RAMB
Revista da Associação Médica Brasileira

AMB
Associação Médica Brasileira

Volume 63
Number 8
August 2017
ISSN 0104-4230
ISSN 1806-9282 (*On-line*)

SECTIONS

THEMATIC ISSUE: UROLOGY

CISBE 2017

CONGRESSO INTERNACIONAL DE SAÚDE BASEADA EM EVIDÊNCIA AMB

17 A 19 DE AGOSTO

CENTRO DE CONVENÇÕES DO CEARÁ
FORTALEZA - BRASIL

Os trabalhos aprovados serão publicados na revista da AMB.

COMISSÃO NACIONAL DE ACREDITAÇÃO CNA AMB

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Realização
AMB
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RAMB

REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA

JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira

www.ramb.org.br

Associação Médica Brasileira

Address: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
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Editor-in-chief: Carlos V. Serrano Jr.
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E-mail: ramb@amb.org.br
Website: www.ramb.org.br

The norms for publication are available on the website www.ramb.org.br

The Journal of the Brazilian Medical Association is affiliated to the ANATEC and indexed in Medline, SciELO, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.

The Journal of the Brazilian Medical Association is an official publication of the Associação Médica Brasileira (AMB), distributed exclusively to the medical community in Brazil and Latin America.

Manole Publisher

Authorizing editor: Sônia Midori Fujiyoshi
Editor: Cristiana Gonzaga S. Corrêa
Publishing production: Quinta Edições
English version: Graziella Risolia Gallo ME
Reviewers: Folgueira Comunicação and Lia Fugita Editorações
Cover: Rafael Zemantauskas
Graphic design: Sopros Design
Layout: Lira Editorial

SUMMARY

Volume 63 – Number 8 – August 2017
ISSN 0104-4230 – ISSN 1806-9282 (*On-line*)

SECTIONS

ORIGINAL ARTICLES

REVIEW ARTICLES

The new Brazilian Society of Urology

A nova Sociedade Brasileira de Urologia

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http://dx.doi.org/10.1590/1806-9282.63.08.663

The Brazilian Society of Urology (SBU) has undergone a restructuring process in recent years. If we currently have a financially balanced and structured organization both from an administrative and a scientific point of view, a lot of that is due to the colleagues that preceded me.

The former directors have promoted reformulations and have, with their effort and dedication, transformed the SBU into an organization that is recognized as an example of efficiency and work.

We know that the Brazilian political and economic situation is not favorable. We have gone and are still going through difficult times, especially from an economic point of view. We are experiencing the result of the actions of a government that institutes disastrous economic and social policies, besides supporting campaigns and projects to defame the medical class in general.

If we have arrived at this moment with reasons to celebrate, it is thanks to the proper planning and hard work of this entire senior management. Efficient teamwork has enabled us to overcome this difficult time.

We cannot lose sight of the idea that taking care of a person's life is one of the noblest activities and we, those who help prepare professionals who will perform such a noble office, have twice the responsibility.

We have a strong continuing education branch and we will continue to strengthen this important initiative. The performance in medical residences and professional valorization are priorities of this administration.

We improve the present without losing sight of the future. The extremely efficient Teaching and Training Commission (TTC) is responsible for the accreditation and supervision of the residency centers. We are launching software to monitor all residency centers, seeking to homogenize the training of the resident doctor.

Also thinking about improving our professionals' performance, we are working with the Specialist Title Commission in order to value our TiSBU more and more.

We have created a Professional Valuation Committee with representation in Brasília and in several organizations such as the Brazilian Medical Association (AMB, in the Portuguese acronym), Federal Board of Medicine (CFM, in the Portuguese acronym), National Regulatory Agency for Private Health Insurance and Plans (ANS, in the Portuguese acronym), Brazilian Health Surveillance Agency (Anvisa, in the Portuguese acronym) and others.

We have gained international recognition by strengthening ties with important organizations such as the American Urology Association (AUA), the European Association of Urology (EAU) and the American Confederation of Urology (CAU, in the Spanish acronym).

With these actions, in addition to developing projects that benefit urologists, we are regaining our organization's credibility.

This work has the purpose of showing some of our scientific activity and sharing achievements with you, as a great team of professionals that are part of the Brazilian Society of Urology.

We appreciate the efforts of all those involved in this project.

Male urinary incontinence: Artificial sphincter

Incontinência urinária masculina: Esfíncter artificial

Authorship: Brazilian Society of Urology (SBU)

Participants: José Carlos Truzzi[1], Carlos R. Sacomani[2], José Prezotti[3], Antônio Silvinato[4], Wanderley Marques Bernardo[4]

Final draft: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.664

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Introduction

Patients with intrinsic sphincter deficiency include men who have undergone retropubic radical prostatectomy (including laparoscopic or robot-assisted radical prostatectomy), radical perineal prostatectomy, or transurethral resection of the prostate (TURP), patients with previous pelvic trauma or history of pelvic radiation, women who have undergone failed anti-incontinence procedures, and patients with spinal cord injury, myelomeningocele or other causes of neurogenic bladder, in which intrinsic sphincter dysfunction may also exist. Urinary incontinence after radical prostatectomy (UIRP) is the most common indication for artificial urinary sphincter (AUS) implantation.[1,2] The main etiology of UIRP is sphincter deficiency in up to 90% of cases, either alone or combined with detrusor overactivity (DO).[3]

The placement of the artificial urinary sphincter should be postponed for at least 6 months to 1 year, given that a portion of the patients redevelop urinary continence in this period. The American Medical Systems 800 (AMS 800) artificial urinary sphincter is the most widely-used device and is considered the gold standard in the treatment of urinary incontinence caused by intrinsic sphincter deficiency, working based on hydraulic mechanics.[4] The system consists of a cuff connected to a reservoir balloon through a pump. The three components are connected with torsion resistant tubes.[5] The sizes (lengths) of the cuffs range from 3.5 cm to 5.5 cm in 0.5 cm increments. The cuff can be implanted in the bulbar urethra (most common) or in the bladder neck. During rest, the reservoir pressure is transmitted to the cuff, causing continence. Digital compression of the pump promotes the transfer of liquid from the cuff to the reservoir, relieving urethral compression and allowing urination. After a period of time (3-5 minutes), the liquid is transferred back into the cuff by compressing the urethra or bladder neck, providing continence. The reservoir balloons come in three preset pressures: 51-60, 61-70, 71-80 cm of water; the lowest pressure required to close the urethra should be used. Migration of components may occur if the cuff is poorly dimensioned, if the pump or balloon is not positioned correctly or if the pipe lengths are incorrect.[6]

The standard placement of an AUS involves a small incision made in the patient's perineum or scrotum. Perineal access is considered the most common;[7] however, authors have also described the scrotal technique, thus, the advantages and disadvantages of each should be considered by the surgeon.[8]

The "cuff," which is the portion of the device that surrounds and obstructs the urethra, is usually placed directly around the urethra (i.e., the "standard" placement). Another variation for cuff placement is the transcorporal (TC) approach. This technique avoids the posterior urethral dissection as well as of the corpora cavernosum. The dorsal dissection plane for cuff placement is through the septum of the corpora cavernosa from one side to the other, resulting in a portion of the ventral tunica albuginea acting as a cushion between the cuff and the dorsal

corpus spongiosum. The transcorporal placement of the cuff was developed in an attempt to improve continence in patients with recurrent incontinence secondary to erosion, urethral atrophy, inadequate urethral coaptation, after radiotherapy, or for patients undergoing revision, in whom more proximal placement could not be achieved.[9]

Proper patient counseling and careful attention to intraoperative and postoperative details are important to achieve good outcomes and high rates of patient satisfaction. Several case series with long-term monitoring have demonstrated efficacy of the AUS and patient satisfaction even when surgical revisions are needed.[10] However, implantation of the AUS is an invasive procedure that can result in complications, such as postoperative infection, urethral erosion and explantation.[11] Furthermore, previous urethral damage (such as failed surgical procedures, urethral atrophy or history of pelvic radiotherapy) may potentially result in technical difficulties and/or reduced surgical efficacy. Urinary incontinence (UI) that can occur after artificial urinary sphincter activation is classified as either early (persistent) or late onset (recurrent).[12] In the case of persistent UI, patients never regain urinary continence following AUS activation, with urinary loss often similar to that experienced prior to implantation and during the deactivation period. Persistent incontinence is usually attributed to a surgical failure or inability to identify detrusor overactivity or any other lower urinary tract abnormality in the preoperative diagnostic evaluation.[13] On the other hand, recurrent or late-onset UI generally occurs after several months or years after the AUS implantation. There are several causes of persistent and/or recurrent UI: unsuitable or accidental pump operation, urinary tract infection (UTI) with detrusor overactivity, overactive bladder, urethral atrophy, urethral erosion of the cuff, inadequate cuff size, insufficient pressure of the reservoir balloon, development (recurrence) of urethral or bladder neck stenosis, as well as device failure with fluid loss or obstruction of the control unit flow.[12,14,15] Revision rates between 8 and 45% have been reported due to mechanical failure, while those derived from non-mechanical complications such as erosion, urethral atrophy and infections are reported between 7 and 17%.[1,16-18]

Certain complications have been described, with the most significant being erosion and/or extrusion of the sphincter, infection and urethral atrophy. In certain situations, there is a need to remove the device.[19] The following are risk factors for complications: pelvic radiotherapy, urethroplasty or any urethral manipulation and antecedent erosion or infection in individuals previously submitted to artificial sphincter implantation.[20-22]

Objective

The objective of our evaluation is to establish guidelines regarding the most important issues related to artificial urinary sphincter implantation: the best practices in the choice and preparation of the AMS 800 urinary sphincter components, preoperative care for patients with indication of artificial sphincter, the best approach for implantation of the artificial urinary sphincter (perineal or transescrotal), to compare the transcorporal placement of the cuff with the "standard" placement (directly around the urethra), regarding efficacy and safety, to assess the best conduct in the perioperative and postoperative period of artificial urinary sphincter implantation, to assess the best conduct in the management of therapeutic failure (early or late onset urinary incontinence) and to evaluate the best strategy against suspected erosion or extrusion, infection and urethral atrophy, considering primary studies.

Method

The initial eligibility criteria for studies were: PICO components (**P**atient, **I**ntervention, **C**omparison, **O**utcome), observational comparative studies (cohort and/or before-and-after), comparative experimental studies (clinical trial), absence of restriction applied to the period of studies, no language restriction and availability of the full text.

Medline (via PubMed), Embase, Central (Cochrane), Lilacs (via BVS) and manual search were the sources of scientific information consulted in this study.

The search strategies used Medline – (Artificial Urinary Sphincter OR Artificial Urinary Sphincters OR Artificial Genitourinary Sphincter OR Artificial Genitourinary Sphincters OR Artificial sphincter OR AMS 800 OR AMS800); other computerized databases – 'artificial AND urinary AND sphincter', and manual search – reference within references, revisions and guidelines.

For study selection initially we searched by the title, then by the abstract, and finally by its full text, the latter being subject to critical evaluation and extraction of results related to the outcomes.

The strength of the evidence from observational and experimental studies was defined taking into account the study design and corresponding bias risks, the results of the analysis (magnitude and precision), relevance and applicability (Oxford/GRADE).[23,24]

The global evidence summary will be presented at the end of the results. The global evidence summary will be elaborated considering the evidence described.

The strength (Oxford/GRADE)[23,24] will be estimated as 1b and 1c (grade A) or strong, and 2a, 2b and 2c (grade

B) or moderate, weak or very weak. The strongest evidence will be considered.

We defined seven main questions regarding male urinary incontinence and artificial urinary sphincter as follows:

1. AMS 800 Model.
2. Preoperative period.
3. Perineal versus scrotal approach.
4. Transcorporal approach.
5. Perioperative and postoperative care.
6. Evaluation and conduction of therapeutic failure after AUS implantation.
7. Complications.

1. AMS 800 Model

The objective of our evaluation is to assess the best practices in the choice and preparation of the AMS 800 urinary sphincter components, considering primary studies.

Clinical question

What conduct should be adopted in the choice and preparation of the components of the artificial urinary sphincter model AMS 800? This question was answered in this evaluation using the PICO method, where P stands for patients with urinary incontinence due to sphincter deficiency, I refers to intervention with implantation of the AUS model AMS 800, C is the comparison with implantation of different components and the preparation of such (cuff and balloon), and O is the outcome of incontinence control and complications. Based on the structured question, we identified the keywords used as the basis for searching for evidence in the databases and after the eligibility criteria (inclusion and exclusion), which were selected to answer the clinical question (Annex I).

Results

In all, 1,757 studies were retrieved. Of these, 20 were selected by title and eight by summary, with reading of the full text in the second case. After the analysis of the full texts, 14 studies were included in our evaluation.[25-38] The main reasons for exclusion were: studies aiming only to describe the surgical technique, a series of cases with a small number of patients included (n < 10), and a narrative review.

The surgeon determines the appropriate cuff size to be used by measuring the circumference of the tissue around the urethra or the bladder neck. A belt is used for cuff measurement, available in the device implantation kit, which should surround the entire urethra circumferentially for proper assessment of its caliber. Additional clearance is required to accommodate the patient's urethral tissue between the transurethral device and the cuff. The thickness of the urethral tissue is patient-specific and requires a surgeon's assessment to determine its impact on sizing. In transcorporal implantation (TC) one must not undersize the cuff size, considering a size 1⁄2 cm greater than the measured value. This is particularly true for older men, since the postoperative urinary retention rate is significantly higher in these patients (32% [TC] vs. 8% in peri-urethral implantation, NNH = 4, 95CI 2-28).[25] **(B)**

A before-and-after study showed that the percentage of patients using two or more pads/day was lower in the larger cuff size group (5.0 to 7.0 cm) compared to patients with a cuff size of less than 5 cm, at a median follow-up of 6.8 years (9.1 vs. 20.5%, NNT = NS). In addition, cuff size did not significantly affect the risk of complications.[26] **(B)**

In a historical cohort (N = 45 men), one group evaluated implantation of the 3.5 cm cuff in primary and revision surgery, after repeatedly observing that loose cuffs led to more severe postoperative incontinence. In this study, compared to a larger one the 3.5 cm cuff showed no difference in explantation rate (9% in both groups; NNT = NS), due to infection and/or erosion, in an average follow-up of 12 months.[27] **(B)**

Another historical cohort (N = 59 men) evaluated the association of the difference between the urethral circumference and the cuff size chosen (ΔC), in its effect on postoperative incontinence in a median follow-up of 4.2 years. The median size of the urethral cuff was 3.8 cm and 66% of the patients had a 4.0 cm cuff implanted. In a long-term follow-up, when ΔC was < 4 mm, a higher rate of urinary retention, erosion and atrophy was observed, and when ΔC was ≥ 4 mm, better continence and satisfaction were observed ($p<0.05$). The results of this study suggest that a moderate increase in cuff size can produce better results in the long run. Furthermore, it demonstrated improvement in continence rates when surgeons opted for a larger cuff size when the urethral circumference was between two cuff sizes.[28] **(B)**

A historical cohort (N = 176 men) evaluated results comparing 100 cuff measuring 3.5 cm with 76 cuffs of larger sizes. Although there was no difference between the two groups regarding continence rates (83 vs. 80%, NNT = NS), patients with a history of irradiation who underwent 3.5 cm cuff implantation (N = 100) presented a 17% increase in the risk of erosion through the cuff (NNH = 6; 95CI 3-22).[29] **(B)**

The pressure-regulating balloon (PRB) determines the amount of pressure applied by the cuff. The surgeon usually implants the PRB in the pre-vesical space. A more recent PRB placement technique (pressure of 61-70 cm of H_2O and filled with 24 cc saline) is high submuscular placement below the rectus abdominis muscle using a

high scrotal incision. This technique was followed for 24 months with no difference in continence rates.[30] **(B)** The surgeon usually selects the lowest balloon pressure needed to maintain closure of the bulbar urethra or bladder neck. The most commonly used balloon pressure is 61-70 cm / H_2O (45-51 mmHg) (94% of cases worldwide). A pressure of 71-80 cm of H_2O may be preferred in patients with a cuff implanted in the bladder neck.[31] **(D)**

The prosthesis may be filled with isotonic sterile sodium chloride solution or contrast, at the surgeon's discretion. The solution must be isotonic to minimize the transfer of fluid through the semipermeable silicone membrane. Some contrast materials are hypertonic and viscous, representing a risk of poor transmission of fluid in the device and transfer of fluid through the reservoir membrane. System pressure changes may occur over time if the balloon is filled with radiopaque solution at an incorrect concentration.[32] **(C)** A history of adverse reactions to the radiopaque solution prevents its use as a filling medium for the prosthesis. If contrast solution is used, the manufacturer's recommendations must be observed.[6] **(D)**

The filling volume of the PRB with the empty cuff should be 22-27 cm, depending on the size and number of cuffs.[31] **(D)**

The manufacturer's recommendation is for the PRB to be filled with 22.5-23 cc of solution while the cuff is empty, subsequently allowing it to fill with at least 2 cc of solution remaining within the PRB in order to maintain the desired pressure range. In selected cases, intraoperative cuff pressurization may be considered to help determine the appropriate volume of total system solution.[6] **(D)**

The length of hospital stay will depend on the time of removal of the urethral catheter. A 12-Fr urethral catheter can be placed at the end of the procedure and left in position overnight. Others advocate not using a catheter, allowing the patient to attempt emptying after recovery from anesthesia. If the patient fails to do so, a new catheter is replaced and a further attempt at emptying it is repeated in 24-48 hours. In the event of persistent urinary retention (catheter > 48 h), a suprapubic cystostomy is preferred in order to reduce the risk of early erosion.[32] **(C)** [33,34] **(B)** The "AUS Consensus Group" (2015) recommends the use of a ≤ 14-Fr catheter and suggests removing it after a brief period (usually overnight) if the surgery was uneventful, as removal on the same day may increase the risk of urinary retention due to pain or inflammation.[31] **(D)**

Several before-and-after studies show an average time of six weeks for activation of the system.[35-38] **(C)** A before-and-after study applied a longer period of primary deactivation (12 weeks) in irradiated patients. There is no evidence to support a primary deactivation period greater than six weeks. The "AUS Consensus Group" (2015) recommends the activation of the system between 4 and 6 weeks for patients undergoing the first AUS implant.[31] **(D)**

Global evidence summary

The choice of cuff size should be made through the precise measurement of the circumference of the tissue around the urethra or the bladder neck. When in doubt, choose the largest size, avoiding placement of a cuff smaller than the measurement of the urethral circumference. **(B)**

The surgeon should select the lowest balloon pressure needed to maintain closure of the bulbar urethra or bladder neck. The most commonly used balloon pressure in the bulbar urethra is 61-70 cm/H_2O and 71-80 cm of H_2O may be preferred in patients with a cuff implanted in the bladder neck. **(D)**

The prosthesis may be filled with isotonic sterile sodium chloride solution or contrast, at the surgeon's discretion. **(C)**

The filling volume of the PRB with the empty cuff should be 22-27 cm, depending on the size and number of cuffs. **(D)**

The catheter left in the postoperative period can be ≤ 14-Fr and should be removed after a brief period (usually overnight). **(D)**

In the case of persistent urinary retention, the placement of suprapubic cystostomy is preferable in order to reduce the risk of early erosion. **(B)**

The AUS can be activated between 4 and 6 weeks in patients submitted to their first implant. **(D)**

2. Preoperative period

The objective of our evaluation is to suggest preoperative care for patients with indication of artificial urinary sphincter, based on primary studies.

Clinical question

How should the preoperative evaluation be performed in patients who will undergo artificial urinary sphincter implantation? This question was answered in our evaluation using the PICO method, where P stands for patients with moderate to severe urinary incontinence; I to intervention with artificial urinary sphincter; C to comparison with taking or not taking certain preoperative conduct; and O to the beneficial or harmful outcome in the postoperative period. Based on the structured question, we identified the keywords used as the basis for searching evidence in the databases and after the eligibility criteria (inclusion and exclusion), which were selected to answer the clinical query (Annex II).

Results

In total, 1,757 studies were retrieved. Of these studies, 28 were selected by title and 20 by summary, with reading of the full text in the second case. After the analysis of the full texts, 17 studies were included in our evaluation.[16,18,24,36,38-44] The main reason for exclusion was lack of response to the PICO.

The AUS should be offered to individuals with stress urinary incontinence (SUI) due to intrinsic sphincter deficiency (ISD) who have failed conservative treatment.[39] **(A)** Patients must have sufficient cognitive ability and function to operate the device.[40] **(D)** There is a risk of mechanical failure of the device after five years and this may be related to other possible (non-mechanical) complications such as infection and erosion or atrophy of the urethra.[18] **(B)** The rate of reoperation for all causes is 26% (varying between 14.8 and 44.8%).[16] **(A)** It is worth mentioning that irradiated patients may constitute a group with a higher risk of complications.[38,41] **(A)** This information must be provided to the patient.

The pre-implantation evaluation includes a clinical history and, occasionally, voiding diary (urine time and volume, diaper use, urinary incontinence episodes), physical examination, pad test, urinalysis, and urodynamic evaluation.[36] **(B)** [42] **(A)**

Cystoscopy and/or urethrocystography prior to AUS implantation are advised when concomitant urethral stenosis is suspected, which may complicate placement or put the AUS at risk of subsequent damage. For example, it was verified that up to 32% of patients presented urethrovesical anastomotic stenosis in the cystoscopy after radical prostatectomy (RP).[43] **(C)** Urethrovesical anastomotic stenosis should be stable prior to implantation.

Sphincter deficiency can be diagnosed by urodynamic examination.[24] **(B)** Less frequently, changes in bladder compliance are described, as well as the occurrence of detrusor overactivity.[44] **(C)**

All sites of infection, including the urinary tract, should be treated prior to the procedure to protect the operative field from bacterial contamination. Prophylactic antibiotic therapy should be administered 60 minutes before the incision; however, there is no standard antibiotic for this procedure.[45] **(B)**

Global evidence summary

The AUS is indicated in urinary incontinence due to intrinsic deficiency of the sphincter, after failure of the conservative treatment. **(A)**

Patients should have sufficient cognitive capacity and function to operate the device. **(D)**

They should be informed of the possible complications (mechanical or otherwise), as well as irradiated patients with greater risk. **(A)**

Advise of the possibility of not remaining 100% dry. **(A)**

The recommended evaluation includes a clinical history and physical examination. Urinary voiding and absorbent tests can be used but are not required. Urodynamics enables the diagnosis of sphincter deficiency. Cystoscopy and/or urethrocystography may be indicated in the analysis of urethral stenosis or vesicourethral anastomosis when these changes are suspected. **(A)**

All infection sites, including the urinary tract, should be treated prior to the procedure. **(B)**

3. Perineal versus scrotal approach

The objective of this evaluation is to suggest the best approach for implantation of the artificial urinary sphincter, considering primary studies.

Clinical question

What should be the surgical approach to artificial urinary sphincter implantation? This question was answered based on the PICO method, where P corresponds to patients with urinary incontinence due to sphincter deficiency; I to intervention with implantation of an artificial urinary sphincter via the scrotal method; C to comparison with implantation via the perineal method; and O to the outcome in relation to control of incontinence and complications. Based on the structured question, keywords were identified and constituted the basis of the search for evidence in the databases. After applying the eligibility criteria (inclusion and exclusion), articles were selected in order to answer the clinical question (Annex III).

Results

1,757 studies were retrieved. Twenty were selected by title and 15 by summary, with reading of the full text in the second case. After the analysis of the full texts, eight studies aiming only to describe the surgical technique were included in our evaluation.[7,8,31,46-50] Series of cases with a small number of patients included (n < 20) and a narrative review were the main reasons for exclusion.

A recent historical cohort study[7] **(B)** including 27,096 adult male patients compared the perineal approach (N = 18,373) to the scrotal approach (N = 8,723) in primary implantation of the AUS. The perineal incision reduced the risk of infection by 1.0% (RRA = 1.0%, 95CI 0.006-0.014; NNT = 100, 95CI 72-161), as well as the risk of cuff erosion by 2% (RRA = 2%, 95CI 0.014-0.024; NNT = 53, 95CI 41-73). There was also a reduction in the risk of explantation of

5.7% (ARR = 5.7%, 95CI 0.048-0.066; NNT = 18, 95CI 15-21) and risk of revision of 2% (ARR = 2%, 95CI 0.12-0.028; NNT = 50, 95CI 36-83). There was no difference between the groups regarding the risk of atrophy.[8] **(C)**

Another historical cohort[46] **(B)** included data from 84 patients with stress urinary incontinence after prostate surgery, monitored for an average of 39.7 months and submitted to AUS implantation (5% primary). In a subgroup analysis, perineal access (N = 24) compared to scrotal access (N = 60) reduced the risk of erosion by 20% (ARR = 20%, 95CI 0.099-0.301; NNT = 5, 95CI 3-10). There were no significant differences between the groups in the number of irradiated and/or anticoagulated patients, nor in the number of patients submitted to double-cuff placement (p=0.44, 0.22 and 0.76, respectively).[46] **(B)** Also, a recent historical cohort[47] **(B)** compared perineal (N = 152) and penoscrotal access (N = 99) in the single cuff implantation. The comparison of the two groups showed that the perineal route reduced the risk of explantation by 10.6%, in the 6-month follow-up (RRA = 10.6%, 95CI 0.017-0.195; NNT = 9, 95CI 5-61).[47] **(B)**

A historical cohort study compared the scrotal to the perineal approach in a total of 126 artificial urinary sphincter cuffs (120 procedures, including double cuff placement in six), implanted in 94 patients, 63 of which were placed via the penoscrotal approach and 63 via the perineal approach.

