenges	Lecture and Q&A
3	11:15-12:00	Exploring Funding Prospects with International Agencies	Lecture and Q&A
3	12:00-12:05	Closing remarks	

DISCUSSION

Importance of obtaining funding for biomedical research

For researchers engaged in biomedical studies, obtaining funding is critical for the development of high quality research (17, 18). The economic resources provide capital for the acquisition of essential equipment, recruitment of skilled work force, and coverage of several research-related expenses. With funding, researchers can conduct higher quality studies that result in increased citations enhancing the overall scientific impact of their work (17, 19, 20).

In addition, securing funding may be important for career advancement. Success in grant applications is often perceived as an important quality and an indicator of potential for academic success in future (21). It not only proves the researcher's capacity to obtain financial resources, but also the ability to conceive and plan robust scientific investigations.

Beyond its impact on individual projects and careers, funding also facilitates broader collaborative studies (22, 23). It encourages the union of diverse academic disciplines, fostering a more comprehensive approach to research. Furthermore, securing funding amplifies a researcher's recognition and credibility within the scientific community. This increases the reach for disseminating their findings, providing better opportunities for sharing their work through publications and presentations. Essentially, funding does not only support the research projects, but also promotes the careers of the scientists behind the research, improving their reputation, and expanding their influence within the academy (24, 25).

For the institutions involved in scientific research, the acquisition of funding may also have a profound impact and may play an important role in ensuring their financial viability and supporting a wide array of institution-related costs (26). Research funds may provide the necessary resources to sustain and enhance the research infrastructure, including the acquisition of lab equipment, restoration of research facilities, and implementation of new research methodologies. Obtaining research funding continuously renders research institutions highly attractive to the most talented prospects within the scientific community, which often drives high quality research and ultimately elevates institution's prestige (27, 28).

Obtaining research funding also plays a pivotal role in preserving employment within the research sector and maintaining the operations of research facilities. Adequate funding ensures the continuation of scientific endeavors and sustains the livelihoods of many within the research realm.

Characteristics of a remarkable research project

Undertaking the preparation and submission of a biomedical research grant application is a significant commitment. This highly competitive task can be threatened by insufficient planning, inadequate preparation, disorganization, and uninspiring presentation. The proponent must be sure to allow sufficient time to plan, organize, and complete a grant application that stands out in the peer review process.

This section provides tips and strategies for planning and organizing your application. It is important to collaborate closely with your institution's grant support office or the equivalent department that oversees sponsored programs, to understand the internal protocols for submitting an application. The advice provided here is primarily oriented towards Research Project Grants. The tips and guidance provided in this document are not intended to supersede an organization's internal guidelines, specific advice from program or grants management staff, or instructions from various application guides. The study proposal must rise above plenty of submissions, demonstrating innovative thinking and scientific rigor. In addition, having the potential to impact public health is certainly an advantage. Considering this, several key characteristics define a remarkable research project suitable for funding:

1. Significance and Innovation: The project must address a significant question or issue whether it pertains to a clinical problem or explores fundamental physiological or pathophysiological topics, using a novel approach. The innovative aspect could stem from the problem itself, the methodology, or the anticipated results. The pro-

posal should make clear the urgency and relevance of the research question and how the innovative approach can provide groundbreaking insights (8, 29).

2. Clear and feasible objectives: A well-defined objective that is based on a testable hypothesis is crucial. It should be relevant, specific, measurable and achievable. It is equally important to ensure that the objectives can be feasibly achieved within the proposed timeframe and budget. It has been shown that completion of a pilot or feasibility study is a strong predictor of success in obtaining funding (30).

3. Scientific and methodological rigor: The project should have a robust and reproducible methodology. This includes clearly defined population and procedures, control measures, and data analyses plans. Rigor and transparency in methodology not only increase the credibility of the project but also allow for replication and validation of the results by other researchers.

