Figure 1 - Comparison of sperm DNA fragmentation rates in ejaculated and testicular sperm of 81 infertile men undergoing ICSI: (A) Use of testicular sperm for ICSI resulted in an absolute reduction of 32.6% (relative reduction of 79.7%) in SDF; (B) Sperm chromatin dispersion (SCD) test for assessing SDF in testicular sperm. A variant of the Halosperm test (Halotech DNA, Spain) that combines a dual fluorescent cocktail probe to discriminate somatic cells from spermatozoa was used. Spermatozoa and somatic cells exhibit differences in... (Page 566)
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IN THIS ISSUE

The July-August 2018 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Infertility, Bariatric Surgery, Bladder Cancer, Erectile Dysfunction, Prostate Cancer, Renal Cell Carcinoma, Prostate Biopsy, Renal stones, epididymo-orchitis, Pelvic Organ Prolapse, Penile Trauma, Nocturnal Enuresis, Prenatal Hydronephrosis, Basic Research, Prostatic Utricle Cyst, Urethral Stricture and Vesico-ureteral Reflux. The papers come from many different countries such as Canada, Egypt, Lebanon, Italy, Brazil, USA, UK, Turkey, China, Taiwan, India and Spain, and as usual the editor’s comment highlights some papers. We decided to comment the paper about a very interesting topic: Bladder Diverticula in BPH.

Doctor Iscaife and colleagues from the FMUSP, Brazil performed on page 765 an interesting study about the bladder diverticula in the prevalence of acute urinary retention in patients with BPH. The objective of the paper was to determine the effect of urinary bladder diverticula (BD) size secondary to benign prostatic hyperplasia on acute urinary retention (AUR) rates in patients with BPH candidates to surgery. The authors studied in a retrospective cohort of 47 patients with BPH and BD who underwent BPH surgery associated to complete bladder diverticulectomy. The authors analyzed risk factors for AUR in patients with BD using univariate, multivariate and correlation analysis and observed that there was a difference in the size of the diverticula, with 6.8 cm vs. 4.5 cm among patients with and without AUR respectively (p=0.005). The ROC curve showed a correlation between the size of BD and the risk of AUR. The value of 5.15 cm presented a sensitivity of 73% and a specificity of 72%. In the multivariate analysis, only the size of the diverticula reached statistical significance (p=0.012). The paper concluded that the diameter of BD is an independent risk factor for AUR in patients with BPH and BD who are candidates to surgery. A diameter greater than 5.15 cm increases the risk of AUR.

Bladder diverticula is a result of bladder mucosa and submucosa herniation through the muscularis propria of bladder wall (1). Inflammation, metaplasia, and dysplasia are commonly seen in vesical diverticula (2). There are two kinds of bladder diverticula: The congenital type, usually seen in association with posterior urethral valve or neurogenic bladder; and the acquired type, which is usually seen secondary to bladder outlet obstruction, mostly seen in association with benign prostatic hyperplasia. Diverticula may harbor neoplasms, most commonly urothelial carcinoma (3, 4).

Bladder diverticulum may be suspected in any patient presenting with symptoms of recurrent infection or difficulty in voiding that suggest blockage of the bladder outlet and urinary stasis. There was no consensus about the indication of surgery for bladder diverticulum in BPH. In the present paper
the authors shows an important and precise information: Bladder diverticulum with more than 5cm leaves to acute urinary retention, so this paper is very important and could be result in a new approach to bladder diverticulum treatment.

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The advent of intracytoplasmic sperm injection (ICSI) has revolutionized the management of male factor infertility (1). Shortly after the technique was introduced, studies demonstrated that ICSI could successfully treat couples with severe male factor infertility. Several investigators reported that neither sperm concentration, morphology, nor progressive motility had any impact on ICSI outcomes (2-4). However, the only sperm characteristic that portended a negative ICSI outcome was the injection of a totally immotile (and presumably dead) spermatozoon (4-6).

More recent publications have shown that ICSI may not overcome significant sperm abnormalities. Mitchell et al. reported significantly lower clinical pregnancy rates in couples with sperm motility <5% compared to those with higher sperm motility (11% vs. 41%, P=0.04 for couples with sperm motility <5% and >5%, respectively) (7). De Vos et al. reported significantly higher clinical pregnancy (37% vs. 20%, respectively, P=0.018), implantation (32% vs. 23%, respectively, P=0.013) and live birth rates (28% vs. 20%, respectively, P=0.006) with the use of morphologically normal vs. morphologically abnormal sperm for ICSI (8). Strassburger et al. studied 1,076 unselected ICSI cycles and reported that cryptozoospermic couples had significantly lower fertilization and clinical pregnancy rates (46% vs. 61%, P<0.0001 and 20% vs. 31%, P<0.05, respectively) and higher miscarriage rates (30% vs. 15%, P<0.03) when compared to couples with a sperm concentration between 1x10^5 sperm/mL and 1x10^7 sperm/mL (9).