In the subgroup analysis with patients undergoing a primary or revision procedure with a single cuff, the number of patients "completely dry" (without using pads) was higher in the "perineal" group (ARA = 28%, 95CI -0.48 to -0.07; NNH = 4, 95CI 2-14). Furthermore, perineal access also showed a greater number of "completely dry" patients (ARA = 28.7, 95CI -0.53 to -0.03; NNH = 3, 95CI 2-27). The number of patients in the trans-scrotal group and in the perineal group who required double cuff implantation due to incontinence was 18 and 3%, respectively (p=0.6, without statistical significance).[48] **(B)**

A before-and-after study (N = 30)[8] **(C)** reported excellent results with an improved technique using a single scrotal incision, allowing a more proximal placement of the cuff and the attainment of a continence rate similar to those obtained with the perineal approach found in the literature.[8] **(C)**

Another before-and-after study[31] **(C)** evaluated 83 highrisk patients (69% prostatectomy only and 31% with radiotherapy and/or cryotherapy) who underwent AUS implantation with a single transverse scrotal incision. In an average follow-up of 18.8 (14.6) months, the number of pads per day decreased from a mean of 6.7 in the preoperative period to 1.1 in the postoperative period. Overall, 83% of the patients (79% of the irradiated ones and 85% of the nonirradiated ones) used ≤ 1 pad/day after surgery.[49] **(C)**

Authors have evaluated the implantation of AUS and inflatable penile prosthesis simultaneously through a single trans-scrotal incision. They included 22 patients with urinary incontinence and erectile dysfunction resulting from radical prostatectomy in 21 patients and radical cystectomy in one. The average follow-up time was 17 (12-36) months. The total revision rate was 14%, due to urethral erosion in two patients and migration of the reservoir in one. All patients reported improvement in urinary loss, requiring ≤ 1 pad/day. No patient suffered prosthesis infection in the postoperative period.[50] **(C)**

A consensus of the International Continence Society (ICS) recommends that the penoscrotal approach be reserved for reoperation; patients with conditions that prevent placement in the lithotomy position (morbid obesity, spine or limb deformities, neuromotor conditions); and patients who will undergo the AUS implantation and inflatable penile prosthesis through a single penoscrotal incision.[31] **(D)**

Global evidence summary

The implantation of the AUS via the penoscrotal route can increase the risk of erosion, infection and explantation. **(B)**

The penoscrotal technique may not provide an advantage in relation to efficacy, and is associated with a lower continence rate than the perineal approach. **(B)**

The penoscrotal approach can be reserved for cases of reoperation; patients with conditions that impede placement in the lithotomy position (morbid obesity, spine or limb deformities, neuromotor conditions); patients who will undergo AUS implantation and inflatable penile prosthesis through a single penoscrotal incision; and patients with a previously implanted sling. **(D)**

The perineal approach should be the usual one. **(B)**

4. Transcorporal approach for cuff placement

The aim of our evaluation is, based on primary studies, to compare the transcorporal placement of the cuff with the "standard" placement (directly around the urethra), regarding efficacy and safety.

Clinical question

What is the best approach for cuff placement in artificial urinary sphincter implant surgery? This question was answered based on the PICO method, in which P stands for patients with moderate to severe urinary incontinence; I is the intervention with transcorporal cuff implantation; C is the comparison with "standard" cuff implantation;

and O stands for the outcome of control of incontinence and complications. Based on the structured question, keywords were identified and constituted the basis of the search for evidence in the databases. After applying the eligibility criteria (inclusion and exclusion), articles were selected in order to respond the clinical doubt (Annex IV).

Results

In all, 1,757 studies were retrieved; ten were selected by title and eight by summary, with reading of the full text in the second case. After the analysis of the full texts, six studies were included in our evaluation.[9,51-55] The main reasons for exclusion were: studies aiming only to describe the surgical technique, a series of cases with a small number of patients included (n < 10), and a narrative review.

The transcorporal approach was introduced by Guralnick ML et al. in an effort to treat patients with previous urethral atrophy or erosion. In a before-and-after study, the results after transcorporal cuff placement were reviewed in 31 patients with an average follow-up of 17 months. A success rate of 84% (26 of 31 patients) was reported, defined as patients with no incontinence or occasional incontinence, requiring 0 to 1 pad per day. In addition, 25 of 26 patients surveyed were very satisfied with the outcome. It is noteworthy that seven of these patients had undergone primary double cuff placement. There were no cases of infection or erosion. Of the 31 patients, 27 had no preoperative erectile function, one had normal erections, one had partial erections with the intra-urethral drug delivery system and two had a penile prosthesis. Postoperative erectile function deteriorated in one patient and remained unchanged in the others.[9] **(C)**

A historical cohort increased the original indications, including not only patients requiring reimplantation around the distal bulbar urethra, but also those submitted to primary cuff placement in the proximal bulbar urethra, with a history of radiotherapy or with a high risk of erosion by the cuff due to previous urethral mobilization for urethroplasty (N = 30; 26 with prostate cancer therapy). Twenty-six (26) patients were compared: 18 with "cuff standard setting" versus eight with "transcorporal approach," after a minimum follow-up of 12 months and a mean follow-up of 31 and 28 months, respectively. Approximately 50% of these patients had a history of radiotherapy. Most of the patients in the transcorporal group had two or more urethral surgeries prior to AUS placement, with a primary indication for TC prior anastomotic urethroplasty. Success rates for social continence (< 2 pads per day) were 61% using the standard approach and 87.5% for the transcorporal group (NNT = NS [not statistically significant]). AUS device explantation due to erosion or infection, retention (need for urethral catheter or suprapubic cystostomy), atrophy and incontinence were more common in the standard technique group. However, the data should be interpreted with caution (NNT = NS for all outcomes), since neither group is balanced. The results of this study showed that the TC group, despite a higher rate of previous urethral surgery and radiotherapy, has reasonable results.[51] **(B)**

In another study, authors evaluated data from 30 patients identified as having a "fragile urethra" post-prostatectomy (pelvic irradiation, prior AUS implant failure, previous urethroplasty or cystoscopic and/or clinical findings of urethral atrophy). Thirteen (13) of these patients underwent transcorporal AUS (TCAUS) and 17 had a "standard" approach to the cuff. Seventeen (17) patients had irradiation, eight had erosion and ten had previous urethroplasty. Five patients had multiple risk factors for urethral erosion. The follow-up time was 34.1 months (range 2-95 months) and 42.2 months (range 4-94 months) in the "standard" and TCAUS groups, respectively. When the TCAUS and "standard AUS" groups were compared, there was no difference in continence rates (≤ 1 pad/day) (NNT = NS), improvement (any reduction in the number of pads/day) (NNT = NS), explantation (NNT = NS) or erosion (NNT = NS), despite a higher proportion of previous urethroplasties in the TCAUS group.[52] **(B)**

The authors prospectively evaluated incontinence control and erectile function after prior surgical failure using the TC approach in AUS cuff implantation. 23 patients with a mean age of 70 were included (age [SD], 60-85 [7]). Of these, 18 patients had urethral atrophy and/or erosion after AUS placement (11 patients), male sling (four patients) or both (three patients), and five patients had severe urethral atrophy after pelvic radiotherapy. There were no perioperative complications. After an average follow-up of 20 months (2-59 [15]) including data from 17 patients, eight were perfectly dry (no pads and no symptoms), five achieved social continence (0-1 pad/day) and four still had incontinence (required two or more pads/day). Among the six patients who had good preoperative erectile function and were sexually active, four had no decrease in the International Index of Erectile Function Questionnaire (IIEF-5) score. Therefore, TC cuff placement is a useful alternative after failure of prior surgical treatment, urethral atrophy or erosion. Erectile function can be maintained using the TC approach.[53] **(C)**

Of the 37 male patients treated with transcorporal AUS cuff, 20 had primary placement of transcorporal cuff, one of them with surgical indication due to previous

radiation, and 25 patients had a secondary procedure after failure of AUS or urinary incontinence surgery. After a median of 32 months (minimum follow-up of two years), the continence rate (0 to 1 pad/day) was 69.7%. A total of 88% of patients reported satisfaction with the AUS. Patients with primary implant due to irradiation were no more prone to revision than non-irradiated patients. Erection preservation was reported in half of the potent patients.[54] **(C)**

A before-and-after study included 18 patients who had implanted AUS with dual cuff, being one or both cuffs placed using the TC approach. Ten patients had a distal cuff implanted transcorporally to complement a proximal bulbar urethral cuff implanted using standard technique. The main indication for this approach was erosion or infection with prior AUS. None of the patients had preoperative erectile function and median follow-up was 26 months (IQR 14-30). Results of 16 patients were analyzed, with continence rate (0 to 1 pad/day) at 38% (one completely dry). In addition, five (31%) patients needed 2 pads/day, and five (31%) used 3 pads/day. Before the implantation of the dual TC cuff, the median daily pad use was 5.0 (IQR 3.5-5). Complications included four (22%) reoperations, one erosion and two infections.[55] **(C)**

Global evidence summary

The TC approach for cuff implantation may be indicated for men with a history of urethroplasty, previous urethral erosion, those treated with radiotherapy, with urethral atrophy, and tissue involvement. **(B)**

An important consideration regarding the use of a transcorporal approach is the erectile function of patients. They should be warned that this approach can lead to erectile dysfunction. **(C)**

5. Perioperative and postoperative care

The objective of this evaluation is to assess the best conduct in the perioperative and postoperative period of artificial urinary sphincter implantation, considering primary studies.

Clinical question

What conduct should be adopted in the perioperative and postoperative period of the implantation of the artificial urinary sphincter in order to reduce the risks of the procedure? This question was answered based on the PICO method, where P stands for patients with moderate to severe urinary incontinence, I is the intervention implantation of the AUS model AMS800® and O is the perioperative and postoperative conduct that can reduce the risks of implantation. Based on the structured question, keywords were identified and constituted the basis of the search for evidence in the databases. After applying the eligibility criteria (inclusion and exclusion), articles were selected in order to answer the clinical question (Annex V).

Results

For this issue, 1,764 studies were retrieved, 35 were selected by title and 32 by summary, with reading of the full text in the second case. After the analysis of the full texts, 29 studies were included in our evaluation.[1,17,26,31,34,45,56-76] Absence to respond to the PICO criteria was the main reason of exclusion.

Evidence on perioperative antibiotic prophylaxis for urinary prosthesis placement is variable, with data extrapolated from meta-analyses on hernioplasty with the use of mesh and orthopedic implant surgeries.[45,56,57] **(A)** Thus, the adequate duration of postoperative antibiotics after implantation remains unknown.[58] **(D)**

The rate of infection in contemporary studies is between 1 and 8%[57] **(A)** [34,59-61] **(C)**, with rates < 2% in high-volume centers.[1,17,62] **(C)** Gram-positive bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermidis* represent the majority of infections, with methicillin resistance (MRSA) reported in 26% of the microorganisms.[63] **(C)** Gram-negative infections account for 26% of infections.[63] **(C)** Perioperative antibiotics are routinely administered; however, there is no standardized antibiotic regimen, and the choice depends on the surgeon's preference. It is recommended to provide both Gram-positive and Gram-negative coverage, including coverage for methicillin-resistant *Staphylococcus*.[31] **(D)** According to the guidelines of the American Urological Association on antimicrobial prophylaxis, this should consist of an aminoglycoside and a first- or second-generation cephalosporin or vancomycin, and should be administered within 60 minutes before skin incision.[64] **(D)**

Perioperative antibiotic therapy and attention to meticulous sterile techniques are the pillars of infection prevention. Authors have reported that a group of patients who rubbed the skin (five minutes rubbing the perineal and abdominal skin twice a day during the 5-day period immediately prior to AUS implantation) preoperatively with 4% topical chlorhexidine were four times less likely to suffer perineal colonization during surgery compared to a group receiving normal hygiene procedures (water and soap) [OR 0.23, p=0.003].[65] **(B)** More recently, it has been demonstrated in a randomized study that alcohol chlorhexidine solution reduced the presence of coagulase-negative staphylococci at the surgical site better than iodopovidone (topical PVP-I).[66] **(A)**

There is no evidence to support routine oral antimicrobial therapy postoperatively, especially in the absence of catheter placement and/or patient risk factors.[31] **(D)** The periods of oral antibiotic therapy (quinolones, cephalosporin or trimethoprim-sulfamethoxazole) in the postoperative period of AUS implantation vary in terms of extension, and are inconsistently reported in before-and-after studies.[67-70] **(C)** Meta-analyses of inguinal hernia repair using mesh[56] **(A)** and orthopedic surgery[57] **(A)** confirm that antimicrobial prophylaxis is beneficial when foreign material is implanted. A prolonged course of antimicrobials has been used by many professionals after penile prosthesis insertion, but evidence from orthopedic literature suggests that prophylaxis for 24 hours or less is adequate.[71] **(D)**

Trauma caused by catheterization or endoscopic manipulation in patients with an activated or malfunctioning device are considered as potential causes of urethral lesions, facilitated by tissue devascularization due to urethral athrophy.[26,72,73] **(C)** Even catheters suitably placed for short periods can be detrimental to the long-term survival of the device. Authors have demonstrated a greater risk of erosion in patients who were catheterized for more than 48 hours at any time after the placement of the AUS.[74] **(C)** Therefore, in situations when catheterization is absolutely necessary, a catheter of the appropriate caliber should be put in place for the shortest possible period of time (although there is no definition of how many days it should remain and this varies depending on the clinical situation). Intermittent urinary catheterization is not a contraindication in the presence of an artificial urinary sphincter, as long as the cuff remains deflated during the procedure.[31] **(D)** Most patients undergoing intermittent catheterization are neurogenic, so the cuff is usually placed around the neck of the bladder, reducing the risk of urethral erosion in comparison with positioning in the bulbar urethra.[74] **(C)** [66] **(D)**

The AUS must remain deactivated for six weeks. The first postoperative clinical visit occurs between 1-2 weeks, when the abdominal and perineal incisions are inspected, assessing the integrity of the skin and the possibility of infection. At the 6-week follow-up, the sphincter is activated by applying a firm and strong grip to the control pump, with the patient being instructed in the proper use of the device by the physician.[75] **(D)** Difficulty in handling the pump leads to inadequate emptying of the cuff, which is the most common cause of postoperative urinary incontinence and sphincter malfunction. In order to identify early complications requiring revision in the first few months of use, 3- and 6-month visits are the most critical, with subsequent frequency adjusted based on individual clinical circumstances. Ideally, standard follow-up should be conducted annually.[31] **(D)** The immediate identification of infection and/or erosion facilitates intervention before other local or systemic consequences occur. Some surgeons advocate nighttime sphincter deactivation, but others believe that this approach is ineffective and imposes unnecessary nighttime incontinence on the patient. A study comparing the two approaches demonstrated a tendency towards a decrease in atrophy with nocturnal deactivation, but the study does not have sufficient power and does not achieve statistical significance (ARR = 27%, 95CI -0.056 to 0.600; NNT = NS; power = 33.57%).[76] **(A)**

Global evidence summary

Perioperative antibiotics are routinely administered; however, there is no standard antibiotic regimen. **(D)**

It is recommended to provide both Gram-positive and Gram-negative coverage, including coverage for methicillin-resistant *Staphylococcus* spp. This should be administered within 60 minutes before cutaneous incision. **(D)**

Alcohol chlorhexidine solution reduces the presence of coagulase-negative staphylococci at the surgical site, and is better than iodopovidone (topical PVP-I). **(A)**

There is no evidence to support routine oral antimicrobial therapy postoperatively, especially in the absence of catheter placement and/or patient risk factors. **(D)**

Trauma caused by catheterization or endoscopic manipulation in patients with an activated or malfunctioning device are considered as potential causes of urethral lesions. **(C)**

In situations where catheterization is absolutely necessary, it is important to place a catheter of the appropriate caliber for as short a time as possible. **(C)**

Intermittent urinary catheterization is not a contraindication in the presence of an artificial urinary sphincter, provided that the cuff remains deflated during the procedure.[66] **(D)**

The first postoperative clinical visit takes place within 1-2 weeks. The device should remain disabled for six weeks after surgery. **(D)**

In order to identify early complications requiring revision in the first few months of use, 3- and 6-month visits are the most critical, with subsequent frequency adjusted based on individual clinical circumstances. **(D)**

Standard follow-ups should be performed annually. **(C)**

6. Evaluation and conduction of therapeutic failure after AUS implantation

The objective of this evaluation is to assess the best conduct in the management of therapeutic failure (early or

late onset urinary incontinence) after artificial urinary sphincter implantation, considering primary studies.

Clinical question

What conduct should be adopted for therapeutic failure of urinary incontinence after implantation of the artificial urinary sphincter? This question was answered in this evaluation using the PICO method, where the P stands for patients with moderate to severe urinary incontinence presenting therapeutic failure after implantation of the AUS model AMS800®, I to intervention with evaluation and conduct during failure and O to outcomes with resolution of persistent or relapsed incontinence. Based on the structured question, we identified the keywords used as the basis for searching for evidence in the databases and after the eligibility criteria (inclusion and exclusion), which were selected to answer the clinical query (Annex VI).

Results

In all, 1,764 studies were retrieved. Of these, 30 were selected by title and 26 by summary, with reading of the full text in the second case. After analysis of the full texts, 24 studies were included in this evaluation.[9,15,17,23,24,53,77-90] The main reason for exclusion was that they did not respond to the PICO.

A careful clinical history and a focused physical examination guide the subsequent investigations necessary to determine the cause of incontinence after implantation of the AUS.

Inadequate AUS operation is the most common cause of immediate UI post-activation. Patients should be taught to completely deflate the cuff and need to understand that emptying the bladder takes time, knowing that repeated recycling may be necessary.

The control pump, if poorly placed in the scrotum, may also be accidentally compressed and cause involuntary deflation of the cuff and UI. When this happens the patient will complain of incontinence in certain body positions. The sitting position, with support directly on the urethral cuff, can also trigger its opening (direct compression). This can be solved by avoiding hard or pointed seats.

Overactive bladder (OAB) symptoms occur in up to 25% of post-prostatectomy patients and may be associated with urinary tract infection. Symptoms of *de novo* OAB, such as urgency, frequency, nocturia and urgency incontinence may develop in up to 23% of patients who did not present these symptoms preoperatively. Those with preoperative OAB will have persistent symptoms in up to 71% of cases.[91] **(C)** A history of urgency urinary incontinence prior to AUS implantation may suggest the diagnosis of detrusor overactivity. Whenever the pathophysiology remains doubtful, urodynamic evaluation is recommended in order to guide treatment.[31] **(D)** Treatment should be similar to that of any overactive bladder.[31] **(D)**

If the patient does not present continence after AUS activation (4-6 weeks post-implantation) in the postoperative period, the most common problem is a very large cuff or a very small reservoir. If the urethral cuff is too large, the coaptation of the urethra becomes insufficient, resulting in persistent incontinence.[17] **(C)** The diagnosis of a cuff with a loose fit can be done by reviewing the surgical notes, urethral pressure profilometry (performed with the cuff in the inflated and deflated modes), urethroscopic evaluation and retrograde perfusion sphincterometry with flexible cystoscope.[77] **(C)** In some cases, the reservoir balloon may not offer sufficient pressure for adequate urethral coaptation, which can be viewed cystoscopically.

Loss of system fluids may present with persistent or recurrent incontinence. Fluid loss sites may include the urethral cuff, any area of the connecting tubing, tubing connections, the reservoir balloon, or rarely the control pump. Once the fluid has been lost from the system, the pumping characteristics will change until the pump is empty. Simple abdominal radiography may exclude fluid loss from the reservoir if the contrast solution is used as the filling medium.[78] **(C)** If isotonic sodium chloride solution is used as a fluid medium, the radiographic evaluation does not help, because the silicone components are not radiopaque. X-rays with insufflation-deflation are necessary to assess the function of the sphincter. When the cuff is closed, a contrast ring should be visible at the cuff site. When the cuff is open, the pump and reservoir should contain some fluid, and the cuff should have minimal fluid. If radiographic contrast is absent, leakage has occurred.[79] **(C)** When an isotonic (sodium chloride) solution is used as the fluid medium, lower abdominal ultrasonography[80] **(C)** or non-contrasted computed tomography (CT) of the abdomen and pelvis can help to assess the volume in the balloon and diagnose fluid loss.[81] **(D)** However, the image will not help to determine the exact location of the leak. During the operative (revision) act, use of the electrical conductance test (ohmmeter) assists in identifying the defective component and the location of the leak.[81] **(D)** If an ohmmeter cannot be used to identify leakage location, the pressure in the reservoir can be measured by connecting the tubes to a pressure transducer or by aspirating and measuring the volume of the balloon.[82] **(C)** Surgical exploration is required when fluid loss occurs. The "AUS Consensus Group" (2015) recommends that the entire AUS device be removed if loss of fluid is evident.[31] **(D)** Nevertheless, studies have argued

that in specific cases when the leakage of a component can be identified intraoperatively and the AUS has been placed for a period of < 3 years, replacement of a single component can be considered.[83,84] **(C)**

Urethral sub-cuff atrophy is defined as a progressive loss of initial continence after AUS implantation in the absence of erosion, mechanical malfunction or leakage and/or bladder-related causes leading to worsening of urinary continence.[31] **(D)** Tissue atrophy results in a loss of urethral compression and occlusion of the lumen. The progression of incontinence increases slowly over months or years and there is often a change in the number (increase) of pump activations required to open the cuff.[15] **(D)** A simple pelvic X-ray will show more fluid in the cuff compared to an immediate postoperative radiograph (if contrast fluid is used). Urethroscopy discards erosion and confirms the diagnosis of atrophy when poor coaptation of the mucosa at the cuff level is observed with it fully inflated.[31] **(D)** Urethral withdrawal pressure profiling can be performed with the cuff in inflated and deflated modes, although it is currently a rarely used resource. A minimal pressure change between the two modes suggests sub-cuff atrophy or sphincter dysfunction.[15] **(D)** A more conservative initial therapeutic approach is preferred, such as reducing the cuff size or replacing the position so that it is more proximal, whenever possible.[17,85] **(C)** Other procedures such as double-cuff[86-88] **(C)**, transcorporal (TC) cuff placement[9,53,89] **(C)** or higher pressures in the reservoir may be considered. The literature is not clear as to the best method for cuff revision. A historical cohort study showed that the placement of a "double-cuff" was more effective than either a "smaller size" (in relation to mechanical failure; p=0.01) or compared to "replacement with a new location" (in relation to continence, p=0.02).[90] **(B)** Another historical cohort compared placement of a double-cuff versus a single-cuff in patients with post-prostatectomy urinary incontinence as initial therapy. In a long follow-up (74-58 months), the study did not show a difference in the continence rate between the groups (NNT = NS). However, the double-cuff group had a higher number of complications requiring additional surgery (ARI = −0.53 to 0.008; NNH = NS; without statistical significance).[88] **(B)**

Global evidence summary

Inadequate AUS operation is the most common cause of immediate UI post-activation. **(D)**

In patients with overactive bladder and persistent UI, when the pathophysiology remains doubtful, a urodynamic assessment is indicated in order to guide treatment, which should be similar to that of any patient with overactive bladder. **(D)**

If the patient does not show continence after AUS activation (4-6 weeks post-implantation) in the postoperative period, the most common problem is a very large cuff or a very small reservoir. **(C)**

The diagnosis of a cuff with a loose fit can be performed by reviewing the surgical notes, urodynamic study, urethroscopic evaluation and retrograde perfusion sphincterometry with a flexible cystoscope. **(C)**

Simple abdominal radiography may exclude fluid loss from the reservoir if the contrast solution is used as the filling medium. **(C)**

When an isotonic (sodium chloride) solution is used as the fluid medium, lower abdominal ultrasonography **(C)** or non-contrasted computed tomography of the abdomen and pelvis can help to assess the volume in the balloon and diagnose fluid loss. **(D)**

The "AUS Consensus Group" (2015) recommends that the entire AUS device be removed if a loss of fluid is evident. **(D)**

In specific cases, when the leakage of a component can be identified intraoperatively and the AUS has been placed for a period of < 3 years, replacement of a single component can be considered. **(C)**

Urethral sub-cuff atrophy is defined as a progressive loss of initial continence after AUS implantation in the absence of erosion, mechanical malfunction or leakage and/or bladder-related causes leading to worsening of urinary continence. **(D)**

A simple pelvic X-ray will show more fluid in the cuff compared to an immediate postoperative radiograph (if contrast fluid is used). Urethroscopy can rule out erosion and confirm the diagnosis of atrophy when poor coaptation of the mucosa at the cuff level is observed with the cuff fully inflated. **(D)**

In atrophy, a more conservative initial therapeutic approach is preferred, such as reducing the cuff size or replacing the position to make it more proximal, whenever possible. **(C)** Other procedures such as a double-cuff **(C)**, transcorporal placement of the cuff **(C)** or higher pressures in the reservoir may be considered.