4. Interdisciplinarity and collaborative approach: Involving researchers with different backgrounds and expertise may improve the quality of a research project (29, 31). Increasingly, biomedical research is becoming interdisciplinary, involving experts from different fields such as biology, epidemiology, medicine, bioinformatics, and more. Such collaborative efforts can help address complex research questions from multiple angles and potentially yield more impactful results (22).

5. Strong research team: The expertise and experience of the research team is essential (31). A diverse team, where each member brings unique skills and knowledge, will add credibility to the project. Government funding agencies value the track record of the Principal Investigator (PI) and team members in carrying out successful research. In addition, working in a well-recognized research institution seems to be a positive characteristic for increasing the odds of getting a research proposal funded (26). Researchers in the beginning of their career may improve their chances of getting funded by collaborating with accomplished investigators (23, 30, 32).

6. Ethical aspects: A high-quality research proposal must clearly address ethical considerations, including patient consent, privacy, and data security. It should demonstrate that the benefits of the research outweigh potential risks to the participants.

7. Dissemination and translation of results: The project should have a plan for disseminating research results, translating the outcomes into policy or practice, or commercialization of the product if relevant. A good dissemination plan increases the potential impact of the research.

8. Patient and public involvement: Research that involves the public or patients in its design and execution can provide real-world context and relevance. It shows the agency that the project is not only theoretically sound but also practical, and that it is likely to make a tangible difference to the intended beneficiaries.

In summary, a remarkable biomedical research project suitable for government funding is characterized by its significance, novelty, feasibility, rigor, collaborative nature, strong team, ethical soundness, and potential for impact. Preparing a project with these features increases the likelihood of securing funding from government agencies (33).

Fundable items in a research project

Generally, government entities that fund scientific research follow comparable guidelines for providing financial support and permit the incorporation of similar expenditure items. Expense items are classified as Capital (permanent material acquired) and Operating Expenses (consumables, third-party services, travel, and daily allowances).

Permanent material includes the purchase of equipment, furniture, computers, machinery, bibliographic material, vehicles, renovations, or installations.

Operating Expenses include consumables, payment for clinical analyses, service providers, air/land travel, and daily allowances.

It is imperative that researchers justify each item requested, based on the proposed objectives and expected results of the study.

In addition to the expense items that are inherent to the study proposal, financing agencies may provide additional resources intended for unforeseen expenses directly related to the projects.

At FAPESP, the "Technical Reserve" is an integral part of most study grants and is divided into 'Complementary Benefit' and 'Direct Infrastructure Costs of the Project.' The 'Complementary Benefit' is primarily intended to cover expenses with participation in scientific or technological meetings, either nationally or internationally. However, if the resource is not used for this purpose, it can cover unforeseen Capital and Operating Expenses in the project. The 'Direct Infrastructure Costs of the Project' is exclusively intended to cover costs/services related to Capital and Operating Expenses NOT initially foreseen in the project.

Research grants from government funding agencies in Brazil do not cover researchers' salaries or stipends. It is expected that these will be provided by the institution to which the principal investigator is affiliated. Associated researchers involved in the study may receive a scholarship that can be included in the study proposal or requested from the funding agency separately, regardless of the specific project.

With respect to studies funded by the pharmaceutical industry, the budget can include all items necessary for conducting the research, including the payment of the researchers involved.

Studies financed by philanthropic or crowdfunding initiatives usually have more flexible resource allocation rules due to a lack of strict oversight on resource utilization. This does not imply unrestricted use of funds, but rather that these projects have less stringent accounting requirements, and their success is generally assessed based on the achievement of initially proposed objectives.

Public funding for biomedical research in Brazil

Brazilian investment in research and development (R&D) is approximately 1.3% of the GDP, according to Unesco (34). This figure is lower than that of top-performing countries such as the USA, which dedicates 2.7% of its GDP to R&D. In countries with substantial R&D investments, the private sector often contributes a significant share, sometimes up to 70%. In Brazil, around 45% of R&D investment originates from the private sector, while the government provides the remainder (35).