Subfertile men with abnormal semen parameters may have an underlying sperm genetic defect that could potentially impact on IVF and ICSI outcomes. Indeed, studies have shown that sperm DNA damage is more common in men with poor semen parameters than in those with normal parameters and in 2008 a systematic review and meta-analysis of 2,162 IVF and ICSI treatment cycles demonstrated a potential adverse effect of sperm DNA damage on the chance of pregnancy, with a diagnostic odds ratio of 1.44 (95% CI, 1.03, 2.03) (10, 11). Moreover, a study of 1,549 IVF/ICSI cycles concluded that sperm DNA damage was predictive of pregnancy loss after IVF/ICSI (combined OR 2.48; 95% CI 1.52-4.04; P<0.0001) (12). More recent meta-analyses have similarly reported that sperm DNA damage is associated with lower clinical pregnancy rates and higher miscarriage rates after IVF and ICSI (13-15).

In 2005, Greco et al., reported their experience with the use of testicular sperm with ICSI in a small
series of couples with sperm DNA damage (16). Greco et al., claimed that there was “no specific treatment” for sperm DNA damage and hypothesized that the DNA damage in ejaculated sperm begins after spermatozoa are released from Sertoli cells. In view of the adverse impact of sperm DNA damage on IVF and ICSI outcomes, Greco et al. proposed using testicular sperm in men with sperm DNA damage with the idea that sperm recovered directly from the testis would show less damage than ejaculated sperm. To test this idea or hypothesis, they (1) compared the DNA damage in ejaculated and testicular sperm in two sequential assisted reproduction cycles performed in couples with high levels of ejaculated sperm DNA damage and (2) evaluated the ICSI outcomes of these couples. Greco et al. reported higher pregnancy rates with ICSI when using testicular rather than ejaculated sperm in couples with sperm DNA damage and observed a higher frequency of sperm showing detectable DNA damage in ejaculated vs. testicular sperm (16). They suggested that the poorer outcome with ejaculated sperm was a result of acquired DNA damage during transit through the epididymis or possibly during ejaculation.

In 2005, Suganuma et al. conducted experimental studies using an animal model with abnormal spermatogenesis (mutant mice with minimal levels of transition nuclear proteins and incomplete sperm nuclear compaction). They planned to investigate whether DNA damage in ejaculated sperm is increased after spermatozoa are released from the testis (17). Suganuma et al. observed that in animals with abnormal spermatogenesis the passage of sperm through the epididymis was associated with a loss of sperm DNA integrity and fertilizing capacity (17). They speculated that in animals with poor sperm nuclear compaction, the sperm DNA is not fully protected during epididymal passage. In contrast, in animals with normal spermatogenesis, the passage of sperm through the epididymis was not associated with a similar loss of sperm DNA integrity and fertilizing capacity. As such, Suganuma et al. proposed that in some men (i.e. those with defective spermatogenesis) the passage of sperm through the epididymis could result in a loss of sperm DNA integrity and fertilizing capacity. This concept (adverse effect of epididymal transit on sperm nuclear integrity) is contrary to the understanding of the biology of sperm maturation, specifically, the acquisition of sperm motility and nuclear compaction during passage of spermatozoa through the epididymis (18, 19).

The idea that the post-testicular environment or epididymal transit can induce sperm damage has led clinicians to utilize testicular rather than ejaculated sperm for ICSI in men with abnormal spermatogenesis and poor sperm DNA integrity. In a recent online survey of Canadian fertility clinics, 70% of the respondents reported performing testicular sperm retrieval (TSR) with ICSI for non-azoospermic men with poor sperm DNA integrity (Zini et al., unpublished observations). Similarly, over 70% of the respondents attending a session on testicular sperm for ICSI at the 2017 annual meeting of the American Society for Reproductive Medicine reported that they would (in selected cases) opt for testicular sperm rather than ejaculated sperm ICSI in men with sperm DNA damage (Zini et al., unpublished observations). However, despite the widespread utilization of TSR with ICSI in these men, there is no consensus or guideline on how to manage these cases in clinical practice.