7. Complications

The objective of our review is to evaluate the best strategy against suspected erosion or extrusion, infection and urethral atrophy.

Clinical question

What is the best strategy against suspected erosion or extrusion and infection? This question was answered in this evaluation using the PICO method, where the P stands

for the patient with urinary incontinence due to sphincter deficiency; I for intervention with an artificial urinary sphincter; and O for urethral erosion and infection. Based on the structured question, we identified the keywords used as the basis for searching for evidence in the databases and after the eligibility criteria (inclusion and exclusion), which were selected to answer the clinical question (Annex VII).

Results

The usual procedure in the treatment of urethral erosion consists of the surgical removal of the cuff, plus passage of a Foley catheter or suprapubic cystostomy.[19,92] **(B)** However, removal of the remaining components is not mandatory, as long as they are not infected. Although the risks and benefits of complete removal have been debated for a long time, acceptance of the maintenance of certain components has been growing.[93] **(C)** A retrospective observational study that analyzed outcomes related to individuals submitted to the installation of urological prostheses in five-year period (penile prostheses installed in 300 individuals and artificial urethral sphincter in 251) verified that among the 120 individuals who required surgical re-attachment due to persistent urinary incontinence, erosion, urethral atrophy, malfunctioning of the prosthesis and pain, 45% of cases (n = 55) did not require complete removal of all components.[94] **(C)** The regulatory balloon, normally placed in the suprapubic region, can be abandoned, provided there is no infection. The pump, however, is commonly removed together with the cuff and connecting tubes between them. Another retrospective study that analyzed 10 years of experience with artificial sphincter implantation found that 31.6% of patients (n = 25) required at least one additional procedure because of urethral atrophy (22.8%) or erosion or infection (8.9%).[95] **(C)** In this analysis, two individuals submitted to the artificial sphincter implant were monitored clinically for several years even after identification of the erosion of the cuff. In this case, both refused surgical treatment and remained continent and uninfected despite chronic erosion for more than five years (15 and 5 years, respectively).[95] **(C)** The maintenance of the cuff is an exception and is not supported in the literature. The usual treatment is removal of the eroded urethral cuff. Urethral erosion may result in stenosis at the affected site and require additional procedures to correct it. Authors have reported that more than 80% of the patients presenting erosion followed by removal of the cuff developed stenosis of the urethra.[96] **(C)** Other authors have described urethroplasty at the same time as removal of the device to prevent subsequent stenosis.[97] **(C)**

With regard to infection, this may occur in the perioperative period or even years after implantation of the device.[37] **(B)** Infection rates in contemporary series have been reported between 1 and 8%, which may be less than 2% in series involving a large number of patients.[17,31,59,63,98] **(C)** [37] **(B)** Gram-positive microorganisms such as *Staphylococcus aureus* and *Staphylococcus epidermidis* are most commonly associated with infection, and Gram-negative bacteria may be identified, such as *Pseudomonas aeruginosa* and *Escherichia coli*.[67] **(C)** In the presence of superficial infection, oral or intravenous antibiotic treatment may be the approach of choice. However, if there is any doubt about the device's impairment, it should be removed, given the possibility of biofilm formation on the prosthesis.[67] **(D)**

Global evidence summary

The recommended conduct for urethral erosion is removal of the cuff and preferably of the other components. In selected cases, parts of the device may be retained. Do not remove the eroded cuff is an exception. In the presence of superficial infection, clinical treatment may initially be attempted. However, the recommended treatment in most cases is removal of the device, providing coverage for Gram-positive and Gram-negative bacteria.

Annex I

AMS 800 Model

Clinical question

What conduct should be adopted in the choice and preparation of the components of the artificial urinary sphincter model AMS 800?

Structured question (PICO)

- **P**atient – Patients with urinary incontinence due to sphincter deficiency.
- **I**ntervention – Implantation of the AUS model AMS 800.
- **C**omparison – Different components and preparation of such (cuff and balloon).
- **O**utcome – Control of incontinence and complications.

Data extraction

The results obtained from the studies included were related to the number of patients who obtained benefit or harm with different components (e.g. better cuff size) or preparation (better balloon pressure and filling liquid of the system).

Data analysis and expression

The results are expressed as absolute risk reduction or increase with their respective 95% confidence intervals. The number needed to treat (NNT) or number needed to harm (NNH) will be calculated.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.
- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).
- It will include the following components: number of patients, type of comparison, magnitude (NNT), and precision (95CI).

Annex II

Preoperative period

Clinical question

How should the preoperative evaluation be performed in patients who will undergo artificial urinary sphincter implantation?

Structured question (PICO)

- **P**atient – Patients with moderate to severe urinary incontinence.
- **I**ntervention – Artificial urinary sphincter.
- **C**omparison – Taking or not taking certain preoperative conducts.
- **O**utcome – Benefit or harm in the postoperative period.

Data extraction

The results obtained from the studies included were related to the preoperative evaluation used and the number of patients who obtained benefits or harm from this measure.

Data analysis and expression

Preoperative care most frequently used in the included studies as well as possible benefits or harm related to this conduct were discussed.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.
- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).

Annex III

Perineal versus scrotal approach

Clinical question

What should be the surgical approach to artificial urinary sphincter implantation?

Structured question (PICO)

- Patient – Patients with urinary incontinence due to sphincter deficiency.
- Intervention – Implantation of artificial urinary sphincter via the scrotal approach.
- Comparison – Perineal implantation approach.
- Outcome – Control of incontinence and complications.

Data extraction

The results obtained from the included studies referred to the number of patients who obtained benefits or harm from one of the two approaches.

Data analysis and expression

The results are expressed as absolute risk reduction or increase with their respective 95% confidence intervals. The number needed to treat (NNT) or number needed to harm (NNH) will be calculated.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.
- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).
- It will include the following components: number of patients, type of comparison, magnitude (NNT), and precision (95CI).

Annex IV

Transcorporal approach

Clinical question

What is the best approach for cuff placement in artificial urinary sphincter implant surgery?

Structured question (PICO)

- **P**atient – Patients with moderate to severe urinary incontinence.
- **I**ntervention – Cuff implantation using a transcorporal approach.

- **C**omparison – "Standard" cuff implantation.
- **O**utcome – Control of incontinence and complications.

Data extraction

The results obtained from the included studies referred to the number of patients who obtained benefits or harm from one of the two approaches.

Data analysis and expression

The results are expressed as absolute risk reduction or increase with their respective 95% confidence intervals. The number needed to treat (NNT) or the number needed to harm (NNH) will be calculated.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.
- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).
- It will include the following components: number of patients, type of comparison, magnitude (NNT), and precision (95CI).

Annex V

Perioperative and postoperative care

Clinical question

What is the best approach for cuff placement in artificial urinary sphincter implant surgery?

Structured question (PICO)

- **P**atient – Patients with moderate to severe urinary incontinence.
- **I**ntervention – Implantation of the AUS model AMS800.
- **C**omparison –
- **O**utcome – Perioperative and postoperative conduct that can reduce risks of implantation.

Data extraction

The results obtained from the studies included were related to the number of patients who obtained benefit or harm with different procedures in the perioperative and postoperative period.

Data analysis and expression

Whenever possible, the results will be expressed as the reduction or increase of the absolute risk with their respective 95% confidence intervals and number needed to treat (NNT) or number needed to harm (NNH) calculated.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.
- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).
- It will include the following components: number of patients, type of comparison, magnitude (NNT), and precision (95CI).

Annex VI

Evaluation and conduction of therapeutic failure after AUS implantation

Clinical question

What conduct should be adopted for therapeutic failure of urinary incontinence after implantation of the artificial urinary sphincter?

Structured question (PICO)

- **P**atient – Patients with moderate to severe urinary incontinence presenting therapeutic failure after implantation of the AUS model AMS800®.
- **I**ntervention – Assessment and conduct during failure.
- **C**omparison –
- **O**utcome – Resolution of persistent or recurrent incontinence.

Data extraction

The results obtained from the included studies were related to the number of patients who obtained benefits or damages with different procedures in the evaluation and conduction of the therapeutic failure after implantation of the AUS.

Data analysis and expression

Whenever possible, the results will be expressed as the reduction or increase of the absolute risk with their respective 95% confidence intervals and number needed to treat (NNT) or number needed to harm (NNH) calculated.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.

- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).
- It will include the following components: number of patients, type of comparison, magnitude (NNT), and precision (95CI).

Annex VII

Complications

Clinical question

What is the best strategy against suspected erosion or extrusion, infection and urethral atrophy?

Structured question (PICO)

- **P**atient – Patient with urinary incontinence due to sphincter deficiency.
- **I**ntervention – Artificial urinary sphincter.
- **C**omparison – None.
- **O**utcome – Urethral erosion and infection.

Data extraction

The results obtained from the included studies referred to the number of patients who obtained benefits or harm from one of the two approaches.

Data analysis and expression

The results are expressed as absolute risk reduction or increase with their respective 95% confidence intervals. The number needed to treat (NNT) or number needed to harm (NNH) will be calculated.

Description of evidence

The available evidence will follow some principles to be displayed:

- It will be shown based on benefit or harm outcomes.
- It will be presented according to study design (randomized controlled trial, clinical trial, before-and-after trial).
- It will include the following components: number of patients, type of comparison, magnitude (NNT), and precision (95CI).

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Association between renal cysts and abdominal aortic aneurysm: A case-control study

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Summary

Objective: To investigate the positive association between the presence of simple renal cysts (SRCs) and abdominal aortic aneurysm (AAA).
Method: In a retrospective case-control study including subjects aged > 50 years, we evaluated the incidence of SRCs on computed tomography (CT) scan. We compared 91 consecutive patients with AAA referred from the Division of Vascular Surgery and 396 patients without AAA, randomly selected after being matched by age and gender from 3,186 consecutive patients who underwent abdominal CT. SRC was defined as a round or oval low-attenuation lesion with a thin wall and size > 4 mm on CT without obvious evidence of radiographic enhancement or septations. Patients were considered as having AAA if the size of aorta was greater than 3.0 cm.
Results: Patients with AAA and without AAA were similar in terms of age (67.9± 8.41 vs. 68.5±9.13 years) (p=0.889) and gender (71.4 vs. 71.2% of male subjects, respectively) (p=0.999). There was no difference in the prevalence of SRC between case and controls. Among individuals with AAA, 38 (41.8%; [95CI 32.5-52.6]) had renal cysts compared to 148 (37.4%; [95CI 32.7-42.2]) in the control group (p=0.473), with a prevalence ratio (PR) of 1.16 (95CI 0.80-1.68).
Conclusion: We found no significant differences in the prevalence of SRCs among patients with AAA and controls. Our findings suggest that the presence of SRCs is not a risk factor or a marker for AAA.

Keywords: cystic kidney diseases, abdominal aortic aneurysm, connective tissue.

Study conducted at Universidade Estadual de Feira de Santana (UEFS), Feira de Santana, BA, Brazil

Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.681

Introduction

Abdominal aortic aneurysm (AAA) is a serious disease, with significant morbidity and mortality.[1,2] The incidence of AAA has been estimated to be 15-37 per 100,000 patients-year, with an increased prevalence in both males and the elderly.[3] Due to the high mortality rate following AAA rupture, ultrasound screening has been recommended for high-risk patients aged 65-75 years.[4,5] Known risk factors for AAA development include smoking, chronic obstructive pulmonary disease, hypertension, atherosclerosis and familial history.[6,7]

Recently, some publications suggested an association between simple renal cysts (SRCs) and AAA.[8-10] Simple renal cyst is the most common structural abnormality observed in human kidneys, with prevalence ranging from 5-41%.[11,12] Similarly to what is seen with AAA, the prevalence of SRCs increases with age and in male population.[13] The majority of SRCs are asymptomatic, not harmful and incidentally found by renal imaging, including computed tomography (CT) and ultrasonography. Most SRCs are clinically irrelevant and seldom require treatment.[11,13] Some authors hypothesized that AAA and SRC might share common pathophysiological mechanisms, including possible manifestation of connective tissue weakness.[14] Furthermore, the association between SCRs and AAA

might be of clinical importance for the early recognition of patients at risk for the aortic aneurysmal disease. So, the aim of our study was to investigate a possible positive association between the presence of SRCs and AAA.

Method

This is a retrospective case-control study aimed to establish the prevalence of SRCs in patients with and without AAA based on CT reports, performed in two private clinics specialized in vascular surgery and diagnostic imaging in the city of Feira de Santana, Brazil. Our study was approved by the institutional review board of both clinics, and requirement for informed consent was waived.

Ninety-one (91) consecutive patients with AAA treated in a private clinic specialized in vascular diseases (L.J.C.S) during the years 2008 and 2011 were included in the study group. Diagnosis of AAA was confirmed by CT. Patients were considered as having AAA if the aorta size was greater than 3.0 cm. A control group was identified by searching the database of a private clinic specialized in radiology (M.V.M.S) for all patients aged > 50 years submitted to CT scan in the same period without the diagnosis of AAA. The absence of AAA was confirmed by CT in all patients. Predisposing factors for renal cyst formation (autosomal-dominant polycystic disease, end-stage renal disease, and hydronephrosis) were excluded. Of 3,186 patients initially selected, 396 age- and gender-adjusted controls were selected. Due to specifics of the radiology database, detailed clinical or demographic information were not available for the control subjects.

All imaging studies were performed, read and reported by an experienced radiology attending physician as part of clinical care and without knowledge of this study. A patient was considered to have a SCR if a round or oval low-attenuation lesion with a thin wall and a size > 4 mm was identified on CT without obvious evidence of radiographic enhancement or septations.

Data were expressed as means ± SD, medians and interquartile ranges, or absolute values and fractions. Student's t-test or Mann-Whitney U test was used to compare continuous variables while categorical variables were compared using Chi-square or Fisher's exact test. All tests were 2-sided, with $p<0.05$ considered statistically significant, and were performed using GraphPad Prism® version 6.02 (GraphPad Software, San Diego, CA, USA).

Results

Among the 91 patients included in the group with AAA, 65 (71.4%) were male and 26 (28.6%) were female. Mean age of the individuals with AAA was 67.91±8.41 years (range 51-89 years). In the control group, 282 (71.2%) patients were male and 114 (28.8%) female. Mean age in the control group was 66.47±9.13 (range 51-89 years). The groups were similar according to mean age (p=0.889) and gender distribution (p=0.999).

In the group of patients with AAA, SRCs were observed in 38/91 (41.7%) individuals. There was no significant difference in the prevalence of SCRs between men and women. Twenty-nine (29) out of 65 male patients (44.6%) and nine out of 26 female patients (34.6%) had SCRs (p=0.482).

In the control group, SRCs were found in 148/396 (37.4%) patients. No significant difference was observed in the prevalence of SRCs compared by gender. Simple renal cysts were seen in 108/275 (39.3%) male patients and in 40/121 (33.1%) female patients (p=0.261).

The prevalence of SCRs among patients with AAA (41.7% [95CI 32.5-52.6]) was similar to the prevalence observed in the control group (37.4% [95CI 32.7-42.2]) (OR = 1.08 [95CI 0.68-1.72]), p=0.473 (Figure 1).

Discussion

In the present study, there was no statistical difference in the prevalence of SRCs in patients with AAA (41.7%) and in the controls (37.4%). Previous publications demonstrated a statistically significant correlation between SCRs and AAA [6,8-10,14] and put SCRs in line with other clinical markers that have been associated with AAA, including smoking, chronic obstructive pulmonary disease, hypertension, atherosclerosis and familial history.[6,7] However, our data oppose these findings and suggest that SCRs cannot be used as a clinical marker for AAA.

Some authors hypothesized the existence of a common pathogenetic pathway for the development of SRCs and AAA. Speculatively, authors suspected an interrelation in the metabolism of collagen and elastin that may be implicated in both entities.[8,9,14] Our data refutes this common pathophysiological pathway, since the prevalence of SRCs were similar in patients with and without AAA.

The difference observed between our data and those of previous published studies may be explained by several factors, including demographic characteristics and selection or allocation bias. Yaghoubian et al.[9] first reported that patients with AAA have a significantly increased prevalence of SCRs on CT scan compared to patients without AAA.[9] The differences with the present data may be explained by demographic and baseline characteristics. In the study published by Yaghoubian et al.,[9] the mean age was higher than in our series (67 vs. 74 years) and a higher prevalence of men (71 vs. 91%) was observed. As previously demonstrated, male gender and old age are consistent risk factors

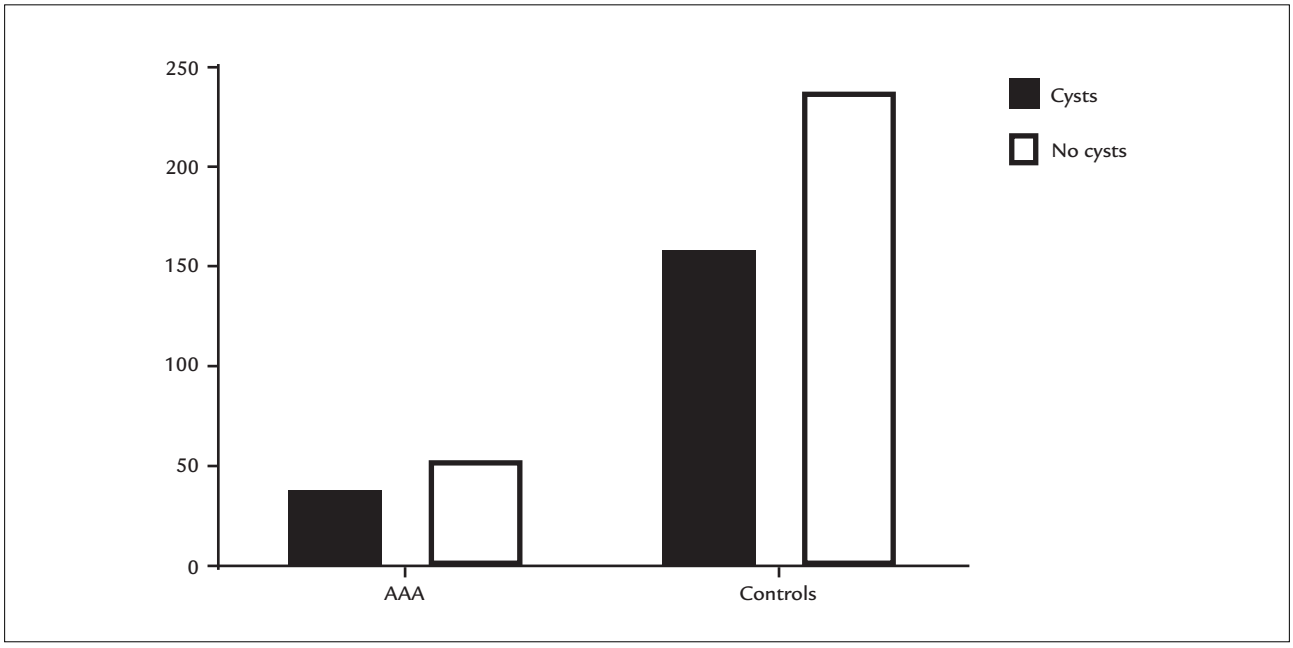

FIGURE 1 Prevalence of simple renal cysts among patients with abdominal aortic aneurysm (AAA) and controls.

for the development of SRCs.[3] These demographic differences may explain the higher prevalence of SRCs observed by Yaghoubian et al.[9] in comparison to our data (54.0 vs. 41.7%). Furthermore, in our data, the prevalence of SRCs in the control group was higher than the prevalence found by Yaghoubian et al.[9] (44.9 vs. 30.0%), which may explain the divergence between the series. The difference may also be explained by an allocation bias. The control group in the Yaghoubian et al.[9] series included patients who underwent a CT scan for traumatic injury. Nevertheless, the inclusion criteria for our control group were age > 50 years old and absence of an AAA on the CT scan. These criteria may allow the inclusion of patients that underwent a CT scan intending to evaluate a cystic renal lesion, increasing the prevalence of SRCs in our control group.

Recently, Ziganshin et al.[15] demonstrated that patients with aortic aneurysm had 2.8 times greater prevalence of renal cyst compared to the control group. Ziganshin et al.[15] demonstrated a prevalence of renal cysts of 15.3% in the control group, compared to the prevalence of 44.9% observed in our control group. This difference may be explained by the average age of our control group, which was significantly higher (63.5 vs. 41.4 years). Our control group was matched by age and gender to the group including patients with AAA, and selection bias may explain the differences observed with our data.

Due to the high mortality rate following AAA rupture, ultrasound screening has been recommended for high-risk patients aged 65-75 years.[4,5] In 2014, the United States Preventive Task Force recommended one-time ultrasound screening for men 65-75 years of age who have ever smoked.[16] Identifying risk factors in order to select populations with higher risk of presenting an AAA is important for daily clinical practice. Unfortunately, our data refute the hypothesis that SRCs are associated with AAA, and thus cannot be used as a marker of this important vascular disease in our population.

Our study has limitations that must be acknowledged. First, the patients included in the study were not a random sample of the general Brazilian population and our data must be extrapolated carefully. Second, due to specificities of the radiology database and the retrospective nature of our study's design, detailed clinical or demographic information were not available for the control subjects and could not be compared between the groups. However, to the best of our knowledge, this is the first series in a Brazilian population. Furthermore, these are the first data to refute the hypothesis that SCRs is associated to AAA. Future multicenter studies are needed to solve this matter, showing whether or not there is a common genesis for both diseases, or even the possible role of renal cysts as a marker of aortic aneurysms.

Conclusion

Our study found no association between SRCs and AAA. Our data suggest that SCRs cannot be used as a risk factor to select patients that should be screened for an AAA.

Resumo

Associação entre cistos renais e aneurismas da aorta abdominal: Um estudo de caso-controle

Objetivo: Avaliar uma possível associação entre presença de cistos renais simples (CRS) e aneurisma aórtico abdominal (AAA).

Método: Em um estudo de caso *versus* controle com sujeitos com idade > 50 anos, avaliamos a prevalência de CRS detectados por tomografia computadorizada (TC). Comparamos os achados de 91 pacientes consecutivos com AAA oriundos da Divisão de Cirurgia Vascular com 396 pacientes sem AAA, randomicamente selecionados e ajustados por idade e gênero dentre 3.186 pacientes consecutivos que se submeteram a TC abdominal. Cisto simples foi definido como lesão hipodensa oval ou arredondada com paredes finas, maiores do que 4 mm em TC sem realce contrastual ou septação. Pacientes foram considerados com AAA quando o diâmetro da aorta era maior que 3,0 cm.

Resultados: Pacientes com AAA e sem AAA eram semelhantes quanto a idade (67,9±8,41 *vs.* 68,5±9,13 anos) (p=0,889) e gênero (71,4 *vs.* 71,2% dos indivíduos masculinos, respectivamente) (p=0,999). Não havia diferença de prevalência de CRS entre casos e controles. Dentre indivíduos com AAA, 38 (41,8%; [IC95% 32,5-52,6]) tinham cistos renais, comparados com 148 (37,4%; [IC95% 32,7-42,2]) no grupo controle (p=0,473), com uma razão de prevalência (RP) de 1,16 (IC95% 0,80-1,68).

Conclusão: Não observamos diferenças significativas na prevalência de CRS entre pacientes com AAA e controles. Nossos resultados sugerem que presença de CRS não é fator de risco ou preditor para AAA.

Palavras-chave: doenças císticas renais, aneurisma de aorta abdominal, tecido conjuntivo.

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Flexible ureterorenoscopy in position or fusion anomaly: Is it feasible?

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Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.685

Summary

Objective: To analyze the results of flexible ureterorenoscopy (F-URS) with holmium laser in the treatment of kidney stones with ectopic and fusion anomalies (horseshoe kidney and rotation anomalies).
Method: We reviewed data from 13 patients with fusion and ectopic renal anomalies that underwent F-URS from April 2011 to April 2017. We analyzed demographic and clinical data (age, gender, BMI, anatomical abnormality, location and dimension of the renal calculi) and perioperative data (method of treatment, stone-free rate, number of days with DJ catheter and perioperative complications).
Results: The mean stone size was 12.23 +/- 5.43 mm (range 6-22mm), located in the inferior (58.33%) and middle (16.76%) calyceal units, renal pelvis (16.67%) and multiple locations (8.33%). All 13 patients were treated with Ho-Yag laser, using dusting technique (25%), fragmentation and extraction of the calculi (58.33%) and mixed technique (16.67%). We did not have any severe perioperative complication. After 90 days, nine patients (75%) were considered stone free.
Conclusion: Our data suggest that F-URS is a safe and feasible choice for the treatment of kidney stones in patients with renal ectopic and fusion anomalies.