Brazil's public funding system for biomedical research has faced challenges over the years. The system, encompassing several governmental agencies, experiences fluctuations and is influenced by the priorities of the current government.

Research funding is provided through different systems and institutions, which are directly or indirectly linked to Brazilian ministries or federal agencies. These include CNPQ *(Conselho Nacional de Desenvolvimento Científico e Tecnológico)*, CAPES (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior)*, FINEP *(Financiadora de Estudos e Projetos)*, and FNDTC *(Fundo Nacional de Desenvolvimento Científico e Tecnológico)* (4).

CNPQ is a federal entity that stands out in the role of promoting scientific and technological research in Brazil. With a mission to foster scientific and technological research, CNPQ has consistently supported researchers in various biomedical fields, including but not limited to medicine, biology, pharmacology and physiotherapy. One of its hallmark initiatives is the provision of scholarships to a diverse group, ranging from budding students to seasoned researchers. This not only aids in the individual growth of recipients but also ensures a constant stream of talent into the field of biomedical research. Through its consistent efforts and initiatives, CNPQ has established its position as a pillar in fostering new biomedical researchers in Brazil.

CAPES primarily funds scholarships at the post-graduate levels (master's, doctorate, and post-doctorate), with limited opportunities for project funding.

The Brazilian Innovation Agency (FINEP - *Financiadora de Estudos e Projetos*) represents the government's commitment to promoting technological and innovative projects, including those within the biomedical field (34). Often, FINEP partners with other agencies and the private sector to fund research with commercial potential. The Brazilian Ministry of Health is also instru-

mental in sponsoring biomedical research, predominantly those linked to pressing public health concerns. Its efforts cover initiatives to enhance healthcare infrastructure and address critical health challenges.

Several state Foundations for Research Support finance research (5, 6) They often collaborate with federal entities and the private sector to sponsor state-level biomedical research. This manuscript focus in the agencies of São Paulo and Rio de Janeiro, the two states with the most substantial research budgets.

FAPESP is a premier Brazilian research agency supporting projects across various disciplines, including biomedical sciences. Researchers should monitor FAPESP's website for the latest funding opportunities. The "Regular project" grant provides up to R$ 300,000.00 for individual principal investigators, while the "Thematic project" offers extensive funding for specific biomedical research led by collaborative teams of experienced scientists. In addition to funding projects, FAPESP offers scholarships from scientific initiation to post-doctoral levels and has special programs to nurture early career researchers, emphasizing research excellence (38).

FAPERJ supports scientific advancement in Rio de Janeiro. Aimed at boosting socioeconomic development through research, FAPERJ offers diverse funding options, benefiting both emerging and established researchers. The agency emphasizes cutting-edge areas like artificial intelligence, biotechnology, renewable energy, and climate change.

The various federal and state agencies typically advertise grant support opportunities in their respective websites. It's essential to seek out opportunities aligned with the applicant´s research interests or apply through generic parent announcements tailored for a broad range of topics.

Industry funding for biomedical research:

Industry funding plays a significant role in advancing biomedical research (36-39). In this session, we will explore three aspects of industry funding in biomedical research: clinical industry-initiated studies, investigator-initiated studies, and collaborative research.

Industry funding through **clinical industry-initiated studies** is essential for evaluating the safety and efficacy of new drugs, medical devices, and therapies in similar or innovative approaches of the pivotal clinical trials (38, 40). Pharmaceutical and medical device companies typically sponsor these studies to expand the knowledge about their products or therapeutic areas. One advantage of industry funding for clinical studies is the substantial financial resources it provides. This funding enables researchers to conduct large-scale trials, recruit participants, and collect comprehensive data, enhancing the statistical power and generalizability of study findings (41, 42). Industry funding also allows for the utilization of specialized equipment, technology, and expertise that may not be readily available in academic or public research settings.