Keywords: urolithiasis, kidney calculi, kidney diseases, fused kidney.

Introduction

Nephrolithiasis is an increasingly common condition, affecting 5-15% of the world's population and mainly individuals at a productive age between the second and sixth decade of life.[1] In recent years in Brazil, according to Datasus, the number of hospital admissions and costs for the treatment of this condition has increased, with a total expenditure of BRL 29.2 million/year with hospital admissions alone, causing a high impact on public health.[2]

Renal anomalies are relatively rare. Horseshoe kidney (HK) represents the most common fusion anomaly, with an incidence of 0.25%, while the incidence of pelvic kidney varies from 1/2,100 to 1/3,000 and the variance of crossed renal ectopia is 1/1,000.[3] These conditions make it even more challenging to treat urinary lithiasis, with lower success rates in endourologic procedures and increased intraoperative risks due to anatomical differences in renal structure, rotation, and vasculature.[4,5]

Extracorporeal lithotripsy (ESWL) and percutaneous nephrolithotripsy (PCNL) are currently the most common treatment methods for kidneys with fusion or position abnormalities.[6-8] The choice of flexible ureterorenoscopy with holmium laser – Yag (Ho-Yag) as the first line of treatment for stones < 20 mm has been increasing due to important technological advances, but only a few studies have reported their results on anomalous kidneys.

Objective

To analyze the results of flexible ureterorenoscopy (F-URS) with Ho-Yag laser in the treatment of stones in kidneys with position and fusion anomalies (horseshoe kidneys, pelvic kidneys and crossed renal ectopia), evaluating stone-free

rates, operative time, difficulty accessing the calyces and complications.

Method

Data collection

We prospectively collected data from 13 patients with fusion or position abnormalities submitted to the F-URS between April 2011 and April 2017 at the Hospital São Paulo (Federal University of São Paulo – Unifesp, SP, Brazil) and at the Denver Health Medical Center (University of Colorado, CO, USA). Demographic and clinical data (age, gender, BMI, anatomical abnormalities, size and location of the stone), as well as perioperative data (stone treatment method, stone-free index, DJ catheter time and perioperative complications) were collected from the medical records. All patients underwent a control exam within 90 days, either by non contrast-enhanced computed tomography for lithiasis investigation or simple abdominal X-ray. The tomography protocol used the low-dose radioactive modulation technique, with the exception of patients with BMI > 30.[9] The abdominal X-ray, in turn, was used for monitoring patients with radiopaque stones and viewed in this examination prior to surgery.

Surgical technique

The surgical procedures were performed by two endourologists with extensive experience in F-URS (AM, WRM), all under general anesthesia and in a lithotomy position. After performing asepsis and placing sterile fields, cystoscopy was performed with identification of the ureteral meatus looking for abnormalities (duplicity). In all cases, after positioning the guidewire, a semi-rigid retrograde ureteroscopy was performed followed by an attempt to pass an 11/13 Fr or 12/14 ureteral sheath (Boston Scientific). After access to the renal pelvis with the flexible ureteroscope (Storz Flex X2, Oympus URFP5) through the ureteral sheath, a 200 or 273 µm laser fiber was used for the treatment of the stone, adjusted according to the stone's location and composition (pulverization, fragmentation and removal or mixed technique). To perform the mobilization or the removal of stones, we used a 1.9 Fr Zero Tip nitinol stone retrieval basket or 1.9 Fr Escape model (Boston Scientific). In all cases, a double J catheter was used postoperatively. Patients in whom residual fragments < 2 mm were found in the control exams after 90 days were considered as stone free.

Results

A total of 13 patients (six male and seven female) with anomalous kidney stones (five with rotational defects and eight with horseshoe kidneys) were submitted to the F-URS between 2011 and 2017. A non contrast-enhanced abdominal CT was used to determine the dimensions of the stones, with a mean value of 12.23 mm +/- 5.43 mm (ranging from 6 to 22 mm), mostly distributed in only one calycinal group (58.33% in upper calyx, 16.67% in medium calyx, 16.67% in pelvis and 8.33% in multiple calyces). All patients were treated with Ho-Yag laser, with fragmentation and removal of stones in seven cases (58.33%), pulverization in three cases (25%) and mixed technique in two cases (16.67%).

In relation to perioperative complications, there were no intraoperative complications and only one patient with a rotational defect had a mild complication in the first 24 hours after the procedure (hematuria). There were no patients with Clavien III or IV complications during postoperative monitoring. The DJ catheter was maintained for an average of nine days +/- 3.46 (ranging from 6 to 14 days). Ninety (90) days after the procedure, nine patients were stone free (75%), while residual stones were identified in only three cases (25%) (Tables 1 and 2).

Discussion

Renal fusion and positional anomalies are related to an increase in the frequency of kidney stones.[10-12] Anatomic factors associated with concomitant metabolic disorders contribute to this condition, and make endoscopic treatment difficult.[13-15]

TABLE 1 Preoperative findings.

	n (%) or n
Age (years)	46.07 +/- 13.97
Sex	
Male	6 (46.1%)
Female	7 (53.8%)
BMI	26.06 +/- 2.4
Anatomical anomaly	
Rotational defect	5 (38.46%)
Horseshoe kidney	8 (61.54%)
Site of the stone	
Lower calyx	7 (58.33%)
Middle calyx	2 (16.67%)
Pelvis	2 (16.67%)
Upper + Middle + Lower calyx	1 (8.33%)
Stone volume (mm)	12.23 +/- 5.43
Stone density (UH)	924 +/- 328.01
Preoperative stent	
Yes	11 (84.62%)
No	2 (15.34%)

TABLE 2 Perioperative findings.

	n (%) or n
Treatment method for the stone	
Fragmentation	7 (58.33%)
Pulverization	3 (25%)
Mixed	2 (16.67%)
Complications within 24h	
No	12 (84.61%)
Yes	1 (7.69%)
Time with stent (days)	9 +/- 3.46
Stone-free rate after 30 d	9 (75%)
Yes	3 (25%)
No	

PCNL is the chosen option for the treatment of anomalous kidney stones, especially for stones larger than 20 mm, with stone-free rates between 80 and 90%.[16-20] The success of the procedure is impaired by features such as renal pelvis and anteriorly positioned calyces, vascular abnormalities and different anatomical relationships with adjacent organs, which increases the risk of perioperative complications and the difficulty of the procedure.[6-8] A routine preoperative abdominal CT scan can reduce the risk of visceral injury in PCNL, especially in pelvic and horseshoe kidneys.[20,21] Auxiliary methods to aid puncture, such as laparoscopy or ultrasonography, have been described, and present good results.[16,17,22] However, the potential severity of these lesions, in addition to increasing the inherent cost of these auxiliary procedures, favors the search for more conservative treatments.

ESWL remains an interesting option for anomalous kidneys due to its non-invasive nature, although anatomical variations (high ureter implantation, JUP stenosis, etc.) make it difficult to pass stones in a significant number of patients, and complementary procedures are usually required.[1,2] The stone-free rates in anomalous kidneys vary in the literature and depend on the dimensions of the stones. Sheir et al.[23] reported a general success rate of ESWL in anomalous kidneys of 72.2%, with only 46.1% for stones > 15 mm.[1] Tunc et al.,[24] in turn, reported a rate of 92% for stones < 10 mm, but 34% for those greater than 30 mm.[3] Coupled with lower efficiency of ESWL in eliminating larger stones, Ray et al.[13] has pointed out that 51% of their patients needed an additional procedure, but that little improvement occurred after the second session, revealing a limitation in the number of attempts that could be made.

The technological advances in flexible ureteroscopy have allowed its use to be expanded, and it is increasingly used in cases of renal anomalies, especially horseshoe kidneys. Its greater deflection capacity (up to 270°), coupled with progressively thinner laser fibers and the development of nitinol stone extractors have allowed the access and treatment of stones located in lower calyces or erratically-positioned calyces, leading to stone-free rates ranging from 70 to 88.2% in up to 1.5 sessions for stones < 30 mm in diameter.[25-28] Techniques such as reallocation of stones from the lower calyx to the middle or upper calyx aid in the success of the procedure by facilitating fragmentation, as well as increasing the useful life of the apparatus by avoiding excessive use of deflection. For cases with residual calculi, ESWL, PCNL or another F-URS session can be performed, but conservative treatment should not be ruled out when possible. In our series of cases, we obtained a stone-free rate of 75% for stones with a diameter of 12.22 mm (+/- 5.43 mm), with minimal complication rates (one case of transient hematuria), reinforcing data in the current literature that F-URS is currently a safe and effective procedure for the treatment of stones < 30 mm in anomalous kidneys.

Conclusion

Patients with renal position and fusion anomalies are predisposed to the formation of stones and lower success rates in interventional procedures. Although traditionally ESWL and PCNL are the treatments of choice for these patients, advances in F-URS technology have now allowed them to be treated less invasively and with excellent results.

Resumo

Ureterorrenolitotripsia flexível no tratamento de cálculos em rins anômalos: Qual a viabilidade?

Objetivo: Analisar os resultados da ureterorrenolitotripsia flexível (ULT-F) no tratamento de cálculos em rins com anomalia de posição e de fusão (rins em ferradura e rins com vício de rotação).
Método: Realizamos a coleta prospectiva dos dados de 13 pacientes com anomalias de fusão e de posição submetidos a ULT-F entre abril de 2011 e abril de 2017. Analisaram-se dados clínicos (idade, gênero, IMC, anormalidades anatômicas, dimensão e localização dos cálculos) e perioperatórios (método de tratamento do cálculo, índice de *stone free*, tempo de cateter DJ e complicações perioperatórias).
Resultados: Nos 13 pacientes, os cálculos mediam em média 12,23 mm +/- 5,43 mm (variando de 6 a 22 mm),

em sua maioria distribuídos em apenas um grupo calicinal (58.33% em grupo calicial inferior, 16.67% em grupo calicial médio, 16,67% em pelve e 8,33% em múltiplos cálices). Todos os pacientes foram tratados com utilização de laser Ho-Yag, com fragmentação e retirada de cálculos em sete casos (58,33%), pulverização em três casos (25%) e técnica mista em dois casos (16,67%). Não houve complicações intraoperatórias ou pós-operatórias graves. Após 90 dias, nove pacientes tornaram-se *stone free* (75%).
Conclusão: A ULT-F apresenta-se como método seguro e eficaz no tratamento de litíase em rins com anomalia de posição e de fusão.

Palavras-chave: urolitíase, cálculos renais, rim fundido, nefropatias.

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Daily use of phosphodiesterase type 5 inhibitors as prevention for recurrent priapism

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Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.689

Summary

Objective: The pathogenesis of recurrent priapism is currently being investigated based on the regulation of the phosphodiesterase 5 (PDE5) enzyme. We explored the daily use of PDE5 inhibitors to treat and prevent priapism recurrences.
Method: We administered PDE5 inhibitors using a long-term therapeutic regimen in seven men with recurrent priapism, with a mean age of 29.2 years (range 21 to 35 years). Six men (85.7%) had idiopathic priapism recurrences and one man (24.3%) had sickle cell disease-associated priapism recurrences. Tadalafil 5 mg was administered daily. The mean follow-up was 6.6 months (range 3 to 12 months).
Results: Daily long-term oral PDE5 inhibitor therapy alleviated priapism recurrences in all patients. Five (71.4%) had no episodes of priapism and two (28.6%) referred decrease in their episodes of priapism. All patients referred improvement in erectile function.
Conclusion: These findings suggest the hypothesis that PDE5 dysregulation exerts a pathogenic role for both sickle cell disease-associated priapism and for idiopathic priapism, and that it offers a molecular target for the therapeutic management of priapism. These preliminary observations suggest that continuous long-term oral PDE5 inhibitor therapy may treat and prevent recurrent priapism.

Keywords: priapism, cyclic nucleotide phosphodiesterases type 5, erectile dysfunction.

Introduction

Priapism is a persistent penile erection that continues for hours and is unrelated to sexual stimulation. The corpora cavernosa are the structures affected although tumescence of the corpus spongiosum has also been observed.[1]

It is commonly perceived to be an infrequently occurring medical disorder, and most recognizably afflicts men with sickle cell disease (SCD), in whom the prevalence rate of priapism exceeds 40% and the rate of erectile dysfunction as a sequela from priapism approximates 30%.[2]

Ischemic priapism, the most common subtype, is associated with acidic and hypoxemic cavernous blood as measured by a pH and pO_2 less than the normal values found in mixed venous blood of 7.35 and 40 mmHg, respectively. It is typically accompanied by pain and is associated with ischemic effects within the penis equivalent to a compartment syndrome of an extremity.

The end-stage pathologic features consist of erectile tissue necrosis and genital organ fibrosis, which hinders normal erectile tissue hemodynamic responses, with a substantial risk of subsequent erectile dysfunction (ED). The initial management of choice is corporal aspiration with injection of sympathomimetic agents. If medical management fails, a cavernosal shunt procedure is indicated.

The natural history of priapism commonly involves recurrent short-lived episodes, which frequently forecast a subsequent major episode.[3]

Stuttering or recurrent ischemic priapism (RIP), a relatively rare condition, is a recurrent form of ischemic priapism in which unwanted painful erections occur repeatedly with intervening periods of detumescence.[2]

The exact mechanism of RIP is unknown and the clinical course of this disorder for many patients includes multiple emergency room visits and surgical shunt procedures. They may necessitate penile prosthesis implantation for irreversible corporal fibrosis and resultant ED.

However, significant advances in the study of erectile physiology during the 1980s and 1990s have led to a bet-

ter understanding of priapism and many pathophysiological hypotheses, including medication-related blockade of vascular tone.

Many preventive systemic therapies have been described, including oral baclofen, digoxin, terbutaline, sympathomimetic drugs and gonadotropin-releasing hormone (GnRH) agonists or antiandrogens.[4]

Current basic science progress in the field suggests that priapism in various instances may result from disturbances in the regulatory control of the main molecular pathway mediating penile erection, the nitric oxide--signaling pathway.

This deregulation specifically involves the reduced expression of phosphodiesterase-5 (PDE5) in the penis.

Based on this theory, we proposed the use of PDE5 inhibitors as a preventative strategy for the disorder.

Method

We evaluated prospectively seven men with mean age of 29.2 years (range from 21 to 35 years) who had presented to our local hospital emergency room or our erectile dysfunction outpatient clinic with repeated episodes of persistent penile erection in the absence of sexual interest or desire.

Six of them (85.7%) had idiopathic priapism recurrences and one (24.3%) had sickle cell disease-associated priapism recurrences.

For each patient, standard history and physical examinations were performed. Clinical histories particularly documented priapism characteristics (e.g., duration, frequency), role of antecedent factors, prior priapism episodes, use and success of relieving maneuvers (Table 1).

Patient 5 was the only one who could achieve spontaneous resolution of the episodes. Six of the patients were submitted to intervention, being that five needed aspiration only, and one (patient 4) needed Winter procedure. None of them had used any preventive therapy before.

They were informed about their risk of progression to developing major complications of priapism recurrence and the possibility of preventing new episodes according to the new theory of recurrent priapism.

The program consisted of using PDE5 inhibitors "off-label" as a long-term, continuous therapeutic regiment. Tadalafil was administered at a 5 mg daily dose.

All patients were informed about the risks and contraindications of the drug.

They were able to reach the urologic staff at any time 24 hours a day in our local hospital. The plan of scheduled contacts included outpatient visits every 3 weeks for the first 6 months. The mean follow-up was 6.6 months (range 3 to 12 months).

Results

Results are displayed in Table 2. Patient 2 was the only one affected by SCD. Mean frequency of priapism was 3.14 episodes/week. The follow-up was 6.6 months. All patients tolerated the use of sildenafil with no adverse effects.

During the treatment, only two men had recurrent priapism episodes but with a reduction in frequency and duration (patients 4 and 6). Five patients (71.4%) had zero episodes of priapism (Table 2).

Patients 1, 2, 3 and 7, who had the lowest frequency, and patient 5, who had spontaneous resolution of the episodes, have not reported any episodes since the beginning of the therapy. After termination of the follow-up program, only patients 4 and 6 had some recurrent priapic episodes, with spontaneous resolution. It is worth noting that patient 4 was the only one to undergo Winter procedure, while patient 6 was the one who had episodes for the longest time.

Discussion

The proposal of using PDE5 inhibitors to prevent RIP would immediately seem illogical based on the knowledge that this drug exerts erectogenic effects.

The implication is that deregulatory mechanisms provide a basis for priapism to occur as a manifestation of an unbalanced erectile tissue response.

TABLE 1 Clinical history of the patients.

Patient	Age	Race	1st episode	Episodes/week	Duration	Etiology	Intervention
1	36	White	3 months	1	12h	idiopathic	aspiration
2	28	White	1 year	1	4h	SCD	aspiration
3	21	White	1 year	1	3h	idiopathic	aspiration
4	36	White	6 months	7	4h	idiopathic	aspiration + Winter
5	25	Black	6 months	7	6h	idiopathic	spontaneous
6	32	White	2 years	3	6h	idiopathic	aspiration
7	27	White	1 year	2	4h	idiopathic	aspiration

SCD: sickle cell disease.

TABLE 2 Study's results.

Patient	Age	Episodes/week	Intervention	Follow-up (month)	Episodes after PDE5
1	36	1	aspiration	5	0
2	28	1	aspiration	7	0
3	21	1	aspiration	12	0
4	36	7	aspiration + Winter	8	1
5	25	7	spontaneous	3	0
6	32	3	aspiration	5	2
7	27	2	aspiration	6	0

PDE5: phosphodiesterase type 5.

Claudino et al. reported that, in mice, relaxation of the cavernosal smooth muscle occurs as a response to activation of the nitric oxide and cyclic GMP (NO-cGMP) signaling pathway. NO produced in nitrergic neurons and sinusoidal endothelium binds the soluble guanylyl cyclase (sGC), increasing the synthesis of cGMP, which leads to smooth muscle relaxation and hence penile erection. cGMP levels are regulated by the rate of synthesis and the rate of hydrolyzing mediated by phosphodiesterase type 5 (PDE5).[5]

Consistent with the physiologic function of cGMP to induce smooth muscle relaxation in the penis required for penile erection, excessive amounts of cyclic nucleotide account for the prolonged erectile tissue relaxation that manifests as priapism.

Champion et al. described the pathophysiology of stuttering priapism on a molecular level in studies using endothelial nitric oxide (eNO) synthase knockout mice, which phenotypically display priapism. They have shown a reduction in PDE5 expression which, when restored, corrects the priapism.[6]

The preventive strategy was based on previous reports on the feasibility of PDE5 for pharmacologic prevention of recurrent priapism in patients with SCD and hemoglobinopathies.[7]

Based on basic research studies, it has been suggested that PDE5 function in the penis may be up-regulated by long-term treatment with PDE5 inhibitor.[8] Burnett and Bivalacqua[9] reported on the therapeutic value of long-term use of PDE5 inhibitor.[9]

While recognizing the limitations of our study regarding the small population and the lack of a control group, the fact that RIP is a relative rare condition must be acknowledged. There are few prospective studies of preventive therapy and these outcomes can lead to other comparative trials.

Conclusion

Our findings suggest the hypothesis that PDE5 deregulation exerts a pathogenic role for both sickle cell disease-associated priapism and for idiopathic priapism, and that it offers a molecular target for the therapeutic management of priapism.

These preliminary observations suggest that continuous long-term oral PDE5 inhibitor therapy may treat and prevent recurrent priapism. A large randomized study is still needed to confirm clinical effectiveness, although advantages have been shown for this revolutionary treatment alternative.

Resumo

Prevenção do priapismo recorrente com a utilização diária de inibidores da fosfodiesterase tipo 5

Objetivo: Uma das teorias propostas para explicar a etiologia do priapismo recorrente está baseada no mecanismo de regulação da fosfodiesterase tipo 5. Estudamos o uso diário dos inibidores de fosfodiesterase tipo 5 no tratamento e na prevenção do priapismo recorrente.
Método: Sete homens com diagnóstico de priapismo recorrente, com idade média de 29,5 anos (21 a 35 anos), utilizaram inibidor de fosfodiesterase tipo 5 em dose diária (tadalafila 5 mg/dia) por período prolongado. Seis homens (85,7%) apresentavam priapismo recorrente de etiologia idiopática, e um homem (24,3%), de etiologia associada à anemia falciforme. O seguimento médio foi de 6,6 meses (3 a 12 meses).
Resultados: Todos os pacientes se beneficiaram com a utilização de inibidores de fosfodiesterase tipo 5. Cinco (71,4%) não apresentaram nenhum episódio de priapismo e dois (28,6%) relataram diminuição dos episódios. Todos os pacientes relataram melhora da função erétil.
Conclusão: Estes achados sugerem que a hipótese do mecanismo de regulação da fosfodiesterase tipo 5 exerce papel importante na patogenia do priapismo recorrente. O uso contínuo e diário de inibidores da fosfodiesterase tipo 5 pode ser uma opção no tratamento do priapismo recorrente.

Palavras-chave: priapismo, fosfodiesterases nucleotídicas cíclicas tipo 5, disfunção erétil.

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Smoking and its association with cryptorchidism in Down syndrome

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Summary

Introduction: Cryptorchidism is a common and prevalent condition in patients with Down syndrome. Environmental factors, such as smoking, can be associated with malformations during fetal development. The study of the prevalence of cryptorchidism and its association with parental tobacco use in Down syndrome can contribute to alert health care professionals, patients and family members regarding the prevention of the harms caused by cryptorchidism and its possible predisposing factors.
Objective: To evaluate the prevalence of cryptorchidism in Down syndrome and its association with maternal and paternal smoking.
Method: Forty (40) patients of a public clinic specialized in Down syndrome were evaluated, using a semi-structured questionnaire for evaluation of antecedents and sociodemographic characteristics, as well as physical and complementary examinations.
Results: Cryptorchidism was observed in 27.5% of the patients (95CI 15.98-42.96). Of these, 55% (5/9) were the children of mothers who smoked during pregnancy, and 19.35% (6/31) were the children of mothers who did not smoke during pregnancy (OR = 5.26 [95CI 1.06-25.41]; p=0.032). Similarly, paternal smoking was also observed in greater frequency among the parents of cryptorchid patients compared with subjects with descended testis, 63.36% (7/11) and 31.03% (9/29), respectively (OR = 3.89 [95CI 0.91-16.73]; p=0.060).
Conclusion: The prevalence of cryptorchidism is high in patients with Down syndrome. We can show a strong association between smoking parents and the occurrence of cryptorchidism, especially when it comes to maternal smoking.

Keywords: smoking, Down syndrome, cryptorchidism, urologic diseases.

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Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.693

Introduction

The technological advances in perinatology in the contemporary world are undisputed, yet pregnancy and birth are frequently surrounded by uncertainty, distress and anxiety.

There is a great number of etiologic factors known to favor congenital malformations, including heredity, alcohol, smoking, pesticides, illicit drugs, infection with cytomegalovirus, rubella or toxoplasmosis, and exposure to medicinal substances and radiation.[1] Environmental factors can be responsible for many congenital defects.[2] Among them, cigarettes, which are socially accepted, globally spread, and historically consumed by both women and men, predispose to fetal[3] and chromosome malformations.[2]

Down syndrome (DS), caused by trisomy 21 (HSA21), is the most frequent genetic anomaly,[2,4-8] occurring in one of every 319 to 1,000 births.[2,9-11] In Brazil, 300,000 people have DS[12] and it is estimated that one case of DS occurs in every 600 to 800 births,[13] about 8,000 cases per year, which may or may not be associated with comorbidities such as cardiac, gastrointestinal, respiratory, renal and urogenital (cryptorchidism and hypospadias) malformations, hypothyroidism, leukemia, Alzheimer's disease, and more.[14-20]

Multiple congenital malformations related to DS include urogenital ones, so that cryptorchidism and hypospadias have been reported.[20,21] It is suspected that the

lifestyle of mothers and environmental exposures during pregnancy may interfere with the normal testicular descent, increasing the risk of urogenital malformations.[19-22]

The aims of our study were to evaluate the prevalence of cryptorchidism and its association with parental smoking in patients with Down syndrome.

Method

This is an observational study in which patients of a public clinic specialized in Down syndrome of the Department of Child and Adolescent Health, in our area, were evaluated using a semi-structured questionnaire for antecedents and sociodemographic characteristics, as well as receiving physical and complementary examinations.

The project was approved by the institution's Research Ethics Committee, and those responsible for the participants signed an informed consent form.