To overcome potential conflicts of interest, researchers must ensure the independence and integrity of the study design, data collection, and analysis to maintain scientific rigor and objectivity. To address these concerns, regulatory bodies and research institutions have implemented transparency and disclosure requirements and the collaboration between academic researchers and industry partners can also help mitigate potential conflicts of interest and ensure the research is conducted in an ethical manner (37, 39).

In addition to industry-sponsored studies, **investigator-initiated studies** that receive industry funding play a crucial role in biomedical research. These studies are initiated and led by independent researchers, who propose research projects aligned with their scientific interests and expertise. These studies offer researchers the opportunity to explore novel hypotheses and investigate innovative approaches. Funding provides financial support for research materials, personnel, data collection, and analysis, enhancing the feasibility and quality of the study. By investing in independent research projects, industries demonstrate their commitment to scientific progress and patient welfare beyond their commercial interests. This can enhance public trust in the industry and strengthen the collaboration between academia and the private sector. As in the industry-initiated studies, researchers must ensure that the funding source does not compromise the study's design, data analysis, or interpretation of results. Transparency in disclosing funding sources

and potential conflicts of interest is essential to assure the scientific rigor.

Academics can provide unbiased expertise and access to patient populations, while industry partners can offer financial support, specialized knowledge, and access to resources. Such collaborations may accelerate the translation of scientific discoveries into clinical applications and contribute to improving patient care.

Collaborative research is a format of sponsored studies practiced by some industries. This alternative allows for the true collaboration between industry and researchers to plan and execute research studies. This partnership is based on similar expertise and research interests from both parts. Leveraging scientific acumen from industry and academia in that particular area of knowledge can strengthen study planning and expedite execution, while optimizing budget. In this type of funding all steps of the research are agreed between both parts.

Those are general approaches to research funded by industry and may vary among the different companies. Generally, a common practice among them is to support research in the therapeutic areas they act on. Requests for funding may be enduring or via specific calls for application. Thus, it is important for researchers to understand the synergy between their field of research and the area of interest of the different companies to explore opportunities. Information can be obtained in companies´ websites and with local Medical Affairs teams.

Finally, industry-sponsored studies often result in unused budget provisions. These surplus funds can be redirected to areas of research that may be underfunded or neglected, addressing unmet medical needs. Alternatively, it can be used for the maintenance or renewal of the institution's infrastructure.

Quality of studies funded by industry:

Industry funding has attracted significant criticism due to its perceived influence on the research agenda and its potential impact on the quality of resulting publications. One of the key concerns raised by critics is the potential for industry sponsorship to shape the direction and focus of research (43). In many cases, industry-funded studies tend to align with the commercial interests of the sponsoring companies, which may prioritize research that supports their products or services rather than pursuing unbiased scientific inquiry (44).

Critics argue that this influence can be seen in various aspects of the research process. For instance, industry sponsorship has been known to impact the selection of research questions (45). Funding from pharmaceutical companies, for example, may result in an overemphasis on drug development and clinical trials for specific medications, while neglecting other important areas of research.

Moreover, industry funding can influence the study design and methodology employed in research projects. Sponsoring companies may exert pressure to use certain methodologies that are more likely to yield favorable results for their products or to exclude certain control groups that could potentially reveal adverse effects (44).

Another concern lies in the interpretation and dissemination of research findings. Critics argue that industry-funded studies tend to present results in a manner that favors the sponsoring company's interests, potentially downplaying negative findings or exaggerating positive ones (44, 45). This selective reporting can skew the overall evidence base and hinder a comprehensive understanding of the subject matter. Reviews support this notion that industry-funded studies often report outcomes more favorable to the sponsor than those not financed by the industry (43-45).

Critics also highlight instances where conflicts of interest are not properly disclosed, leading to a lack of transparency in the research process. Failure to disclose financial ties between researchers and industry sponsors can undermine the credibility and objectivity of the research, raising doubts about the reliability of the findings (46).

While concerns about bias exist, industry-funded studies are often high-quality multicenter studies, with a large sample size that supports generalizability. It would be ideal to use such robust studies to obtain strong and meaningful scientific results.

Influencing the industry's research agenda may be challenging, but strategies can be employed

to lessen bias within industry-funded research. Adherence to ethical principles must be rigorous across all stages of research to sustain its integrity and reliability. Furthermore, peer review has a major role in assuring research quality. It serves as an external control for research methodology and findings and is key to ascertain their validity. The association of rigorous scrutiny provided by peer review and the transparency and collaboration fostered by open science creates a powerful framework for ensuring robust, credible, and accessible scientific research.

Other funding opportunities in Brazil

In recent years, the global landscape of research funding has undergone a significant transformation. A number of countries worldwide, including Brazil, have encountered notable constraints in obtaining government research funding (5, 7, 36, 47). This phenomenon is particularly pronounced in the field of biomedical research, typically characterized by substantial financial requirements due to the high costs of experimentation and clinical trials. This situation has brought the search for alternative sources of funding to the forefront of discussion, with the exploration of new strategies for overcoming these challenges.(4, 10, 14, 36, 48, 49).

One such innovative approach that has emerged in the landscape of research funding is **Crowdfunding**, that has been used to support research studies in many countries (50-52). It engages large groups of people who make small contributions to support a research study, providing a method for researchers to engage with the public (50, 53). Crowdfunding provides a way for communities and stakeholders to invest in locally relevant topics and directly contribute to scientific research.

Based on the principles of community contribution and democratization of support, crowdfunding empowers researchers to bypass the limitations imposed by traditional funding channels and directly appeal to the public for financial support (10-12). Through the use of online platforms, researchers are enabled to present their projects to a broad, diverse audience, thereby reaching out to individuals who are passionate about specific medical areas and/or interested in the advancement of medicine.

This strategy for funding presents an opportunity for researchers who may have found difficulties in obtaining grants through conventional means to nonetheless pursue their research goals (12). Secondly, by engaging the general public in the research process, it favors a sense of community involvement in scientific advancements. This not only generates financial support but also improves public understanding and appreciation of science (54, 55).

Crowdfunding also allows for a distinct degree of flexibility, which traditional funding sources often lack. Unlike these conventional sources, which typically have rigid requirements and timelines, crowdfunding allows researchers to set their own goals and adapt their projects according to evolving circumstances and findings. This adaptability proves particularly beneficial for exploratory or innovative research projects that may be less appropriate for standard funding models.

Moreover, crowdfunding serves as a potent tool for networking and increasing exposure. Crowdfunding campaigns offer researchers a platform to showcase their work, gaining visibility within the medical community and beyond. Through social media and online platforms, researchers can attract attention from potential collaborators, industry partners, and even traditional funding agencies. This increased exposure can facilitate the building of a network of supporters, creating opportunities for future collaborations and additional funding avenues.

In Brazil, the **Serrapilheira Institute** serves as an example of a non-governmental organization contributing substantially to the funding of scientific research. The Institute, with its mission of supporting innovative and high-impact projects, offers several opportunities for medical researchers. By providing grant programs designed to support medical research initiatives, it allows scientists to explore novel and risky research projects. From 2018 to August/2022 it invested R$ 51.868.416,42, distributed to 152 different research projects (56).

The Institute encourages collaborative research initiatives and supports events like workshops and conferences. In addition, it offers opportunities for professional development and networking. Additionally,

recognizing the critical role of effective science communication, the Institute has implemented communication and outreach programs that assist researchers in disseminating their findings to a broader audience.

The shift in the landscape of research funding presents both challenges and opportunities for the world of biomedical research. While traditional government funding remains an essential component of the research ecosystem, the growth of alternative funding avenues, including crowdfunding and non-governmental organizations, provide a more diversified and democratic model. As researchers continue to navigate these changes and explore diverse funding opportunities, it's clear that these alternative sources will play an increasingly important role in driving scientific progress and fostering a vibrant and robust research community in Brazil and beyond.