The data are expressed as mean ± standard deviation (SD), median and interquartile interval, or absolute values and fractions. Student's t-test or Mann-Whitney test, ANOVA or Kruskall-Wallis were used to compare the continuous variables, while categorical variables were compared using Fisher's exact test or Chi-square test. Odds ratio and confidence intervals of 95% were used to describe the magnitude of the association between categorical variables. All the tests were two-sided, with $p<0.05$ considered statistically significant. Analyses were conducted using a commercially available statistical software (Graph Pad Prism, version 6.03 for Windows, San Diego, California, U.S.A.).

Results

Of the 166 patients registered in the Down Syndrome Clinic, contact was possible with 114 (68.7%), of which 40 (35.1%) were male. Cryptorchidism was observed in 11 patients in the evaluated sample, indicating a prevalence of 27.5% (95CI 15.98-42.96). In these patients, cryptorchidism was observed in 55% (5/9) of children with smoking mothers and in 19.35% (6/31) of those whose mothers did not smoke (OR = 5.26 [95CI 1.06-25.41]; p=0.032) (Figure 1).

Similarly, paternal smoking was also observed in greater frequency among the parents of cryptorchid patients compared with subjects with descended testis, 63.36% (7/11) and 31.03% (9/29), respectively (OR = 3.89 [95CI 0.91-16,73]; p=0.060). The age of the mothers was 27.1±6.17 and that of the fathers was 31.4±7.25 years.

Discussion

The occurrence of cryptorchidism in this series was 27.5%, similarly to observed in the literature, where ectopic testis was found in 14 to 27% of patients with DS. This is the most frequent urogenital tract abnormality in this population.[22] The high prevalence and drawbacks reinforce the idea that such a condition cannot be neglected in the clinical evaluation of children with Down syndrome.

Cigarette smoke contains mutagenic and carcinogenic agents,[3] as well as toxic agents, which can lead to fetal alterations[23-25] such as in the reproductive function stages (folliculogenesis, steroidogenesis, embryo transport,

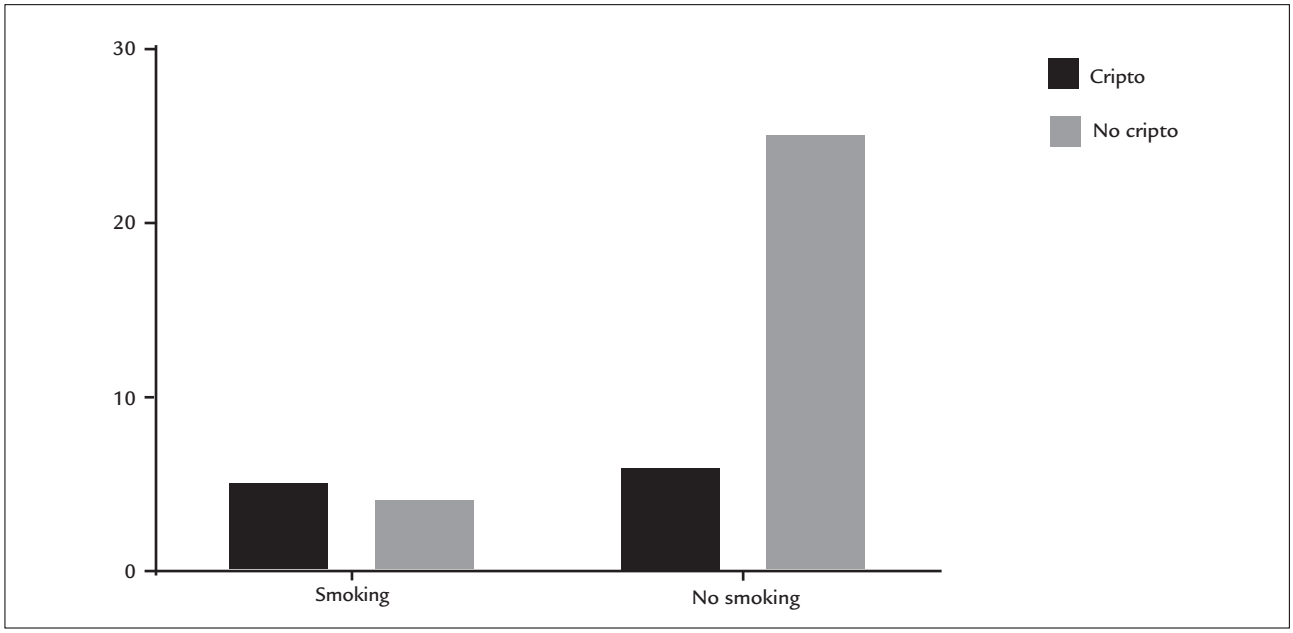

FIGURE 1 Position of the testis according to maternal smoking habit.

endometrial receptivity, angiogenesis, uterine blood flow and in the uterine myometrium) and the occurrence of chromosome malformations.[2]

Furthermore, ectopic testis can be associated with cancer in an occurrence estimated to be 3 to 48 times higher than in the general population.[26-28] Cryptorchidism is one of the main predisposing factors for seminoma tumors.[27,28]

Maternal smoking, as well as use of nicotine substitutes, was previously associated with an increased risk in the reduction of spermatozoids and cryptorchidism.[1,15] An increased risk of cryptorchidism was also observed among sons of mothers who smoked ten cigarettes or more per day during pregnancy.[16]

According to other authors, there has been a positive association between paternal exposure to pesticides and paternal smoking with cryptorchidism.[26]

Our results corroborate these findings. The possible adverse effects of maternal smoking were incontestable. Limitations due to the size of the sample make it impossible for us to show a statistically significant association with paternal smoking. We believe that studies with larger samples, and with greater power, can confirm this association.

According to data in the literature, the risk of hypospadias seems to increase with the age of the mother, mainly when she is over 40 years old, as well as with other factors, such as the use of progesterone in the beginning of pregnancy and smoking parents.[21,22,26] Although there are uncertainties whether maternal smoking is associated with congenital defects, positive associations with cryptorchidism were found, but not with hypospadias.[1,22,26] In our series, of the 40 patients with DS, only one (2.5%) presented hypospadias. The low prevalence of this malformation found in this group of patients hinders an assessment of the significance of smoking habit in the genesis of hypospadias in DS boys.

More and more consistently, congenital abnormalities such as cryptorchidism and hypospadias seem to be associated with cigarette consumption throughout pregnancy and even before conception.

The damages provoked by these environmental factors can be permanent and irreversible. We hope that our study can contribute to alert health care professionals, patients and family members regarding the prevention of harm caused by urogenital malformations and its predisposing factors. Although the number of cigarettes was not measured, it is believed that there is no safe dose for its use during pregnancy.

Conclusion

The prevalence of cryptorchidism is high in patients with Down syndrome. A strong association between smoking parents and occurrence of cryptorchidism was verified, especially when it comes to maternal smoking.

Acknowledgements

We thank all the patients with Down syndrome, parents and family members who believed and contributed to this study, and the Down Syndrome Clinic of the Department of Child and Adolescent Health (DSCA), of the Secretary of Health of the city of Juiz de Fora, Minas Gerais (Brazilian Public Health System).

Resumo

Associação entre tabagismo e criptorquidia na síndrome de Down

Introdução: A criptorquidia é uma condição comum e prevalente em pacientes com síndrome de Down. Fatores ambientais, como o tabagismo, estão associados a malformações fetais. A avaliação da prevalência do criptorquidismo e a associação com tabagismo dos pais na síndrome de Down podem contribuir para alertar os profissionais de saúde e familiares sobre a prevenção dos danos causados pelo criptorquidismo e os possíveis fatores predisponentes.
Objetivo: Avaliar a prevalência de criptorquidismo na síndrome de Down e a associação com tabagismo materno e paterno.
Método: Quarenta (40) pacientes acompanhados em um centro de referência para atendimento da síndrome de Down foram avaliados por meio de questionário semiestruturado para avaliação de antecedentes parentais e características sociodemográficas, bem como de exames físico e laboratoriais complementares.
Resultados: Criptorquidia foi observada em 27,5% dos pacientes (IC95% 15,98-42,96). Nesses pacientes, o criptorquidismo foi encontrado em 55% (5/9) das crianças cujas mães fumavam e em 19,35% (6/31) daquelas cujas mães não fumavam (OR = 5,26 [IC95% 1,06-25,41]; p=0,032). Do mesmo modo, o tabagismo paterno foi observado com maior frequência entre crianças com criptorquidia, 63,36% (7/11) e 31,03% (9/29), respectivamente (OR = 3,89 [IC95% 0,91-16,73]; p=0,060).
Conclusão: A prevalência de criptorquidismo é alta em pacientes com síndrome de Down. Podemos mostrar uma forte associação entre hábito tabágico dos pais e ocorrên-

cia de criptorquidismo, especialmente no caso de tabagismo materno.

Palavras-chave: hábito de fumar, síndrome de Down, criptorquidismo, doenças urológicas.

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Overcoming male factor infertility with intracytoplasmic sperm injection

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Summary

Objective: To evaluate the effect of male factor infertility on intracytoplasmic sperm injection (ICSI) outcomes compared with a control group presenting isolated tubal factor.

Method: This retrospective study included 743 couples undergoing ICSI as a result of isolated male factor and a control group consisting of 179 couples undergoing ICSI as a result of isolated tubal factor, performed in a private university-affiliated in vitro fertilization center, between January/2010 and December/2016. Patients were divided into two groups according to maternal age: women ≤35 years old and >35 years old. The effects of infertility causes on laboratorial and clinical ICSI outcomes were evaluated using Student's t-test and χ^2 test.

Results: No differences in controlled ovarian stimulation outcomes were observed between male factor cycles and tubal factor cycles in the two age groups. Implantation (male factor 35.5% vs. tubal factor 32.0%, p=0.340), pregnancy (male factor 46.9% vs. tubal factor 40.9%, p=0.184) and miscarriage (male factor 10.3% vs. tubal factor 10.6%, p=0.572) rates were similar between the infertility groups, irrespective of female age. Considering maternal age, the cancelation rate was higher in older women (>35 years old) undergoing ICSI as a result of male factor infertility (17.4% vs. 8.9%, p=0.013).

Conclusion: Our results showed that there is no difference in the outcomes of pregnancy between couples with male or tubal factor infertility, which indicates that ICSI surpasses the worse specific outcomes associated with male factor.

Keywords: spermatozoa/abnormalities, intracytoplasmic sperm injections, evaluation of results of therapeutic interventions, pregnancy.

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Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.697

Introduction

The male factor, which is the single most common cause of infertility, is solely responsible for 30% of infertility cases and contributory in an additional 30% of cases.[1-3] Although successful outcomes have been obtained in cases of male factor infertility, conventional in vitro fertilization (IVF) has proved ineffective for patients with seminal parameters that do not meet the minimum cut-off values determined by the World Health Organization.[4,5]

The advent of intracytoplasmic sperm injection (ICSI) improved the odds of pregnancy in patients with seminal abnormalities, such as reduced sperm count, motility and percentage of morphologically normal cells.[6] Through ICSI, it is now possible to obtain satisfactory pregnancy rates even when few spermatozoa are found in the ejaculate or surgically recovered from testicles/epididymis, which was almost impossible through classical IVF.[7]

Even though the general consensus is that ICSI should be the first treatment option only in the presence of extremely poor sperm samples,[8] it is routinely used for causes of infertility other than male factor. It has been reported that ICSI usage in the United States of America has in-

creased, from 2008 to 2012, whereas the incidence of male factor infertility has remained unchanged.[9] Therefore, the increase in ICSI usage is likely to be also occurring in couples with infertility causes other than male factor, despite the evidence that ICSI does not benefit non-male factor patients.[10]

The Center for Disease Control reported that ICSI was used in up to 78% of non-male factor ART cycles in the USA.[11] In fact, ICSI overcomes some IVF difficulties, such as zona pellucida abnormalities that prevents sperm fusion to the oolema;[12,13] zona pellucida hardening and consequent inhibition of natural sperm penetration in cryopreserved oocytes;[14,15] and DNA contamination from additional sperm that would be adhering to the zona pellucida in preimplantation genetic diagnosis (PGD) cycles.[16]

Overall, the use of ICSI has not been shown to cause any more negative effects than those seen with IVF.[9,17] ICSI actually enhances normal fertilization rate, since the requirement for cumulus cells removal allowed a better visualization of oocytes structure and maturity, and led to a better oocyte selection.[18] Moreover, spermatozoa selection made ICSI the preferred line of treatment regardless of the infertility cause.[19,20]

Few studies have investigated whether or not ICSI surpasses the worse specific outcomes associated with male factor. Therefore, the goal of this study was to evaluate the effect of isolated male factor on laboratorial and clinical ICSI outcomes compared with a control group presenting isolated tubal factor, according to maternal age.

Method

Study design

This retrospective study included 922 ICSI cycles, of which 743 were attributed to isolated male infertility and 179 to isolated tubal factor. Only first cycle with fresh own embryo transfer were included. Cycles were performed in a private university-affiliated IVF center, between January 2010 and December 2016.

In the first analysis, the effects of infertility causes on (i) the number of follicles; (ii) the number of retrieved oocytes; (iii) oocyte yield; (iv) number of mature oocytes; (v) mature oocyte rate; (vi) fertilization rate; (vii) normal fertilization rate; (viii) embryo quality at cleavage stage; (ix) blastocyst formation rate; (x) cycle's cancelation rate; (xi) implantation rate; (xii) pregnancy rate and (xiii) miscarriage rate were compared between the groups.

In the second analysis, women were divided into two groups according to maternal age: ≤ 35 y-old group (n=643) and > 35 y-old group (n=279).

Written informed consent, in which patients agreed to share the outcomes of their cycles for research purposes, were obtained, and the local institutional review board approved the study.

Controlled ovarian stimulation

Controlled ovarian stimulation (COS) was achieved using a daily dose of recombinant FSH (r-FSH, Gonal-F®, Merck KGaA, Darmstadt, Germany), beginning on the third day of the cycle. Pituitary blockage was performed using a GnRH antagonist (GnRHa, Cetrotide®; Merck KGaA, Darmstadt, Germany), beginning when at least one follicle measuring ≥ 14 mm in diameter was visualized on ultrasound exam.

When adequate follicular growth and serum E2 levels were observed, recombinant hCG (r-hCG, Ovidrel®, Merck KGaA, Darmstadt, Germany) was administered to trigger final follicular maturation. The oocytes were collected 35 hours later through transvaginal ultrasound-guided ovum pick-up.

Preparation of oocytes

Retrieved oocytes were maintained in culture medium (Global® for fertilization, LifeGlobal, Connecticut, USA) supplemented with 10% protein supplement (LGPS, LifeGlobal, Connecticut, USA) and covered with paraffin oil (Paraffin oil P.G., LifeGlobal, Connecticut, USA) for 2 to 3 hours before the removal of cumulus cells. The surrounding cumulus cells were removed after exposure to a HEPES-buffered medium containing hyaluronidase (80 IU/mL, LifeGlobal, Connecticut, USA). The remaining cumulus cells were mechanically removed by gently pipetting with a hand-drawn Pasteur pipette (Humagen Fertility Diagnostics, Charlottesville, USA).

The oocyte morphology was assessed immediately before sperm injection (four hours after retrieval) using an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon®, Tokyo, Japan) with a Hoffmann modulation contrast system under 400X magnification. Oocytes that released the first polar body were considered mature and used for ICSI.

Intracytoplasmic sperm injection

Intracytoplasmic sperm injection was performed in a microinjection dish prepared with 4-µL droplets of buffered medium (Global® w/HEPES, LifeGlobal, Connecticut, USA) and covered with paraffin oil on the heated stage of an inverted microscope (37.0 ± 0.5°C). Approximately 16 hours after ICSI, fertilization was confirmed by the presence of two pronuclei and the extrusion of the second polar body. Embryos were maintained in a 50-µL drop of culture medium (Global®, LifeGlobal, Connecticut, USA), supplemented with 10% protein supplement and covered with paraffin oil in a humidified atmosphere under 6% CO_2 at 37°C for five days.

Embryo morphology evaluation

Embryo morphology was assessed 16-18 hours post-ICSI and on the mornings of days 2, 3 and 5 using an inverted Nikon Diaphot microscope (Eclipse TE 300; Nikon, Tokyo, Japan) with a Hoffmann modulation contrast system under 400X magnification.

To evaluate cleavage-stage morphology, the following parameters were recorded: number of blastomeres, percentage of fragmentation, variation in blastomere symmetry, presence of multinucleation, and defects in the zona pellucida and cytoplasm. High-quality cleavage stage embryos were defined as those with all of the following characteristics: 4 cells on day 2, or 8-10 cells on day 3, < 10% fragmentation, symmetric blastomeres, absence of multinucleation, colorless cytoplasm with moderate granulation and no inclusions, absence of perivitelline space granularity, and absence of zona pellucida dysmorphisms. Embryos lacking any of these characteristics were considered to be of low quality.

To evaluate the blastocyst-stage morphology, the size and compactness of the ICM and the cohesiveness and number of TE cells were recorded. The ICM of full, expanded, hatching and hatched blastocysts were classified as either high-quality (tightly packed with many cells) or low-quality (loosely grouped with several or few cells). Similarly, the TE were classified as either high-quality (many cells forming a cohesive epithelium) or low-quality (few cells forming a loose epithelium or very few cells).

Embryo transfer was performed on the third or fifth day of development.

Clinical follow-up

A pregnancy test was performed 12 days after embryo transfer. All women with a positive test had a transvaginal ultrasound scan two weeks after the positive test. A clinical pregnancy was diagnosed when the fetal heartbeat was detected.

Implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred per patient. Pregnancy was defined as the presence of a gestational sac with heartbeat visualized by ultrasound 4-6 weeks after embryo transfer. Pregnancy rates were calculated per transfer. Miscarriage was defined as pregnancy loss before 20 weeks.

Statistical analysis

The effects of infertility causes on aforementioned laboratorial and clinical outcomes were evaluated by Student t-test for continuous variables and Chi-square test for categorical variables. The results are expressed as means ± standard deviation (SD) and p-value for continuous variables, while percentages and p-value are used for categorical variables. The α adopted was 5%. Statistical analysis was performed using IBM SPSS 20 Software.

Results

From a total of 3,273 first ICSI cycles with fresh own embryo transfer performed between January 2010 and December 2016, 922 were suitable for analysis. Of those, 743 cycles were attributed to pure male infertility factors and 179 to pure tubal infertility factor were included in the analysis.

In the first analysis, mean female age was higher in tubal factor patients, while mean male age was higher in male factor patients. Patients with tubal factor had worse ovarian response to COS, represented by lower number of aspirated follicles, retrieved and mature oocytes. However, a higher fertilization rate was noted compare to male factor patients. Despite the higher number of transferred embryos in male factor patients, the implantation rate was similar between groups. The cancelation rate was higher in patients with male factor, but pregnancy and miscarriage rates were similar between the groups (Table 1).

In the second analysis, in order to exclude a possible influence of maternal age on the results, women were divided into two groups according to age: ≤ 35 y-old group (531 male factor cases and 112 tubal factor cases); and > 35 y-old group (212 cases male factor cases and 67 tubal factor cases).

The effects of the infertility cause on the outcomes of ICSI in the ≤ 35 y-old group are described in Table 2. No differences in COS outcomes were observed between the groups. The fertilization rate remained higher in tubal factor patients, while the number of transferred embryos was higher in male factor patients. Clinical outcomes were similar between the groups.

The effects of the infertility cause on the outcomes of ICSI in the > 35 y-old are described in Table 3. The only significant difference observed was in cycle cancelation rate, which was higher in male factor patients. All the other analyzed variables were similar between the groups.

Discussion

Before 1992, conventional IVF could not address many issues related to male factor infertility and relied on normal or nearly normal sperm counts. The development of ICSI has revolutionized the field with regard to male infertility, but outcomes from such cases have not been well elucidated. Our study evaluated the effects of male factor, compared to a control group with isolated tubal factor, on laboratorial and clinical ICSI outcomes. Tubal factor was chosen as a reference group to act specifically as the control for the iat-

TABLE 1 Effects of the infertility causes on laboratorial and clinical ICSI outcomes.

Variables	Male factor (n=743)	Tubal factor (n=179)	p-value
Female age (y-old)	33.16±3.91	33.85±3.79	0.033
Male age (y-old)	37.75±7.37	36.59±5.65	0.022
COS outcomes			
Aspirated follicles (n)	19.98±10.74	17.93±10.44	0.022
Retrieved oocytes (n)	14.79±8.91	13.39±8.81	0.060
Oocyte yield (%)	73.55±18.53	74.80±19.00	0.422
Mature oocytes (n)	10.97±6.91	9.58±6.40	0.014
Mature oocyte rate (%)	74.26±18.13	72.77±18.74	0.329
Laboratorial outcomes			
Fertilization rate (%)	82.28±18.09	85.64±14.81	0.010
Normal fertilization rate (%)	75.72±20.50	78.42±18.36	0.109
High-quality embryo at D3 (%)	48.26±28.56	44.51±29.83	0.158
Blastocyst formation rate (%)	42.10±26.64	43.00±29.04	0.772
Transferred embryos (n)	1.68±0.67	1.50±0.61	0.004
Clinical outcomes			
Implantation rate (%)	35.55±42.21	32.00±42.20	0.340
Cancelation rate	121/743 (16.3%)	18/179 (10%)	0.036
Pregnancy rate	292/622 (46.9%)	66/161 (40.9%)	0.184
Miscarriage rate	31/302 (10.3%)	7/66 (10.6%)	0.572

COS: controlled ovarian stimulation.

TABLE 2 Effects of the infertility causes on laboratorial and clinical ICSI outcomes in the ≤ 35 y-old group.

	≤ 35 y-old women		
Variables	**Male factor (n=531)**	**Tubal factor (n=112)**	**p-value**
Female age (y-old)	31.36±2.99	31.71±3.05	0.273
Male age (y-old)	36.27±6.98	35.02±5.27	0.036
COS outcomes			
Aspirated follicles (n)	21.40±10.92	19.93±10.87	0.198
Retrieved oocytes (n)	15.96±9.21	15.04±9.40	0.340
Oocyte yield (%)	74.40±18.13	76.08±18.74	0.376
Mature oocytes (n)	11.87±7.18	10.65±6.66	0.099
Mature oocyte rate (%)	74.75±17.19	73.08±17.12	0.353
Laboratorial outcomes			
Fertilization rate (%)	82.66±17.32	86.43±14.08	0.015
Normal fertilization rate (%)	76.41±19.71	78.78±18.41	0.245
High-quality embryo at D3 (%)	49.71±27.72	45.29±28.10	0.172
Blastocyst formation rate (%)	43.55±26.93	45.76±29.59	0.565
Transferred embryos (n)	1.70±0.63	1.52±0.61	0.012
Clinical outcomes			
Implantation rate (%)	37.33±42.06	34.52±43.36	0.553
Cancelation rate	84/531 (15.8%)	14/112 (12.5%)	0.232
Pregnancy rate	222/447 (49.6%)	42/98 (43%)	0.456
Miscarriage rate	22/222 (9.9%)	3/42 (7.1%)	0.369

ICSI: intracytoplasmic sperm injection; COS: controlled ovarian stimulation.

TABLE 3 Effects of the infertility causes on laboratorial and clinical ICSI outcomes in the > 35 y-old group.

	> 35 y-old women		
Variable	**Male factor (n=212)**	**Tubal factor (n=67)**	**p-value**
Female age (y/o)	37.66±1.68	37.43±1.54	0.336
Male age (y/o)	41.55±6.99	39.16±5.33	0.004
COS outcomes			
Aspirated follicles (n)	16.44±9.43	14.63±8.82	0.165
Retrieved oocytes (n)	11.87±7.36	10.67±6.99	0.240
Oocyte yield (%)	71.45±19.39	72.68±19.37	0.651
Mature oocytes (n)	8.71±5.56	7.81±5.53	0.247
Mature oocyte rate (%)	73.03±20.28	72.25± 21.27	0.789
Laboratorial outcomes			
Fertilization rate (%)	81.33±19.92	84.31±15.99	0.270
Normal fertilization rate (%)	73.98±22.33	77.83±18.40	0.206
High-quality embryo at D3 (%)	44.66±30.33	43.31±32.53	0.772
Blastocyst formation rate (%)	37.70±25.36	37.96±27.73	0.960
Transferred embryos (n)	1.62±0.75	1.48±0.62	0.161
Clinical outcomes			
Implantation rate (%)	31.03±42.38	28.12±40.37	0.635
Cancelation rate	37/212 (17.4%)	4/67 (8.9%)	0.013
Pregnancy rate	70/175 (40%)	24/63 (38%)	0.456
Miscarriage rate	8/70 (11.4%)	4/24 (16.6%)	0.338

ICSI: intracytoplasmic sperm injection; COS: controlled ovarian stimulation.

rogenesis of ICSI technique. Our results showed that there is no difference in the pregnancy and miscarriage rates between couples with male or tubal factor, irrespective of maternal age.