FUNDING FROM FOREIGN INSTITUTIONS

National Institutes of Health (NIH)

The National Institutes of Health (NIH) is a leading global medical research agency that provides a wide range of funding opportunities to support biomedical research. The NIH categorizes its funding based on various research, conditions, and disease categories. These categories are based on grants, contracts, and other funding mechanisms used across the NIH (57). Additionally, disease burden data published by the National Center for Health Statistics (NCHS) at the Centers for Disease Control & Prevention (CDC) are also reported alongside the budgeting categories.

Foreign researchers can apply for NIH grants through a similar process as domestic researchers. The application process generally involves identifying the appropriate funding opportunity, preparing a detailed research proposal, and submitting it through the NIH's electronic submission system. In general, foreign institutions and international organizations, including public or private non-profit or for-profit organizations, are eligible to apply for research project grants (58). However, some NIH programs/mechanisms have a citizenship requirement. Any citizenship requirement will be stated in the program announcement (PA) or request for applications (RFA).

Foreign institutions and international organizations are not eligible to apply for Kirschstein-NRSA institutional research training grants, program project grants, center grants, resource grants, SBIR/STTR grants, or construction grants. However, some activity codes, such as program project grants (P01), may support projects awarded to a domestic institution with a foreign component. Foreign applications must be presented to the NIAID advisory Council as a special issue to obtain approval. A foreign component cannot be added to a grant without obtaining prior approval of the grants management officer (GMO) (58).

Bill & Melinda Gates Foundation

The Bill & Melinda Gates Foundation is a leading global philanthropic organization that provides a wide range of funding opportunities to support research in various fields (59). The foundation awards the majority of its grants to U.S. organizations and other tax-exempt organizations identified by their staff. However, they also welcome applications from international researchers. The application process for foreign researchers is similar to that of domestic researchers. The first step in the application process is identifying the appropriate funding opportunity. The foundation does not make grants outside its funding priorities. In general, they directly invite proposals by contacting organizations. However, they do occasionally award grants through published Requests for Proposals (RFPs). Therefore, it is crucial for researchers to keep an eye on the list of current RFPs.

Once an appropriate funding opportunity has been identified, the next step is preparing a detailed research proposal. The proposal should include a comprehensive narrative of the proposed research, a detailed budget, and sometimes a results framework and tracker. After the proposal has been prepared, it should be submitted through the foundation's electronic submission system. Once a grant is approved, the grantee will typically rely on the investment document progress narrative section and grant budget to report formally on progress, challenges, and financial status. It's important to note that the foundation does not make grants directly

to individuals except in specific circumstances as noted on certain grant applications. Also, they make grants to organizations directly rather than through individual fundraising activities (59).

In conclusion, while the process of applying for resources at the Bill & Melinda Gates Foundation as a Brazilian researcher involves several steps and requires careful preparation, it is certainly feasible. By staying informed about current RFPs, preparing a thorough research proposal, and following the foundation's application guidelines, Brazilian researchers can successfully navigate this process.

Impact of collaboration for improving funding

Collaborative research plays a pivotal role in advancing biomedical knowledge and fostering innovation. Within the context of biomedical research funding, promoting collaborations among academic institutions, industry partners, and governmental agencies is essential (60).

Collaborative research brings together diverse expertise and resources from multiple stakeholders (23). By combining knowledge and capabilities, researchers can tackle complex questions and interdisciplinary challenges (61, 62). It facilitates access to specialized medical equipment, state-of-the-art facilities, and extensive medical databases that may not be readily available to individual researchers or institutions. This amplification of expertise and resources enhances the overall appeal and competitiveness of research proposals (63).