Adequate female age is a pivotal factor determining successful outcomes, even when severe male factor is the main fertility cause.[21] In our study, we subdivided our sample into two age groups, younger women (≤ 35 years old) and older women (> 35 years old), to reduce the bias of maternal age on outcomes. In younger women, we observed a higher fertilization rate in the tubal factor group and a higher number of transferred embryos in the male factor group, but these differences did not impact the implantation rate and subsequent pregnancy rate, which were similar between infertility groups.

A higher cancelation rate was observed only in couples with male factor and older women. In this group, paternal age was also higher and may have impacted this outcome, since sperm morphology parameters decline significantly with age and may affect the availability of good spermatozoa to fertilize.[22,23]

The high normal fertilization and implantation rates after ICSI evidences that male factor do not interfere with the success rate of this technology, as was also reported by many other groups.[24,25]

The embryo quality and blastocyst formation were not influenced by male factor infertility. In fact, other studies comparing embryos obtained through classical IVF or ICSI with sperm from severe male infertility showed that they had potential similar developmental viabilities,[26,27] and pregnancy, miscarriage and live birth rates are similar after adjustment for maternal factors.[9,21]

A similar study comparing male and tubal factors showed that male factor infertility was related to lower pregnancy rate and a trend toward lower live birth rate.[28] Concerning perinatal outcomes, ICSI for male factor infertility was also not associated with changes in length of gestation, baby birth weight, sex ratio, rate of pregnancy loss and congenital malformations in other reports.[28-30]

The main limitations of this study are (i) its retrospective nature and (ii) the fact that male factor was defined as the cause of infertility, but it was not subdivided into different male infertility diagnoses as they exist for female factor infertility, so the severity of the male factor infertility could not be determined.

Conclusion

Our results showed that there is no difference in the clinical outcomes between couples with male or tubal factor infertility, which indicates that ICSI surpasses the worse

specific outcomes associated with male factor. An appropriate COS and endometrial preparation may have major impact on ICSI outcomes, rather than the infertility cause.

Resumo

Superando o fator masculino de infertilidade com injeção intracitoplasmática de espermatozoides

Objetivo: Avaliar o efeito do fator masculino de infertilidade em resultados de injeção intracitoplasmática de espermatozoides (ICSI) em comparação com um grupo controle que apresenta o fator tubário isolado.
Método: Este estudo retrospectivo incluiu 743 casais submetidos a ICSI por fator masculino e 179 casais por fator tubário, realizada em um centro privado de fertilização *in vitro* associado à universidade, entre janeiro de 2010 e dezembro de 2016. Os pacientes foram divididos em dois grupos de acordo com a idade materna: mulheres ≤ 35 e > 35 anos de idade. Os efeitos das causas de infertilidade nos resultados laboratoriais e clínicos da ICSI foram avaliados pelos testes T de Student e Qui-quadrado.
Resultados: Não foram observadas diferenças nos parâmetros de estimulação ovariana entre os ciclos com fatores masculinos e com fatores tubários. A taxa de implantação (fator masculino 35,5% *vs.* fator tubário 32,0%, p=0,340), de gravidez (fator masculino 46,9% *vs.* fator tubário 40,9%, p=0,184) e de aborto (fator masculino 10,3% *vs.* fator tubário 10,6%, p=0.572) foram semelhantes entre os grupos de infertilidade, independentemente da idade feminina. Considerando a idade materna, a taxa de cancelamento foi maior em mulheres > 35 anos cuja causa de infertilidade era o fator masculino (17,4% *vs.* 8,9%, p=0,013).
Conclusão: Não há diferenças nos resultados de gravidez entre casais com infertilidade dos fatores masculino ou tubário isolados, o que indica que ICSI supera os piores resultados associados ao fator masculino.

Palavras-chave: espermatozoides/anormalidades, injeções intracitoplasmáticas de espermatozoides, avaliação de resultado de intervenções terapêuticas, gravidez.

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Low serum testosterone is a predictor of high-grade disease in patients with prostate cancer

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Summary

Objective: To evaluate the relation between serum total testosterone (TT) and prostate cancer (PCa) grade and the effect of race and demographic characteristics on such association.
Method: We analyzed 695 patients undergoing radical prostatectomy (RP), of whom 423 had serum TT collected. Patients were classified as having hypogonadism or eugonadism based on two thresholds of testosterone: threshold 1 (300 ng/dL) and threshold 2 (250 ng/dL). We evaluated the relation between TT levels and a Gleason score (GS) ≥ 7 in RP specimens. Outcomes were evaluated using univariate and multivariate analyses, accounting for race and other demographic predictors.
Results: Out of 423 patients, 37.8% had hypogonadism based on the threshold 1 and 23.9% based on the threshold 2. Patients with hypogonadism, in both thresholds, had a higher chance of GS ≥ 7 (OR 1.79, p=0.02 and OR 2.08, p=0.012, respectively). In the multivariate analysis, adjusted for age, TT, body mass index (BMI) and race, low TT (p=0.023) and age (p=0.002) were found to be independent risk factors for GS ≥ 7. Among Black individuals, low serum TT was a stronger predictor of high-grade disease compared to White men (p=0.02).
Conclusion: Hypogonadism is independently associated to higher GS in localized PCa. The effect of this association is significantly more pronounced among Black men and could partly explain aggressive characteristics of PCa found in this race.

Keywords: prostate cancer, hypogonadism, testosterone.

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Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.704

Introduction

Prostate cancer (PCa) is the second most common cancer in males in western countries[1] and the known risk factors are age, diet, race and family history.[2] The relationship between PCa and testosterone was first described by Huggins over 70 years ago[3] and has become controversial as accumulated evidence demonstrating potentially opposing effects of androgens on cancer.[4-6] Testosterone is vital for normal development and growth of the prostate and, conversely, androgen deprivation therapy in metastatic PCa significantly decreases symptoms and disease progression. On these grounds, high levels of testosterone are believed to increase the risk of developing PCa. However, epidemiological investigations failed to demonstrate such association.[7] Morgentaler et al.[8] reported a high prevalence of PCa among asymptomatic men with low levels of total and free testosterone. This was the first study to show that low testosterone levels do not provide protection to the development of PCa.

Attention has also been drawn to the effect of testosterone on the histological grade of PCa, with a number of studies suggesting that low serum total testoster-

one (TT) may be associated with higher-grade disease. Park et al.[9] retrospectively evaluated 681 patients undergoing prostate biopsy and found an independent association between laboratorial hypogonadism, defined as TT below 300 ng/dL, and high-grade PCa at biopsy. Studies performed in patients presenting PCa with clinically localized disease treated with radical prostatectomy (RP) also demonstrated that low levels of TT preoperatively were associated with more aggressive disease based on higher pathological stage, positive surgical margins and Gleason score (GS).[10,11] However, an independent association has not been uniformly demonstrated in all investigations.[12,13] Most studies have been performed in Caucasian and Asian populations, yet without specifying the effect of demographic characteristics on the association between TT and higher-grade PCa. Possible explanations for the inconsistency between existing studies include demographic variability, variable cutoffs for hypogonadism and biased samples.

The purpose of our study was to evaluate if serum TT levels are associated with higher-grade PCa and to evaluate the effect of race and other demographic predictors in this association in a multiethnic population.

Method

Institutional Review Board approval was obtained prior to the beginning of investigations. We retrospectively reviewed charts of 695 patients undergoing RP from January 2010 to December 2011 at a single tertiary care center. Patients who had TT levels measured from 6 months to 1 day before the surgery totalized 423 and were included for analysis. If more than one TT measurement was performed, levels obtained the closest to the surgery were used. TT measurement was performed at the discretion of the attending physician; TT results obtained more than 6 months prior to surgery were not included, which caused a number of subjects to be excluded from analysis.

We studied the association between preoperative serum TT levels and the pathological outcomes of the surgical specimens. Only patients with clinically localized disease who underwent RP as treatment were included. Salvage radical prostatectomies were excluded from analysis.

Statistical analysis

Patients were divided into groups of normal and low testosterone based on 2 threshold levels for TT: threshold 1 (< 300 ng/dL vs. ≥ 300 ng/dL) and threshold 2 (< 250 ng/dL vs. ≥ 250 ng/dL). High-grade PCa was considered as a Gleason score ≥ 7.

Fisher's exact test was used to evaluate associations between binomial variables. To compare means between groups, we used the t-Student test for independent samples with normal distribution or the nonparametric Kruskal-Wallis when appropriate. We evaluated the relation between TT and pathological findings such as: pathological stage, GS and positive lymph nodes. Multivariate analysis considering age, body mass index (BMI), TT and race was performed for the outcomes of interest. A linear regression model was used to evaluate the relationship between PSA and testosterone levels. All statistical analyses were performed using SPSS 20.0 (IBM Software).

Results

Table 1 shows the clinical preoperative data for age, BMI, testosterone levels and PSA. Table 2 depicts the pathological characteristics of patients according to race, age-adjusted Charlson comorbidity index, prostate-specific antigen (PSA), TT levels (threshold 1 and threshold 2) and pathologic evaluation of RP specimens. Of 423 patients, 37.8% had hypogonadism based on threshold 1 and 23.9% based on threshold 2.

On univariate analysis, patients with hypogonadism had higher prevalence of GS ≥ 7 in RP specimens for both thresholds. There was no difference between groups in terms of rates of lymph node metastases and pathological stage (Table 3 and Table 4). Considering the levels of TT as a continuous variable, we observed that decreasing TT levels were associated with a progressive increase in the risk of having GS ≥ 7 (p-value = 0.0157). Levels of TT did not correlate with levels of PSA on a linear regression fashion (R square goodness-of-fit 0.0002; p=0.77).

On multivariate analysis, adjusted for age, TT levels, BMI and race, only low TT levels (p-value = 0.0231) and advanced age (p-value = 0.0018) were independent risk factors for high-grade disease (Gleason ≥ 7).

In our data, Black men had a higher incidence of hypogonadism compared to Caucasians (p-value = 0.0103). Variations of TT levels had a higher impact on predicting high-grade disease (GS ≥ 7) among Black men compared to White men (p=0.02) (Figure 1). We also observed that obese patients had a higher prevalence of hypogonadism compared to men with normal BMI (p-value < 0.001).

Discussion

We present the results of a retrospective assessment of the association between serum testosterone levels and PCa grade in a large Latin American cohort. In our results, low TT was an independent predictor for high-grade PCa among patients undergoing RP. This effect was signifi-

TABLE 1 Characteristics of patients.

Variable	Results
BMI (Mean ± SD)	26.8±4.3
Age (Mean ± SD)	63.6±6.6
Testosterone (Mean ± SD)	380.0±183.2
PSA (Median, IQR)	13.0 (6.1-14.7)

BMI: body mass index; PSA: prostate-specific antigen; IQR: interquartile range; SD: standard deviation.

TABLE 2 Clinicopathological characteristics of the 423 patients included in the study.

Variables	Groups	N (%)
Race	Asian	3 (0.7%)
	Caucasian	360 (86.3%)
	Black	20 (4.8%)
	Pardo (Brown multiracial)	34 (8.2%)
Pathological stage	< T3a	291 (71.1%)
	≥ T3a	118 (28.9%)
Positive lymph nodes	Absent	211 (95.0%)
	Present	11 (5.0%)
Gleason score	< 7	107 (25.4%)
	≥ 7	314 (74.6%)
Age-adjusted Charlson comorbidity score	0	15 (3.7%)
	1	90 (22.2%)
	2	204 (50.4%)
	≥ 3	96 (23.7%)
PSA	< 10	197 (53.4%)
	≥ 10	172 (46.6%)
Testosterone levels (threshold 1)	< 300	160 (37.8%)
	≥ 300	263 (62.2%)
Testosterone levels (threshold 2)	< 250	101 (23.9%)
	≥ 250	322 (76.1%)
Risk stratification (NCCN)	Low	50 (14.4%)
	Intermediate	213 (61.4%)
	High	84 (24.2%)

PSA: prostate-specific antigen.

TABLE 3 Comparison of pathological characteristics of patients with hypogonadism vs. eugonadism (classified using the 300 ng/dL threshold).

		Testosterone levels		
Variables	**Groups**	**< 300**	**≥ 300**	**p-value**
Pathological stage	< T3a	114 (73.1%)	177 (70.0%)	0.5744
	≥ T3a	42 (26.9%)	76 (30.0%)	
Positive lymph nodes	Absent	86 (93.5%)	125 (96.2%)	0.5319
	Present	6 (6.5%)	5 (3.8%)	
Gleason score	< 7	30 (18.9%)	77 (29.4%)	0.0207
	≥ 7	129 (81.1%)	185 (70.6%)	
Risk stratification (NCCN)	High/Inter	113 (88.3%)	184 (84.0%)	0.3422
	Low	15 (11.7%)	35 (16.0%)	

TABLE 4 Comparison of characteristics of patients with hypogonadism vs. eugonadism (classified using the 250 ng/dL threshold).

		Testosterone levels		
Variables	**Groups**	**< 250**	**≥ 250**	**p-value**
Pathological stage	< T3a	66 (68.0%)	225 (72.1%)	0.4438
	≥ T3a	31 (32.0%)	87 (27.9%)	
Positive lymph nodes	Absent	54 (90.0%)	157 (96.9%)	0.0733
	Present	6 (10.0%)	5 (3.1%)	
Gleason score	< 7	16 (16.0%)	91 (28.3%)	0.0126
	≥ 7	84 (84.0%)	230 (71.7%)	
Risk stratification (NCCN)	High/Inter	69 (88.5%)	228 (84.8%)	0.4688
	Low	9 (11.5%)	41 (15.2%)	

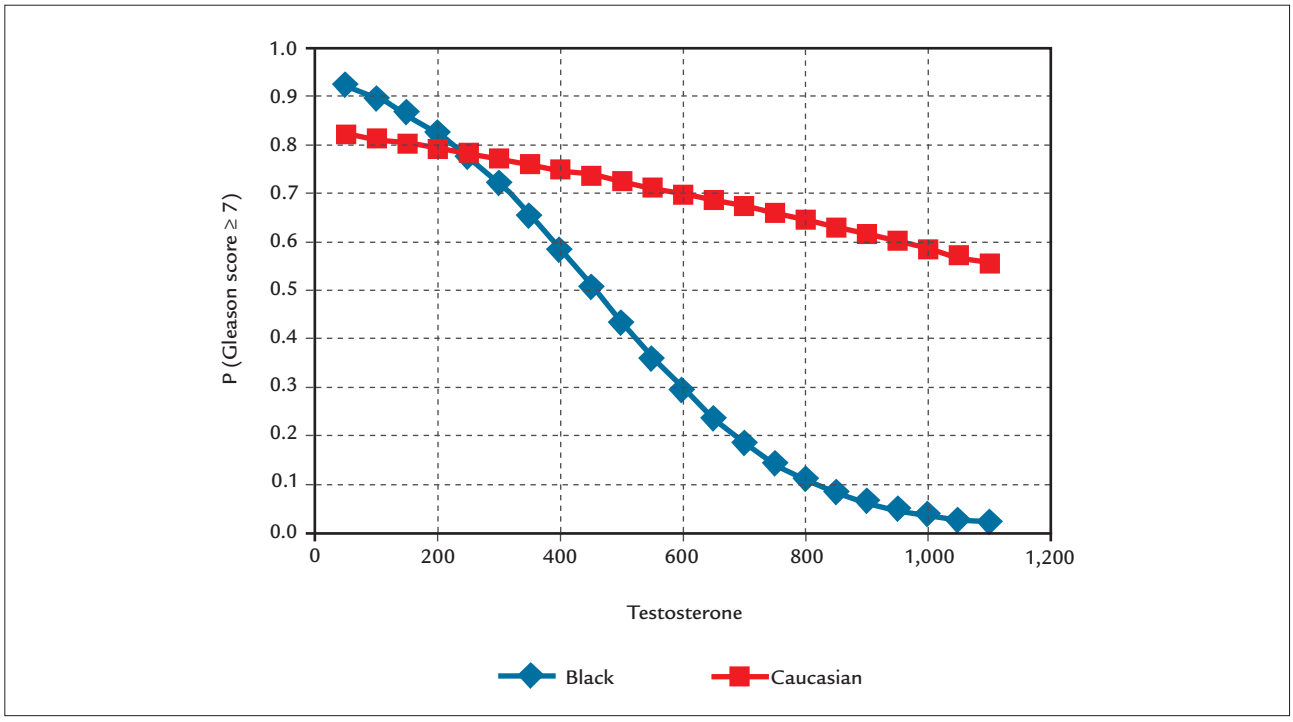

FIGURE 1 Interaction between TT levels and race in predicting the risk of high-grade PCa. Among Black individuals, hypogonadism had a stronger effect in predicting high-grade disease (p=0.038), although there was a similar trend among Caucasians (p=0.06). Both groups differed significantly in this behavior (p=0.02).

cantly more pronounced among Black men, who also had higher incidence of hypogonadism. These results may reveal an underlying mechanism for higher-grade PCa found in Black race, and may also partly explain inconsistencies between previous investigations regarding the association between TT and PCa grade.

Although the response of metastatic PCa to androgen deprivation therapy is well established, it is still controversial whether androgens are responsible for the initiation of PCa. Age, one of the strongest risk factors for PCa, is knowingly associated with a gradual decline in testosterone levels. However, that does not preclude a pathogenic role for androgens, given the long preclinical phase of PCa. Yet, multiple population-based studies have failed to show an association of circulating testosterone, dihydrotestosterone (DHT) or other sex steroids with PCa risk.[14,15]

The Endogenous Hormones and Prostate Cancer Collaborative Group reviewed 18 prospective studies and failed to demonstrate an association between endogenous testosterone and PCa risk. Also, testosterone levels did not correlate to PCa aggressiveness.[5] Similarly, many studies have shown that testosterone replacement therapy

(TRT) promotes limited changes in PSA levels when men with hypogonadism are treated to normalize testosterone.

Morgentaler and Traish proposed a saturation model theory of testosterone and the prostate.[16] According to this theory, PCa is testosterone-sensitive at low testosterone levels, but after androgen receptors are fully occupied, further testosterone increments have modest or no effect on the prostate or PCa dynamics. This hypothesis is supported by studies in men on TRT showing modest or no PSA increase after initiating testosterone injections, as well as no increased risk for cancer.[17,18]

There are many reports on the role of testosterone in predicting high-risk disease, although with contrasting results and employing different methodological standards and outcomes. Schatzl et al. reported on a higher risk for high-grade Gleason scores in men with low serum testosterone among patients diagnosed with PCA.[19] Similarly, Pichon et al. showed, among subjects undergoing RP for PCa, that lower testosterone levels were associated with higher-grade PCa and with increased risk of GS upgrading from prostate biopsy to specimens from surgery.[20] Park et al.[9] demonstrated a correlation between hypogonadism and unfavorable outcomes in prostatic biopsies, such as increased incidence of GS ≥ 8. Several studies, despite adopting different thresholds for the definition of hypogonadism, have confirmed an association between low testosterone levels and adverse characteristics and outcomes for PCa, including higher Gleason score,[21,22] higher pathological stage[10,22] and increased risk for disease progression.[23]

However, a number of investigations failed to show an association between low serum testosterone levels and high-risk characteristics of PCa specimens. Salonia et al.[12] found an association between androgens and higher risk PCa that was not proven to be independent on multivariate analysis. Other studies showed no association,[12,24] while Porcaro et al. suggest a direct relation between testosterone levels and Gleason score, a result that opposes the findings described previously.[25]

In our study, we evaluated 423 patients and tested two thresholds, 250 and 300 ng/dL, for the definition of hypogonadism. We used pathological findings from RP specimens in order to most accurately reflect tumor characteristics. In keeping with other reports, we found a significant and independent correlation between low TT levels (threshold 1 and threshold 2) and high-grade disease (GS ≥ 7). We also analyzed the correlation between preoperative hypogonadism and pathological stage and the presence of lymph nodes involved by the disease. This relationship proved to be non-significant, although there was a trend towards higher stage (≥ T3a) on threshold 2 and positive lymph nodes in both thresholds.

In our cohort, low TT levels were also significantly associated with race and BMI characteristics. This resulted in a significant interaction between these variables and the outcome of higher grade PCa. We hypothesize that inconsistencies between previous studies on this subject may be due to demographic variability between cohorts, owing to the effect that interaction with race may produce. We also hypothesize that low serum testosterone may be one of the mechanisms mediating previously reported associations between demographic groups and increased risk for high-grade PCa.

Nunzio et al., in a prospective multicenter study, evaluated the association between abdominal obesity, PCa diagnosis and grade in 668 patients undergoing prostate biopsy. PCa was detected in 246 patients (38%), of whom 110 had a higher-grade cancer (GS ≥ 7). Logistic regression showed that BMI and waist circumference were significant predictors of high-grade PCa. Furthermore, obesity with central adiposity was significantly associated with high--grade disease.[26]

Black men have a 67% higher incidence of PCa compared to Caucasians.[27] While population-level studies have consistently shown that the incidence and mortality burden is highest among Black men, it remained unclear whether this can be explained by inadequate access to medical care.[28] Gaines et al., in a population-based study involving 887 men, evaluated the association between race and low- and high-grade PCa in men undergoing initial prostate biopsy in an equal access medical center. Of the 887 men, 499 had PCa on biopsy (56.3%). Black men were significantly more likely to have PCa on biopsy than White men 61,9% vs. 50.9% (p≤0.001). In multivariate analyses, Black race was significantly predictive of high-grade.[29]

In our study, on multivariate analysis adjusted for BMI and race, only low levels of TT and advanced age had a significant impact in predicting GS ≥ 7. Low TT was associated with increased BMI, and hypogonadism was a stronger predictor of high-grade PCa among Black individuals. Based on these observations, we hypothesize that low serum testosterone may be an underlying mechanism involved in higher-grade PCa found in both obese and Black men in previous reports. These results should be further confirmed in larger populations and tested on molecular level.

It has been hypothesized that patients with low TT would have lower PSA and for this reason would take longer to be diagnosed with PCa, hence explaining the

association between low TT and high-grade PCa. However, our findings confront this hypothesis, as changes in serum testosterone did not correlate with changes in PSA. This is in consonance with previous investigations.[9] Furthermore, low TT predicted high-grade PCa independently of age at diagnosis, which also opposes this conjecture. Rather, we believe that, according to the Saturation Model, patients with hypogonadism do not reach levels of testosterone necessary for physiological proliferation of the epithelium, leading to a greater risk of abnormal proliferation and differentiation, resulting in greater risk for high-grade cancer.

Our results should be interpreted in the context of a number of limitations. The retrospective nature of the study, the lack of a standardized protocol for testosterone measurement and the selection of patients from a high-volume cancer center imply biases for epidemiological observations. Many patients were not included in the study because their TT measurement had been performed prior to 6 months from surgery, introducing a bias that excluded patients who waited longer until radical prostatectomy. Furthermore, our observations on the effect of low TT in Black men are based on a limited sample. However, we believe that our study provides meaningful insight into associations between testosterone levels, prostate cancer grade and race interactions, and should warrant further prospective investigations.

Conclusion

According to our findings, hypogonadism is an independent risk factor for developing higher GS in localized PCa. Low levels of TT might be related to the carcinogenesis of higher grade cancer and is a potential marker of prognosis in PCa. In our sample, low TT level was a stronger predictor of high-grade PCa in Black men compared to White men, which could partly explain the behavior of the disease in this ethnic group and should warrant further investigation.

Resumo

Baixa testosterona sérica é prognóstica de doença de alto grau em pacientes com câncer de próstata

Objetivo: Avaliar a relação entre testosterona sérica total (TT) e grau do câncer de próstata (CP) e o efeito da raça e de características demográficas sobre essa associação.
Método: Foram analisados 695 pacientes submetidos a prostatectomia radical (PR), dos quais 423 tinham medidas dos níveis séricos de TT. Os pacientes foram classificados como portadores de hipogonadismo ou eugonadismo com base em dois limites de testosterona: limite 1 (300 ng/dL) e limite 2 (250 ng/dL). Avaliou-se a relação entre nível de TT e escore Gleason (GS) ≥ 7 em amostras de PR. Os resultados foram avaliados por análises univariada e multivariada, com ajuste para raça e outros fatores prognósticos demográficos.
Resultados: Do total de 423 pacientes, 37,8% apresentavam hipogonadismo com base no limite 1, e 23,9% com base no limite 2. Os pacientes com hipogonadismo, independentemente do limite de referência, tiveram uma chance maior de GS ≥ 7 (OR 1,79, p=0,02 e OR 2,08, p=0,012, respectivamente). Na análise multivariada, após ajuste para idade, TT, índice de massa corporal (IMC) e raça, baixo TT (p=0,023) e idade (p=0,002) foram considerados fatores de risco independentes para GS ≥ 7. Entre os indivíduos negros, baixo TT sérico foi mais preditivo de doença de alto grau em comparação com os brancos (p=0,02).
Conclusão: O hipogonadismo é independentemente associado a escores mais altos de GS no CP localizado. O efeito dessa associação é significativamente mais pronunciado entre homens negros, o que poderia explicar, em parte, as características agressivas do CP observadas nessa população.