When academia collaborates with industry partners, the research becomes more closely aligned with healthcare market needs, ensuring its clinical relevance and potential for commercialization (64). This alignment enhances the chances of securing funding from industry sponsors. The active involvement of healthcare providers and stakeholders throughout the research process also augments the likelihood of achieving real-world impact, thereby increasing the prospects for funding support.

Collaboration also distributes inherent research risks. There is a significant challenge in moving from promising scientific observations to the creation of effective therapies. This process is not only expensive, but many times frustrating since most therapeutic developments stumble at the preclinical stage. By sharing responsibilities and resources, the burden on individual medical researchers or institutions is significantly reduced (65). This is especially true for therapies for niche diseases, that might serve only specific markets. The pharmaceutical industry often shies away from early-stage programs, especially for rare or 'orphan' diseases. Recognizing this gap, federal agencies have developed programs to spark innovation and lower the hurdles for new therapeutic introductions (66).

Beyond resources, collaborations facilitate knowledge exchange, offering researchers fresh perspectives and innovative methodologies. It also helps establishing robust collaborative networks, even on an international scale, enabling access to international funding opportunities and global medical research networks.

In summary, collaborative research is critical for securing research funding. It optimizes proposal competitiveness, amplifies societal impact, and manages risks effectively. As such, fostering and supporting these collaborations is paramount for both researchers and funding agencies. To maintain the highest integrity in research, investigators involved in these collaborations must disclose any relationships that could potentially influence the outcomes or interpretation of their projects.

CONCLUSION

Biomedical research thrives with adequate funding, a cornerstone essential for driving innovations and advancing healthcare. A standout research project poised for funding typically showcases clear objectives, rigorous methodology, and the potential for a marked impact. Collaborations, involving both local and international researchers, not only bolster funding opportunities but also amplify the potential results and significance of the research.

In Brazil, the mainstay of research funding stems from public entities, with agencies such as CNPq, CAPES, and state bodies like FAPESP, FAPERJ, FAPEMIG and others at the forefront. Concurrently, industry funding offers viable pathways, especially through industry-

sponsored studies, investigator-led projects, and collaborative initiatives. The Brazilian funding landscape is further enriched by innovative platforms, including crowdfunding and the contributions of institutions like the Serrapilheira Institute. Internationally, esteemed organizations such as the National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation stand out as potential funders.

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CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

TRAUMA

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Editorial Comment: Risk Factors for Penile Fracture After Intralesional Collagenase Clostridium histolyticum in Peyronie's Disease

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COMMENT

The treatment of Peyronie's disease (PD) is challenging. The paper of Zucker et al. (1) shows an important complication after the use of Intralesional Collagenase Clostridium histolyticum (CCh) in PD: Penile fracture. Sexual intercourse represented the main cause of PF in USA, Europe and Brazil because intercourse is generally associated with high-energy traumas (2). Recent papers showed that, the positions with the "man on top" and "doggy style" were considered the most severe, presenting greater association with urethral and bilateral lesions of the corpora cavernosa (2, 3).

In the present paper the authors studied retrospectively 1541 patients that received at least one injection of CCh for PD. Of them, 0.7% (11/1541) suffered corporal rupture occurred at a median of 8 days after CCh injection. The majority of fractures were secondary to spontaneous erections or sexual intercourse. Finally, six patients had their fracture repaired surgically while the remaining were managed conservatively. The authors concluded that intralesional CCh can lead to corporal rupture and the most fractures occurred within 2 weeks of CCh injections and were associated with sexual intercourse and spontaneous morning erections.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robot-assisted retroperitoneal lymph node dissection as primary treatment for stage II seminoma germ cell tumor

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ABSTRACT

Introduction: Historically, therapeutic avenues for patients with clinical stage II seminoma germ cell tumors (SGCT) were confined to radiotherapy and chemotherapy. While survival rates with these modalities are commendable, both entail substantial long-term morbidities. Furthermore, this youthful patient cohort exhibits elevated rates of secondary malignancies, surfacing decades post-successful primary cancer treatment (1). Recently, retroperitoneal lymph node dissection (RPLND) has emerged as a primary treatment consideration for individuals with low-volume metastatic seminoma (2-4). However, there is a dearth of video documentation illustrating the robotic assisted (RA) bilateral approach (5- 7).