Palavras-chave: câncer de próstata, hipogonadismo, testosterona.

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Contemporary surgical treatment of benign prostatic hyperplasia

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Summary

Benign prostatic hyperplasia (BPH) is a common condition in adult men and its incidence increases progressively with aging. It has an important impact on the individual's physical and mental health and its natural progression can lead to serious pathological situations. Although the initial treatment is pharmacological, except in specific situations, the tendency of disease progression causes a considerable portion of the patients to require surgical treatment. In this case, there are several options available today in the therapeutic armamentarium. Among the options, established techniques, such as open surgery and endoscopic resection using monopolar energy, still prevail in the choice of surgeons because they are more accessible, both from a socioeconomic standpoint in the vast majority of medical services and in terms of training of medical teams. On the other hand, new techniques and technologies arise sequentially in order to minimize aggression, surgical time, recovery and complications, optimizing results related to the efficacy/safety dyad. Each of these techniques has its own peculiarities regarding availability due to cost, learning curve and scientific consolidation in order to achieve recognition as a cutting-edge method in the medical field. The use of bipolar energy in endoscopic resection of the prostate, laser vaporization and enucleation techniques, and videolaparoscopy are examples of new options that have successfully traced this path. Robot-assisted surgery has gained a lot of space in the last decade, but it still needs to dodge the trade barrier. Other techniques and technologies will need to pass the test of time to be able to conquer their space in this growing market.

Keywords: benign prostatic hyperplasia, surgical treatment, minimally invasive techniques, laser, videolaparoscopic, robot-assisted surgery, bipolar.

Study conducted at Urology Clinic, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, and at Urology Clinic, Hospital Militar de Área de São Paulo – Exército Brasileiro, São Paulo, SP, Brazil

Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.711

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in adult men, with a tendency to progress with aging and which, in most cases, causes lower urinary tract symptoms (LUTS), with a prevalence of around 30% in individuals over 50 years. It leads to important impacts on physical and mental health.[1,2] The treatment of LUTS due to infravesical obstruction secondary to BPH is constantly evolving. Therapeutic modalities for moderate and severe conditions begin with pharmacological treatment and may progress to minimally invasive, laparoscopic, robot-assisted or open surgical alternatives.[3] The objective of this review is to present the entire surgical treatment program that has some scientific support, as well as new modalities that are starting to be practiced.

Transurethral resection of the prostate

Until recently, monopolar transurethral resection of the prostate (M-TURP) was considered a gold standard for the treatment of prostates with a volume lower than 80 cm³ due to its effectiveness and low cost.[4-7] However, this established technique is associated with some relevant complications, such as urethral stenosis, bleeding, bladder neck sclerosis and especially post-TURP syndrome, due to the need for hypotonic infusion fluid to avoid electrical conduction. Post-TURP syndrome consists of water intoxication alongside hyponatremia, and can lead to the occurrence of cerebral edema.[8]

The incorporation of bipolar technology (B-TURP) represents a significant evolution in the TURP technique in recent years. B-TURP presents a considerable advantage

given the fact that it can be performed with normal saline solution, with excellent results in relation to a greater volume of resection within the same surgical time.[9,10]

In a recent prospective randomized clinical trial (RCT) comparing M-TURP with B-TURP, 497 patients with a mean age of 67.4 years and a prostate volume of 54 cm³ were divided into the two groups and monitored for 36 months. There was no statistical difference in the parameters of surgery time, catheterization time, PSA drop, peak flow improvement (Qmax), occurrence of urinary retention, and IPSS and quality of life (QoL) scores. On the other hand, B-TURP proved to be superior to M-TURP in relation to hospitalization time, blood transfusion rate, post-TURP syndrome, serum sodium rate and lower occurrence of urethral stenosis.[11]

In a systematic review and meta-analysis evaluating the efficacy (Qmax and IPSS) and safety of the two techniques, 31 RCTs with 3,669 patients were included.[12] Regarding efficacy, relevant clinical differences in the Qmax were observed in favor of B-TURP. Regarding safety, the almost non-occurrence of post-TURP syndrome and the low incidence of clot retention, urethral stenosis and bladder neck sclerosis have recently favored a greater use of B-TURP compared with M-TURP, resulting in its recent inclusion as the first line of treatment for enlarged prostates in the current guidelines of the European Association of Urology (EAU).[13]

GreenLight XPS (GL-XPS) Photoselective Vaporization of the Prostate – NE 1 GR A

The modern GreenLight system with an LBO crystal adaptation to the Nd:YAG system was released in 2006, after a redesign of the laser generator. With a wavelength of 532 nm (using oxyhemoglobin as chromophore), it was initially defined as a high power system (HPS), which had a 120 W output and was often referred to as photovaporization of the prostate.[14] Its latest generation, the XPS system is capable of generating 180 W of high frequency pulses of laser energy in a wider beam, improving vaporization efficiency. Hueber et al.[15] evaluated the surgical performance of the GL-XPS system compared with the old HPS system in 1,809 patients in seven international centers. The new system has significantly reduced laser and operative time. The number of fibers used during the procedure was significantly reduced using the XPS system, while the total energy used was also lower. They concluded that the GL-XPS demonstrates significant advantages over HPS regardless of prostate size for all operative parameters.

In a prospective randomized controlled trial comparing TURP with the GL-XPS laser system, with two years of follow-up, 29 centers were included in nine European countries involving 281 patients with BPH. There was no change in IPSS and Qmax between groups. The proportion of patients without complications during 24 months was 83.6% for GL-XPS versus 78.9% for TURP. Reductions in PV and PSA were similar in both branches and maintained throughout the study. Compared with the first year of the study, few adverse events or retreatment were reported in any of the groups, thus showing the similar efficacy and safety between the two techniques.[16]

Although its short- and medium-term efficacy for small and medium adenomas is well established, there is limited evidence on the use of GL-XPS laser in very large prostates. Recently, the safety and efficacy of the GL-XPS system has been demonstrated using a vapoenucleation technique in prostate glands measuring more than 150 mL. They included 70 patients with a mean prostate size of 202 mL (152-376 mL), 59% of which were using a permanent preoperative catheter. The mean surgical time was 180 minutes and an average of three fibers were used per case. The mean length of stay and catheterization time was one day. The IPSS and QoL scores improved from 16 to 3.5 and from 4 to 1 in 24 months, respectively. At 12 months, Qmax and post-void residual test (PVR) improved from 10.1 to 22.4 mL/s and from 84 to 31.4 mL, respectively. The PSA also demonstrated a sustained reduction from 8.3 ng/mL at the start to 3.0 ng/mL at 24 months. Retreatment was required in only 2.9% of patients.[17]

Holmium Laser Enucleation of the Prostate (HoLEP) – NE 1 GR A

The Ho:YAG laser operates at 2,120 nm, with tissue water as the chromophore and its pulsed beam with high-energy concentration results in blisters leading to rupture of the prostatic tissue. Tissue penetration of the laser is only 0.4 mm in the prostate, which produces adequate coagulation and minimum carbonization. The physical properties of this laser allow its use in different tissues and stones. In the prostatic tissue, it can be used for ablation (HoLAP), resection (HoLRP) and enucleation (HoLEP), being that the latter is the most commonly used technique.

HoLEP has the largest number of randomized clinical trials compared with TURP and open prostatectomy than any other available laser technology. Based on a recent meta-analysis, the functional results are similar, and the catheter time and hospital stay were shorter in patients with HoLEP.[18] It is also the only laser with long-term results published in the scientific literature in prospective and randomized studies. Compared with TURP, similar functional results were observed after an average of 7.6 years of follow-up.[19]

The need for morcellation of the prostatic tissue within the bladder at the end of the procedure and the

long learning curve are the two main disadvantages of the method. According to a recent analysis, the rate of enucleation efficiency was significantly different between cohorts, and the threshold was generally observed after 50-60 cases conducted. Likewise, a significant difference is shown for efficiency of morcellation with stabilization in performance after 60 cases.[20]

To date, there is only one prospective, randomized study comparing HoLEP to the GL-XPS laser for the treatment of BPH. In it, 50 and 53 patients were included in the HoLEP and GL-XPS groups, respectively. Surgical time, hospital stay and catheter removal time were comparable between groups. There was a significant and comparable improvement in the score of symptoms and post-void residual test at 1, 4 and 12 months. After four months, the reduction of prostate size was significantly higher in the HoLEP group (74.3 vs. 43.1%). At 12 months, the Qmax was significantly higher in the HoLEP group (26.4±11.5 vs. 18.4±7.5 mL/s). Reintervention was required in two and three cases in the HoLEP and GL-XPS groups, respectively. The mean cost estimated for the HoLEP procedure was significantly lower than for the GL-XPS procedure.[21]

Faced with such facts, HoLEP has stood out as the technique used the most in North America and Europe and already appears in the guidelines of these societies as the first-line treatment.

Simple prostatectomy

Patients diagnosed with infravesical obstruction (IVO) secondary to BPH with enlarged prostate (> 80 mL) and moderate and severe IPSS symptoms present higher failure rates for drug therapy and disease progression, requiring more frequent surgical treatment. In these cases, the first-line surgical treatments recommended by the current guidelines of the EAU are: endoscopic enucleation with bipolar energy, endoscopic enucleation with HoLEP and simple open prostatectomy.[13]

Despite the emergence of new technologies, the standard treatment for large adenomas is still open simple prostatectomy (SP), due to the limited availability of these technologies in care centers and the advantage that open access offers when additional joint treatment is needed, such as cystolithotomy and bladder diverticulectomy. However, we know that SP is invasive and presents higher morbidity, with higher rates of bleeding and blood transfusion ranging from 7 to 14%,[22-24] bladder neck stenosis in up to 6%,[22,25,26] reintervention in up to 3.6%,[27] in addition to prolonged hospitalization time and bladder catheterization in the postoperative period, with higher occurrence the greater the prostate volume.[28] A prospective study showed a lower rate of intra- and postoperative bleeding as well as blood transfusion when the modified Millin technique was performed compared to conventional transvesical prostatectomy.[29]

Over the years, new endoscopic and video-assisted techniques have emerged to reduce morbidity in the standard open technique.

Video-assisted surgery

Video-assisted surgery involving the prostate was initiated in 1992 with Schuessler et al.,[30] who reported the first videolaparoscopy radical prostatectomy. Mariano et al.[31] published the technique to perform simple laparoscopic radical prostatectomy (LRP) for BPH and in 2008 robot-assisted simple prostatectomy (RASP) was first reported.[32] The term minimally invasive simple prostatectomy (MISP) refers to the LRP and RASP joint technique, which allows for transcapsular or transvesical adenomectomy either through extraperitoneal access, usually used in the LRP, or intraperitoneal, most commonly used in RASP.

Simple open prostatectomy vs. simple laparoscopic prostatectomy

Comparing SP with LRP, a retrospective study did not demonstrate a significant difference in the incidence and severity of complications, with similar functional results.[33] In a prospective and randomized study, similar functional results were described, but with rats bleeding less, and with statistical significance in the LRP using extraperitoneal access.[34] Another prospective study involving 280 patients found statistically significant advantages for LRP, such as shorter hospital stay, shorter intravesical catheter time and lower rates of urinary tract infection. There was no difference regarding functional results; however, surgical time in the open procedure was shorter.[35]

Simple open prostatectomy vs. laparoscopic simple prostatectomy vs. robot-assisted prostatectomy

With the advent of robotic surgery in reference centers, new comparative studies are emerging between SP, LRP and RASP techniques.

In a recent meta-analysis, 27 studies involving 764 MISP (LRP and RASP) were evaluated, concluding that minimally invasive techniques have a longer surgical time, offer similar improvement in functional outcome, Qmax and IPSS compared to SP, with the advantage of having less blood loss and shorter hospital stay.[36]

The largest retrospective multicenter study evaluating minimally invasive techniques with 487 RASP and 843 LRP,

totaling 1,330 patients in 23 American and European institutions, concluded that the functional results are similar, regardless of the technique used, with similar IPSS, Qmax and sexual function (Trifecta) in a 12-month follow-up.[37]

Current scientific evidence tends to qualify the feasible minimally invasive techniques as a safe and effective therapy for prostates with a volume above 80 mL, with a level of evidence of 2A.[13] However, many of these studies are retrospective and need to be validated by prospective randomized studies with long-term follow-up and comparative cost analyses between different endoscopic and conventional open techniques in order to corroborate not only the efficacy but also the effectiveness and reproducibility in other care centers.

As such, we can consider these different approaches as alternatives for treatment of enlarged prostates, with apparent similarity of efficacy and functional results. The new minimally invasive technologies are attractive options aimed at reducing morbidity, time of intravesical catheter use and hospitalization period, with reduction in the final cost of treatment, although still lacking scientific evidence to prove these benefits.

Prostatic artery embolization (PAE)

For more than 30 years, embolization of hypogastric arteries has been proposed to control severe prostatic hemorrhage with satisfactory results.[38-40]

In 2000, PAE was correlated for the first time with the relief of LUTS due to BPH in a patient with massive prostatic hematuria who had a surgical contraindication due to his clinical condition, submitted to the right super-selective PAE, and, after a 12 month follow-up period, presented a decrease of 11 points in the IPSS and a reduction of 40% in prostate volume and 90% in PSA.[41] In the following years, other case reports and clinical series were described with super-selective PAE.[39,40] However, only recently, following evidence in an experimental study in pigs, PAE has emerged as an option for the primary treatment of LUTS related to BPH.[42] The first two cases were described by Carnevale et al.[43]

The analysis of the clinical and urodynamic data of 11 patients with urinary retention due to BPO showed that spontaneous urination was obtained in ten of them (91%) with an average follow-up of 22.3 months. However, according to the Bladder Obstruction Index, despite the statistically significant improvement in IPSS, QoL, Qmax and detrusor pressure, only one third of the patients were unobstructed postoperatively.[44]

To date, there is only one prospective, randomized study comparing TURP with PAE. This study analyzed 114 patients monitored for 24 months. Clinical failure rates were 3.9 and 9.4%, respectively. Compared to the preoperative values, both treatments presented improvements at all times. However, TURP presented a higher degree of improvement in the IPSS, QoL, Qmax and RPM after 1 and 3 months in relation to the PAE group, as well as higher reductions for PSA and PV levels at all follow-up times. The PAE group had a greater number of adverse events and complications, mainly related to acute urinary retention (25.9%) and post-embolization syndrome (11.1%).[45]

A systematic review and recent meta-analysis evaluated the efficacy of PAE in LUTS caused by BPH in the short and medium term. A total of 484 patients from seven eligible studies were included. The mean differences in IPSS at 3, 6, 12 and 24 months were -14, -12, -16 and -17, respectively. Furthermore, mean Qmax, RPM, PV and QoL compared between the follow-up period and the baseline were significantly improved.[46] Long-term studies are still needed to establish the actual efficacy of PAE for the treatment of BPH.

Certain complications have been reported to be associated with PAE. Among the 250 cases described in another study, 9.2% of patients had burning sensation in the urethra and/or anus during the procedure. Urinary tract infection occurred in 7.6%, transient hematuria in 5.6%, transitory hematospermia in 0.4%, discreet rectal bleeding in 2.4%, and balanitis in 1.6% of patients, all of which were self-limiting. Six patients had transient acute urinary retention after PAE. According to the authors, among 199 patients with IIEF follow-up data, the score improved in 48.2%, remained stable in 21.6% and worsened in 30.2%. There were no cases of sexual impotence or retrograde ejaculation.[47]

New techniques

The search for new therapeutic modalities for any disorder is necessary and natural, even more so in times of rapid technological evolution. This is no different in the treatment of BPH, and new options are already beginning to be established in clinical practice in accordance with the consolidation and scientific support for such. We currently have two innovative techniques that present promising experimental results and in early clinical trials.

Prostate ablation using hydrodissection uses a high-speed, robot-assisted, image-guided saline jet, requiring no electrical current or high temperature and the procedure, with greater accuracy in the target tissue, minimize bleeding and indirect effect in relevant adjacent structures such as the prostatic capsule, bladder neck and external sphincter, as well as potential preservation of ejaculatory function.[48-51]

Another promising technique is that of prostate hydration, which uses convective energy transfer properties (advantageous to conductive techniques) of steam over the defined space of the prostatic tissue (transition zone), reaching around 103 °C in the interstitial space and dispersed slowly and gently by the target tissue at temperatures up to 70-80°C, causing instantaneous cell death (WAVE® technology). The procedure is performed via cystoscopy and a needle is inserted into each prostate lobe at a time for as many times as are necessary to cover the extent of the prostate mass. The vapor steam released for approximately nine seconds at a 120° range circumferentially to the tip of the needle. The preliminary results of a single RCT comparing cystoscopy with a control and one year of follow-up in 197 men with BPH demonstrated significant reduction of IPSS and Qmax in the treated group, with no relevant adverse effects, except for one case of urinary retention resolved in the short term.[52,53]

Finally, the UroLift technique® (NE 1 GR B), which consists of minimally invasive implantation of clamps in the lateral prostatic lobes with retraction of such, allowed an increase of the prostatic urethra's lumen. It can be performed on an outpatient basis, presents a slightly inferior efficacy to the M- or B-TURP and HoLEP techniques, but with a much lower incidence of adverse effects, as well as significantly lower cost, thus constituting a considerable alternative for the surgical treatment of BPH.[54]

Resumo

Tratamento cirúrgico contemporâneo da hiperplasia prostática benigna

A hiperplasia prostática benigna (HPB) é uma condição comum em homens adultos, de incidência progressiva com o envelhecimento, com importante impacto nas saúdes física e mental do indivíduo e história natural que pode levar a situações patológicas graves. Embora o tratamento inicial, salvo em situações específicas, seja farmacológico, a tendência de progressão da doença leva uma considerável parcela dos pacientes a necessitar do tratamento cirúrgico. Neste caso, existem diversas opções hoje disponíveis no arsenal terapêutico. Dentre estas, as técnicas consagradas, como as cirurgias por via aberta e a ressecção endoscópica por energia monopolar, ainda ocupam extenso terreno na escolha dos cirurgiões por serem mais acessíveis, tanto do ponto de vista socioeconômico na imensa maioria dos serviços médicos quanto do de aprendizado por parte das equipes médicas. Por outro lado, novas técnicas e tecnologias surgem sequencialmente no intuito de minimizar a agressão, o tempo cirúrgico, as complicações, bem como favorecer a recuperação, otimizando resultados em relação ao binômio eficácia/segurança. Cada uma destas tem seu próprio curso em relação à disponibilidade de acesso em decorrência de custo, curva de aprendizagem e consolidação científica, a fim de atingir conceituação e utilização de ponta no meio médico. O uso da energia bipolar na ressecção endoscópica da próstata, as técnicas de vaporização e enucleação a *laser* e a videolaparoscopia são exemplos de novas opções que trilharam esse caminho com sucesso. A cirurgia robô-assistida tem conquistado bastante espaço na última década, embora ainda esbarre na barreira comercial. Outras técnicas e tecnologias devem passar pelo crivo do tempo para poderem cavar espaço neste mercado que, tempo após tempo, torna-se mais vasto.

Palavras-chave: hiperplasia prostática benigna, tratamento cirúrgico, técnicas minimamente invasivas, *laser*, videolaparoscopia, cirurgia robô-assistida, bipolar.

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Is a safety guidewire needed for retrograde ureteroscopy?

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Summary

Introduction: It is generally advised to have a safety guidewire (SGW) present during ureteroscopy (URS) to manage possible complications. However, it increases the strenght needed to insert and retract the endoscope during the procedure, and, currently, there is a lack of solid data supporting the need for SGW in all procedures. We reviewed the literature about SGW utilization during URS.

Method: A review of the literature was conducted through April 2017 using PubMed, Ovid, and The Cochrane Library databases to identify relevant studies. The primary outcome was to report stone-free rates, feasibility, contraindications to and complications of performing intrarenal retrograde flexible and semi-rigid URS without the use of a SGW.

Results: Six studies were identified and selected for this review, and overall they included 1,886 patients where either semi-rigid or flexible URS was performed without the use of a SGW for the treatment of urinary calculi disease. Only one study reported stone-free rates with or without SGW at 77.1 and 85.9%, respectively (p=0.001). None of the studies showed increased rates of complications in the absence of SGW and one of them showed more post-endoscopic ureteral stenosis whenever SGW was routinely used. All studies recommended utilization of SGW in complicated cases, such as ureteral stones associated with significant edema, ureteral stricture, abnormal anatomy or difficult visualization.

Conclusion: Our review showed a lack of relevant data supporting the use of SGW during retrograde URS. A well-designed prospective randomized trial is in order.

Keywords: safety guidewire, ureteroscopy, retrograde intrarenal surgery, meta-analysis, kidney stone, ureteral calculi.

Study conducted at Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil, and at Denver Health Medical Center, University of Colorado, Denver, CO, USA

Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.717

Introduction

Ureteroscopy (URS) has become the standard of care for treating urolithiasis less than 2 cm, mainly due to the development of small flexible ureteroscopes, the improvement of laser lithotripsy and the quality of disposable materials.[1] It is generally advised to have a safety guidewire (SGW) present during URS to allow placement of a ureteral stent in order to manage possible complications.[2,3] However, there is a lack of solid data to support this long-standing principle in endourology.

The forces needed to insert and retract the endoscope during URS with an SGW in place are considerably higher when compared with procedures that not involve SGW.[4] Although not completely proved, this fact raises the question that placement of an SGW could eventually increase the risk of harming the ureter in some patients.

Moreover, some data advocate that working without an SGW often facilitates access, scope manipulation and stone basketing. There is less friction passing the ureteroscope over than alongside a guidewire and increased torque to rotate the scope.[5]

On the other hand, as patient safety should continue to be the highest priority, having an SGW during the entire procedure may be advised because of the risk of ureteral injury requiring prompt placement of ureteral stent.[6]

The following publication aimed to look at SGW utilization during URS, reviewing the current literature available for both semi-rigid and flexible URS.

Method

A review of the literature was conducted through April 2017 using PubMed, Ovid and The Cochrane Library

databases to identify relevant studies. Six separate searches were done by applying the following free-text search terms: "Safety guidewire ureteroscopy," "Safety guidewire flexible ureteroscopy," "Safety wire ureteroscopy," "Safety wire retrograde intrarenal surgery" and "Safety wire upper ureter." Article selection was done based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[7] (Figure 1). Titles of articles were first reviewed to determine whether they might fit the inclusion criteria. After assessing the abstract, a more detailed subsequent assessment was performed by looking at the full text. References of included studies were also reviewed to identify additional studies of interest.

Two reviewers (R.P and W.M) independently screened all the titles and abstracts to minimize selection bias. The quality of the evidence was evaluated based on comprehensiveness of the data and precision of the reporting according to the criteria provided by the Centre for Evidence-Based Medicine in Oxford, UK (website, same 18 as Cryometa). Only studies where an SGW was both used and omitted in the same cohort of patients were included. The initial literature search identified 72 potentially relevant studies. Their titles and abstracts were screened for relevance, resulting in 44 potential articles after excluding duplicate results. Four reports were excluded because they were review URS articles and 35 were excluded because they didn't specifically addressed the use or not of an SGW. Therefore, five articles were included and one additional record was added after reference list survey (Figure 1). The primary outcome was to report feasibility, contraindications to and complications of performing intrarenal retrograde flexible and semi-rigid URS without the use of an SGW. Secondary outcomes were to compare stone-free rates and complications between cases where an SGW was used or omitted for the treatment of ureteral and kidney stone disease. Patients were considered stone-free if they had remnant fragments of up to 2 mm in follow-up tomography or intravenous urography six weeks to three months after the main procedure. The Clavien-Dindo classification was used to report complication.[8]

Results

Six studies (Table 1) were identified and selected for this review. Overall, they included 1,886 patients, and either semi-rigid or flexible URS was performed without the use of an SGW for the treatment of urinary calculi disease. Four of them were retrospective observational non-comparative studies (level of evidence 4)[6,9-11] and two were retrospective observational non-consecutive comparative studies (level of evidence 3b).[4,11]

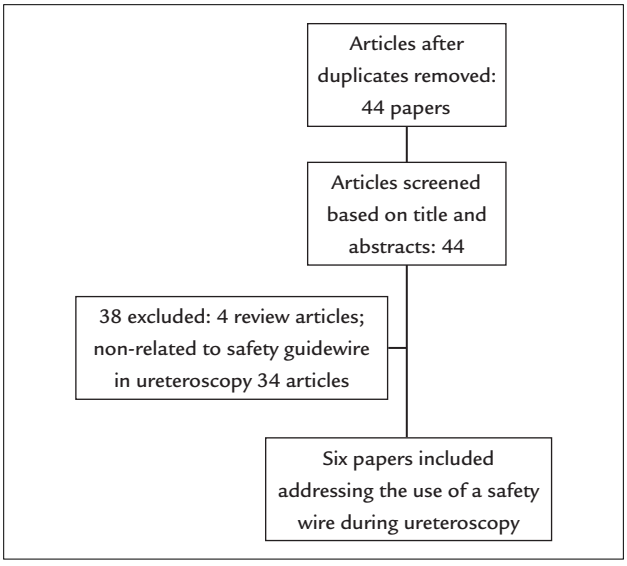

FIGURE 1 Paper selection.