Methods: We present the case of a 24-year-old male who underwent prior left orchiectomy for seminoma (pT1b). Despite negative serum tumor markers, a 1.7 x 1.4cm lymph node enlargement was identified in the aortic bifurcation after 4 months, classifying the patient as stage IIA per the IGCCCG risk classification. Subsequently, a RA bilateral template RPLND was performed due to the patient's refusal of chemotherapy, citing concerns about offspring.

Results: The surgery was performed, incorporating nerve sparing techniques, lasting 4h13minutes, an estimated bleeding rate of 400ml, without intraoperative complications. The patient was discharged within 24 hours of the procedure, following a prescribed low-fat diet.

Conclusion: The patient experienced postoperative well-being, painlessness, and resumed work three weeks post-procedure. Preserved ejaculation was noted, and adjuvant therapy was performed with 2 cycles of EP due to the anatomopathological result. The feasibility of robotic primary RPLND for SGCT was demonstrated, showing reduced postoperative pain and early hospital discharge. Further studies are necessary to validate our findings regarding oncological, safety, and functional outcomes.

CONFLICT OF INTEREST

None declared.

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Applicability and feasibility of robot-assisted cystectomy and intracorporeal urinary diversion in a patient with right renal pelvic ectopia

Stefano Puliatti [1, 2], Stefania Ferretti [1], Natali Rodriguez Peñaranda [1], Ahmed Eissa [3], Marco Ticonosco [1, 2], Andrea De Faveri [1, 2], Cosimo De Carne [1], Pawel Wisz [4], Riccardo Ferrari [1, 2], Greta Tosi [1, 2], Filippo Annino [5], Giampaolo Bianchi [2], Salvatore Micali [1, 2]

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ABSTRACT

Background: The ectopic pelvic kidney, a common renal anomaly, is often smaller and malformed, with a shorter and sometimes tortuous ureter (1). Muscle-invasive bladder cancer (MIBC), constituting 15-25% of bladder cancer cases (2), mandates radical cystectomy with a 50% 5-year survival rate (2). Despite the growing use of robot-assisted radical cystectomy (RARC) (3, 4), there is limited data on its application in ectopic kidneys. Only one RARC case has been reported (5), in contrast to numerous open radical cystectomies (1, 6) involving an ectopic kidney.

Patient and methods: After being diagnosed with T2 high-grade urothelial carcinoma, the 66-year-old patient, previously treated with multiple transurethral resections and adjuvant BCG therapy, received neoadjuvant chemotherapy. Preoperative staging CT revealed a 2.6 x 2.2 cm bladder neoformation and an ectopic right pelvic kidney.

Results: Using the da Vinci Surgical System, radical cystectomy with ileal conduit (sec Wallace II) and lymphadenectomy were performed. During the demolition phase, the shorter right ureter was dissected with care to avoid damage to the renal pedicle. The reconstructive phase included intracorporeal urinary diversion (ICUD) and uretero-ileal anastomosis, facilitated by the favorable position of the kidney. The 8-hour console surgery resulted in minimal blood loss. Discharged on day 16 due to COVID-19, the patient exhibited positive outcomes. A 2-month CT follow-up revealed no cancer recurrence, metastasis, hydronephrosis, and complete regression of the lymphocele. Imaging follow-up continues without postoperative adjuvant chemotherapy.

Conclusion: Robotic surgery with intracorporeal urinary diversion holds potential for right-sided pelvic kidney cases, but additional studies are necessary for validation.

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Stefano Puliatti, Stefania Ferretti contributed similarly as first author

CONFLICT OF INTEREST

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- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
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- A list of abbreviations is provided.