Johnson et al.[10] studied retrospectively a single-surgeon prospective database of flexible URS. A total of 186 patients were submitted to wireless flexible URS for the treatment of intrarenal stones. They reported a stone-free rate of 90, 89 and 75% after primary therapy of intra-renal calculi of < 1.0 cm, 1.0 to 2.0 cm, and > 2.0 cm, respectively. Stone-free rates after primary treatment of ureteral calculi were 93, 96 and 100% for proximal, medial and distal third location, respectively. Inability to access the lower pole was reported in six cases and inability to reach the kidney, in one. There were no false passages or ureteral perforations secondary to endoscope placement. Minor complications were limited to postoperative pyelonephritis in five individuals and gross hematuria in three, both treated successfully with antibiotics and with conservative measures, respectively.[10]

Dickstein et al.[6] reported their experience with flexible URS for the treatment of ureteropelvic junction (54) and renal calyces (216) stones in 270 consecutive patients. In all cases, lithotripsy was performed with a Holmium:YAG laser until calculi pulverization, without the use of a basket for extraction of fragments. The average stone size was 9.1±3.5 mm, and stone-free rate was 88.9% (240 of 270). There were no intraoperative complications, no cases of lost access, ureteral perforation, avulsion, or the need for a percutaneous nephrostomy tube placement (PCNT). However, the authors still recommended the use of an SGW in cases of complicated cases, such as encrusted ureteral stents, ureteral stricture requiring

dilation and concomitant longstanding obstructive ureteral stones.[6]

Two other groups reported independently their results of semi-rigid and flexible URS for the treatment of stone disease without an SGW.[5,9] Eandi et al.[9] reported no intraoperative complications related to lack of a safety wire over 322 semi-rigid and flexible URS performed for the treatment of urolithiasis. Patel et al.[5] described their experience with flexible URS for the treatment of calyceal and pelvic stones on 268 patients with the use of a working wire alone. In all, 20% of the patients needed ureteral dilation, and 15% had a ureteral access sheath placed intra operatively. The overall complication rate was 2.6%. There were no intraoperative complications (no ureteral avulsions or ureteral perforations). Overall, six patients had urinary tract infection (Clavien grade II), two of whom needed post procedure hospital admission and treatment with intravenous antibiotics. One patient had a urinary retention (Clavien grade I). Access into the renal pelvis was obtained in all patients except for one who had multiple ureteral strictures necessitating a nephrostomy tube placement with subsequent percutaneous nephrolithotomy.[5] However, the authors acknowledge that their study included only patients with kidney stones and that, for the treatment of concomitant ureteral stones associated with significant edema, ureteral strictures, abnormal anatomy or difficult visualization, a safety wire should be placed.[5]

The only two available comparative studies in the literature that studied the role of an SGW for semi-rigid and flexible URS are depicted in Table 1. Moran and Bratslavsky[11] compared a single urologist's experience with flexible ureteroscopic laser lithotripsy without the use of an SGW to a contemporary, large single-center's experience with 11 treating urologists. A total of 340 flexible ureteroscopies were performed over a single working wire placed prior to laser lithotripsy, whereas 1,500 laser lithotripsies were done at a single center with an SGW in place. Targeted stone destruction occurred in 98% of these cases and the stone-free rates were lower in 96% (326/340) for those that did not use an SGW. Failures in this cohort were infrequent and occurred in seven patients with high grade obstruction and/or impacted calculi. On the other side, in the entire series of 1,500 patients the targeted stone destruction occurred in 98% and stone-free rate was 96%, results identical to the technique without the safety wire. There were no complications in the group without a safety wire secondary to loss of upper tract access.[11]

Ulvik et al.[12] compared the results of URS for the treatment of ureteral stones at two different hospitals where the SGW was either routinely used or omitted. Both groups had 500 patients each. Pretreatment stone status differed in many aspects between groups. The hospital where an SGW was routinely used treated more proximal stones, more cases with obstruction and more urgent cases. As a result, flexible endoscopes were employed in 39.8 and 4.4% of the procedures in the group with an SGW and without it, respectively ($p<0.0005$). Similarly, access sheaths were used in 31.6% of the cases in the group with SGW compared to only one case in the group without it ($p<0.0005$).[12]

The reported success rates of passing the ureteroscope through the ureteral orifice, the ability to access the ureteral stone and the ability to place a ureteral stent when needed after the endoscopy were not significantly different between the two groups of patients.[12] There was no significant difference in the overall intraoperative complication rates at the two hospitals. The overall stone-free rates were 77.1% and 85.9% with and without the SGW, respectively ($p=0.001$). However, according to the stone location, the stone-free rates were 61.2 and 70.2% for upper ($p=0.135$), 72.6 and 81.1% for mid ($p=0.305$), and 89.8 and 93.9% for lower ureteral stones ($p=0.102$) with and without SGW, respectively. A significant increase in the number of patients (14 patients, 3.4%) was found to have post endoscopic ureteral stenosis at the hospital where the SGW was routinely used than at the hospital where an SGW was omitted (six patients, 1.2%), $p=0.039$.[12]

Discussion

The advantage of using an SGW is to ensure a prompt stent placement in an event of a major ureteral perforation or bleeding precluding continuing URS.[3,13] However, what we found on the literature is that the cumulative evidence that endorse the routine use of an SGW during URS is very weak (level of evidence grade C). It seems that there is a belief that the routine use of an SGW may not be necessary and may even be deleterious, mainly due to the fact that working without a safety wire often facilitates access to the kidney (less friction passing the ureteroscope), scope manipulation (less torque to rotate the scope), and makes it easier to laser and basket fragments.[5,9,12] Moreover, many publications have described their successful experience with both semi-rigid and flexible URS for the treatment of both ureteral and renal stones without the use of an SGW.[5,6,9-12]

The idea of historical longstanding dogma of "SGW always in endourology" may have come from a time when the ureteroscopes, lithotripsy equipment and disposable materials were under development. Nowadays, small digital flexible ureteroscopes with 270 degrees of deflection, small laser fibers, hydrophilic ureteral access sheaths, hybrid guide-

TABLE 1 Summary outcomes of selected publications.

Study	LOE	SGW use	Stones treated (n)	Type of scope	Ureteral sheaths (n)	Stone-free rates (%)	Could not access stone (n)	Ureteral perforation (n)	Ureteral avulsion (n)	Perc tube used (n)
Dickstein et al.[6]	4	No SGW	270	Flexible	0	88.9	0	0	0	0
Eandi et al.[9]	4	No SGW	322	Semi-rigid and flexible	0	N/A	0	0	0	0
Johnson et al.[10]	4	No SGW	186	Flexible	4	N/A	1	0	0	0
Moran and Bratslavsky[11]	3b	No SGW	340	N/A	N/A	96	N/A	N/A	N/A	N/A
		SGW	1,500	N/A	N/A	96	N/A	N/A	N/A	N/A
Patel et al.[5]	4	No SGW	268	Flexible	40	N/A	1	0	0	1
Ulvik et al.[4]	3b	No SGW	500	Semi-rigid and flexible	1	85.9	15	6	1	N/A
		SGW	500	Semi-rigid and flexible	158	77.1	20	11	1	N/A

SGW: safety guidewire; LOE: level of evidence.

wires and nitinol baskets have raised the safety and precision of the procedure to a new level. Despite technological progress, endoscopic intervention can still result in unpredictable and difficult to solve situations. Therefore, we concur with the recommendations to use an SGW whenever a more difficult procedure is anticipated such as in cases with ureteral edema, ureteral strictures, abnormal anatomy, sub-optimal visualization, encrusted ureteral stents and concomitant longstanding obstructive ureteral stones.[5,6]

The main limitation of our study is the low level of evidence of the articles available. Most of them are retrospective analysis of series of cases without a comparative group. Moreover, the best comparative available study has a lot of limitations itself, as described previously. However, it should be noted that this major drawback is also present in the literature supporting the use of ureteral stents after URS.

In conclusion, our review showed a lack of relevant data supporting the use of SGW during retrograde URS. A well-designed prospective randomized trial is necessary.

Resumo

Fio guia de segurança é necessário na ureteroscopia?

Introdução: O uso de fio guia de segurança (FGS) costuma ser recomendado para a realização de ureteroscopia para prevenir e solucionar complicações durante o procedimento. Seu uso, porém, aumenta a força necessária para manipular o aparelho endoscópico dentro da luz ureteral e, atualmente, existe uma carência de dados consistentes que indiquem o uso do FGS em todos os procedimentos.
Método: Uma revisão da literatura foi realizada em abril de 2017 utilizando as ferramentas PubMed, Ovid e The Cochrane Library para identificar estudos relevantes. O desfecho primário da análise foi reportar taxas de resolução dos cálculos, viabilidade, contraindicações e complicações relacionadas ao não uso do FGS.
Resultados: Seis estudos foram incluídos na análise, totalizando 1.886 pacientes, nos quais foi realizada ureteroscopia semirrígida ou flexível sem o uso do FGS no tratamento de cálculos renais ou ureterais. Somente um estudo relatou taxa livre de cálculos com ou sem FGS, sendo 77,1 e 85,9%, respectivamente (p=0.001). Todos os estudos mostraram não haver aumento da taxa de complicação na ausência do FGS e um deles relatou aumento de estenose ureteral pós-endoscopia no grupo que utilizou o FGS. Todos os estudos recomendam o uso do FGS em casos complicados, como cálculos ureterais associados a edema de mucosa, estenose ureteral, anomalias anatômicas ou dificuldade de visualização do cálculo.
Conclusão: Nossa revisão mostrou que faltam dados relevantes para justificar o uso do FGS durante a ureteroscopia.

Palavras-chave: fio guia, ureteroscopia, cirurgia intrarrenal retrógrada, metanálise, litíase renal, cálculos ureterais.

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PSA screening for prostate cancer

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Article received: May 2017
Accepted for publication: July 2017

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http://dx.doi.org/10.1590/1806-9282.63.08.722

Summary

Screening of prostate cancer with prostate-specific antigen (PSA) is a highly controversial issue. One part of the controversy is due to the confusion between population screening and early diagnosis, another derives from problems related to the quality of existing screening studies, the results of radical curative treatment for low grade tumors and the complications resulting from treatments that affect the patient's quality of life. Our review aimed to critically analyze the current recommendations for PSA testing, based on new data provided by the re-evaluation of the ongoing studies and the updated USPSTF recommendation statement, and to propose a more rational and selective use of PSA compared with baseline values obtained at an approximate age of 40 to 50 years.

Keywords: PSA, prostate cancer, screening, prostate.

In Brazil, prostate cancer is the most frequent malignant tumor in men, except for non-melanoma skin tumors. More than 62,000 new cases and almost 14,000 deaths are estimated for 2016/2017.[1]

Autopsy studies show that up to 60% of men over the age of 70 may have prostate cancer. However, only a small proportion of these tumors are clinically significant. These tumors of indolent clinical behavior are known as latent cancer, and their diagnosis should be avoided.[2]

Prostate cancer is classified based on the Gleason grading system, which provides scores for each tumor. Due to the common heterogeneity found in these tumors, two scores are stipulated for the predominant pathological aspect of each case, numbered from 1 to 5. Therefore, the final grades vary from 2 (1+1) to 10 (5+5). The higher the score, the more undifferentiated is the tumor, the greater the chance of metastatic disease, and the worse the patient's prognosis. An international consensus of pathologists in 2004 decided to abolish the use of scores 1 and 2 and denote all low grade tumors as 3. Thus, the lowest currently possible Gleason score is 6 (3+3), representing tumors of low histological aggressiveness; Gleason 7 (3+4 or 4+3) of intermediate aggressiveness and Gleason 8-9-10, representing aggressive tumors with a high level of anaplasia. Recently, after an analysis of more than 16,000 patients undergoing radical prostatectomy and monitored for several years, the International Society of Urological Pathology (ISUP) recommended a new tumor classification, as follows: GS 6 (3+3 = ISUP 1) and 7 (3+4 = ISUP 2) representing tumors of lower aggressiveness, GS 7 (4+3 = ISUP 3) and GS 8 (4+4 = ISUP 4), representing tumors of intermediate risk, and GS 9 and 10 (ISUP 5), representing aggressive tumors.[3] Usually, the tumors found in the screening programs are ISUP 1 or 2.[4]

Over the past 20 years, since the clinical introduction of prostate-specific antigen (PSA), the incidence of metastatic prostate cancer and mortality from prostate cancer has significantly decreased. Although there is no absolute proof that the use of PSA was responsible for this decrease, in the 1980s, localized prostate tumors represented less than 60% of the cases and in recent years less than 5% of patients have initial metastatic presentation. Five-year cancer-specific survival increased from 69% in the 1970s to more than 95% nowadays, coinciding with the widespread use of this examination.[5]

An ideal screening program should focus on diseases with high clinical impact on public health; screen the population with a long life expectancy; be able to identify asymptomatic disease at a treatable stage during its natural course; have a high-accuracy, non-invasive, easy-to-apply, low-cost diagnostic tests that does not detect latent tumors; have a treatment capable of modifying the natural history of the disease, reducing mortality without worsening quality of life.

By not fulfilling all these criteria, the screening of prostate cancer with PSA is a controversial topic. One part of the controversy is due to the confusion between population screening and early diagnosis, another derives from problems related to the quality of existing studies, the results of radical curative treatment and the complications arising from these treatments that affect patient quality of life, such as urinary incontinence and erectile dysfunction.

There are five studies on population screening of prostate cancer. Two of them, which are now old, were performed in Quebec in Canada and Norrköping in Sweden and presented discordant results.[6,7] A review by the Cochrane Library concluded that these two studies had enormous methodological limitations, preventing any appropriate conclusions.[8] Three other more recent studies presented a better level of evidence.[9-11]

The European Prostate Cancer Screening Trial (ERSPC) randomized a population of 162,243 men between 55 and 69 years for PSA screening (n = 81,816) or control without PSA (n = 99,184). Several centers participated in the study, but the protocol was not the same across all centers. Most of them used a PSA value ≥ 3.0 ng/mL to indicate prostate biopsy. The PSA level was performed, on average, only every four years. After monitoring for 11 years, screening reduced the risk of metastases by 41% and the chance of death from prostate cancer by 21% (p=0.04). Given the total number of patients submitted to biopsy, 76% had benign tissue, demonstrating a high index of false-positive results. Of the 781 patients that needed to be screened, 27 were diagnosed and treated to prevent tumor-related death.[9,10]

The American Prostate Cancer Screening Trial (PLCO) study randomized 76,693 men aged 55 to 74 years for annual screening with PSA and rectal exam (n = 38,343) or control group with the "usual urological care," that is, at the discretion of the urologist (n = 38,350). The PSA value used to indicate biopsy was ≥ 4.0 ng/mL. After seven years of monitoring, mortality was similar between the two groups (p, non-significant).[11] The problem in this study was the control group. Since "usual care" in the USA includes PSA, in this case almost half of the patients in the control group did the test compared to the randomized group. Therefore, it was to be expected that there would be no difference between groups. At the time of publication, this study was interpreted as being a comparative analysis between two types of PSA screening, one more intense than the other. However, a recent reanalysis of the data showed that in fact more than 85% of the men in the control group had also undergone PSA testing (and not about 40%, as originally described), which explains more clearly the reason why the result of the study was negative.

In a study conducted in Gothemburg, in Sweden, 20,000 men were randomized 1:1 for PSA screening every two years or control without PSA. Their age ranged from 50 to 64 years (median = 56 years). The PSA value used to indicate the biopsy was between 3.0 and 4.0 ng/mL. After a 14-year follow-up, there was a relative decrease in prostate cancer mortality of 44%. Prostate cancer was diagnosed in 12.7% of the patients in the screening group and in 8.2% of those in the control group. In this study, 293 cases needed to be screened and 12 treated for prostate cancer to prevent one tumor-related death.[12] These figures are similar to those for breast cancer screening.

However, at the end of 2011 the United States Preventive Services Task Force (USPSTF) issued a report opposing the use of PSA in screening for prostate cancer giving equal weight for all studies. This recommendation has received a "D" grade recommendation, meaning that, in the committee's view, existing scientific data demonstrate that there is more harm than good with the use of this test.[13] The reasons for this recommendation were diverse.

A major problem for prostate cancer screening with PSA is tumor hyper-detection or over-diagnosis, characterized by excessive diagnosis of clinically insignificant tumors. In fact, in the ERSPC study the finding of low risk tumors (PSA < 10 ng/mL and Gleason score ≤ 6) was almost three times higher in the screened group than the control group.[9,10]

In the randomized PIVOT trial comparing radical prostatectomy versus observation in the PSA era, it was shown that there was no benefit from radical surgery for patients with low-risk tumors, which are precisely the majority of cases found in screening programs. In this study, there was no difference in mortality after 20 years of monitoring for patients with prostate adenocarcinoma with a Gleason score of 6 between those who did and did not undergo surgery. There was only increased survival in the cases of more aggressive tumors.[14]

Prostate biopsy indications have also changed over the years. After the Prostate Cancer Prevention Trial (PCPT) study showed cancer in at least 15% of patients with PSA < 4 ng/mL, prostate biopsy began to be recommended with lower PSA values of around 2.5 ng/mL, and this has contributed to the progressive finding of clinically insignificant tumors of lower biological aggressiveness.[15]

The interpretation of the role of PSA becomes even more complex when, in addition to this tumor over-diagnosis, we include the lead time bias and the migration of the screening programs in survival analyses, due to their potential to artificially modify the statistics.

As a counterpoint to the USPSTF recommendations, in 2013, the American Urological Association (AUA) published its recommendations on using PSA for the early detection of prostate cancer. The panel of urologists recommended PSA screening every 1 to 2 years for men aged 55 to 69 years after a decision shared between the doctor and the patient about the risks and benefits of the test. The text further states that, except for men with risk factors for prostate cancer, routine use of PSA is not recommended for other age groups or if life expectancy is less than 10-15 years.[16]

It is reasonable to accept that universal screening of the male population, regardless of age and family history, may not be the best approach, but on the other hand there are many methodological flaws in the published studies that have not been correctly interpreted. In addition, one important neglected point in the studies concerns the criteria used to measure the benefit of screening, which is usually only cancer-specific survival. The chance of decreased metastases, quality of life or other benefits that may result from an earlier diagnosis of the disease were not used as a primary parameter in any of the studies.

Vickers et al. demonstrated that PSA levels around 45 years in patients with no family risk factors could provide data on the chance of developing aggressive prostate cancer and risk of death from the tumor in the coming decades. In 21,277 men living in Malmö in Sweden and monitored since 1984, the authors identified that 44% of deaths from prostate cancer occurred in patients whose PSA value was above the 10th population percentile. When the baseline PSA values were below the population median according to the different age ranges – namely: up to 42 years: ≤ 0.6 ng/mL; up to 50 years: ≤ 0.7 ng/mL and up to 55 years: ≤ 0.9 ng/mL –, the chance of death from prostate cancer in 25 years was estimated at 0.1, 0.5 and 0.8%, respectively. These authors suggest that only three PSA measurements, the first performed at around 45 years, the second at the beginning of the fifth decade of life, and the third at 60 years may be sufficient for a safe risk assessment for half of the population.[17]

More recently, the European ERSPC study, now with almost 14 years of median follow-up, confirmed that prostate cancer mortality in PSA screened patients decreased by 32%.[10]

Thus, as additional evidence published since 2012 continues to show a progressive reduction in prostate cancer mortality with the use of PSA, the USPSTF just promoted a change in its guidelines in May 2017.[18]

The new recommendation is now grade "C," suggesting that there is a benefit to the use of PSA but that the test should be used selectively based on the professional judgment and patient preferences, recommendations similar to those proposed by the AUA in 2013.

Priority should be given to a shared decision between the physician and the patient about the risks and benefits of using PSA. The USPSTF concludes that there is a small overall benefit after a decade with the use of PSA, but continues to note that damages may occur during this screening period. However, there is still a major age-related problem in this current recommendation, because studies have predominantly included patients aged 55-70 years. Thus, the new USPSTF will not recommend PSA for men over 70 years nor for those under 55 years, which seems inadequate, given that it does not take into account clinical characteristics nor individual volition.[18]

However, this change in guidance seems to be better than the previous one and also occurred because there was a greater acceptance of active surveillance as a therapeutic form for low risk prostate cancer. The use of this approach was only used in 10% of low-risk prostate cancer cases between 2005 and 2009, and became higher than 40% between 2010 and 2013, creating the concept of not necessarily relating the diagnosis of prostate cancer with the intervention (diagnosis ≠ prostatectomy or radiation therapy).

A recent study confirms the validity of this approach.[19] In the ProctecT trial, 1,643 patients with prostate cancer GS ≤ 6 (ISUP 1) were randomized 1:1:1 among radical prostatectomy, external radiation therapy or active surveillance. After 10 years of monitoring, there was no difference in mortality from prostate cancer between the groups, which was 1%, suggesting an equivalence of therapeutic results and minimal risk of disease progression in this time interval. There were, however, differences between therapeutic approaches. Patients undergoing active surveillance were twice as likely to develop metastases in 10 years compared to those treated radically. Therefore, a longer monitoring period will be necessary to verify if the increased risk of death among the patients under surveillance is actually due to tumor progression or age-related comorbidities.[19]

The Brazilian Society of Urology maintains its recommendation that men over 50 years should seek a professional for an individualized evaluation. Those with first-degree relatives with prostate cancer should begin at age 45. Screening should be conducted after extensive discussion of the risks and potential benefits. After 75 years, it should be performed only for those with a life expectancy of over 10 years.[20]

Resumo

Rastreamento do câncer de próstata com PSA

O rastreamento do câncer de próstata com antígeno prostático específico (PSA) é uma questão altamente controversa. Parte da polêmica se deve à confusão entre rastreamento populacional e diagnóstico precoce, e outra parte está ligada a problemas relacionados à qualidade dos estudos de rastreamento recentes, a resultados do tratamento curativo radical para tumores de baixo grau ou em estágio precoce, e a complicações advindas de tratamentos que afetam a qualidade de vida do paciente. Nossa revisão teve como objetivo analisar criticamente as recomendações atuais para o teste de PSA, com base em dados obtidos da reavaliação de estudos em andamento e na recomendação atualizada do USPSTF, e propor o uso mais racional e seletivo do PSA comparado a níveis iniciais obtidos em uma idade aproximada de 40 a 50 anos.

Palavras-chave: PSA, câncer de próstata, rastreamento, próstata.

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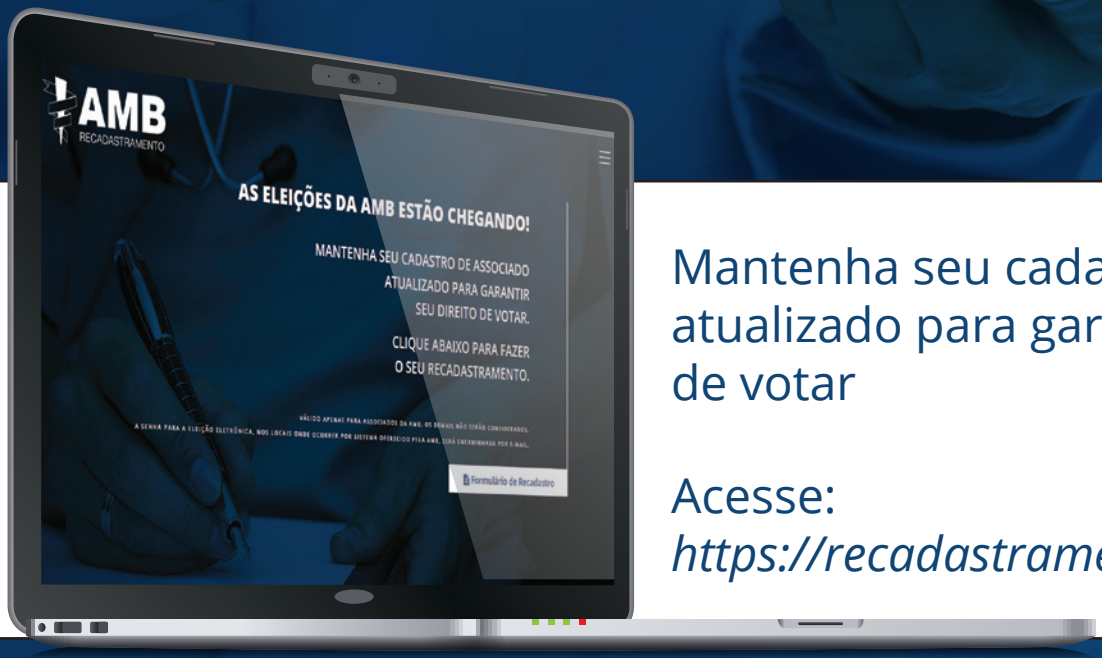

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