In this issue of the International Brazilian Journal of Urology, Dr. Sandro Esteves and Dr. Mark Sigman present the Pro and Con perspectives, respectively, of using testicular rather than ejaculated sperm in non-azoospermic couples with high sperm DNA fragmentation (20, 21). Dr. Esteves discusses the adverse impact of sperm DNA damage on reproductive outcomes and demonstrates that sperm DNA damage is lower in testicular than in ejaculated sperm. Dr. Esteves presents a systematic of the literature and provides us with compelling evidence in support of the use of testicular rather than ejaculated sperm in these couples. Dr. Sigman argues that the quality of the studies on testicular sperm-ICSI is moderate at best and that there is insufficient evidence to adopt the practice of testicular sperm retrieval in these couples. Moreover, Dr. Sigman also cautions that sperm DNA testing requires further validation as a diagnostic test and in this context as well.
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Testicular versus ejaculated sperm should be used for intracytoplasmic sperm injection (ICSI) in cases of infertility associated with sperm DNA fragmentation | Opinion: Yes

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**Keywords:** Semen; Infertility, Male; Sperm Injections, Intracytoplasmic; Sperm DNA Fragmentation; Testicular Sperm

The use of testicular in preference over ejaculated sperm for intracytoplasmic sperm injection (ICSI) has gained increased attention due to reports of better pregnancy outcomes using testicular sperm for cases of infertility associated with high sperm DNA fragmentation (SDF) (reviewed by Esteves et al. [1]). Indeed, it has been a common practice to perform testicular sperm retrieval for ICSI (Testi-ICSI) in selected groups of non-azoospermic men. In a recent survey study involving infertility experts from 19 countries, 67% responders admitted that an abnormal SDF test result would affect their decision to utilize testicular instead of ejaculated sperm for ICSI [2]. Interestingly, identical numbers were reported by attendees of an interactive debate session held during the 2017 annual meeting of the American Society for Reproductive Medicine (unpublished data).

The matter concerned has been subjected to opinionated debate as Testi-ICSI represents a paradigm shift in clinical practice [1, 3-5]. I defend the argument that “Infertile couples undergoing ICSI, whose male partners have elevated SDF levels in the neat ejaculate, should be offered testicular sperm in the next ICSI cycle, provided SDF is persistent after treatment of the underlying condition, or the clinical scenario does not allow treatment”. There are three essential, evidence-based premises supporting this clinical approach, which I will discuss in the next paragraphs.

First, SDF not only impacts *in vitro* fertilization (IVF) and ICSI pregnancy outcomes but also contributes to pregnancy loss. In fact, results from the most recent and largest systematic review and meta-analysis about the impact of SDF on assisted reproductive technology (ART), which pooled data from 70 studies and over 17,000 IVF and ICSI cycles, indicate that SDF reduces the probability of a successful pregnancy following ART [6]. This observation holds true for both IVF and ICSI studies [IVF studies: odds ratio [OR] 1.15, 95% confidence interval [CI] 1.05-1.27; P=0.003; ICSI studies: inverse OR 1.12, 95% CI 1.01-1.25, P=0.02] and the four most common assays (TUNEL-terminal deoxynucleotidyl transferase dUTP nick end labeling, SCD-sperm chromatin dispersion, Comet-single cell gel electrophoresis, and SCSA-sperm chromatin structure assay) utilized for SDF assessment. Notably, the magnitude of effect size was amplified...
when female infertility factors were excluded (1704 cycles, OR 1.37, 95% CI 1.11-1.68, P=0.003), thus stressing the importance of the male factor concerning SDF.

Along the same lines, the risk of miscarriage is increased in couples with high SDF subjected to IVF and ICSI. Of the systematic reviews with meta-analysis, Robinson et al. aggregated the evidence of 16 studies and showed a significant increase in miscarriage rates in couples whose male partners had high SDF compared with those with low SDF (Relative Risk [RR] 2.2, 95% CI 1.54-3.03, P<0.00001) (7). Likewise, Zhao et al. pooled data from over 2,500 couples and showed that SDF had a detrimental effect on pregnancy after IVF/ICSI (All studies: OR 2.3; 95% CI 1.55-3.35, P<0.01; ICSI studies only: OR 2.7, 95% CI 1.40-5.14, P=0.003) (8). Despite using different SDF assays and not controlling for all confounding factors, both studies concluded that SDF testing should be offered to couples following IVF/ICSI failure, which is consonant with the recommendations of the recent clinical practice guidelines (CPG) on SDF testing issued by the Society for Translational Medicine (9). In practical terms, the OR of 2.7 means that an IVF Clinic performing 1,000 ICSI cycles a year with an overall clinical pregnancy rate (CPR) of about 40% will lose 82 pregnancies as a result of SDF, which means an absolute pregnancy reduction of 21%.

Second, testicular sperm have lower DNA fragmentation than ejaculated counterparts in men with elevated SDF in the neat ejaculate. This conclusion derives from a recent systematic review and meta-analysis, including five studies and 143 patients who served as their control, that is, SDF was measured in ejaculated and testicular specimens obtained from the same men (10). Four studies used the TUNEL assay whereas one study used the SCD assay. Overall, SDF rates were markedly lower in testicular than ejaculated sperm (Mean Difference [MD] -24.6%, 95% CI -32.5% to -16.6%, P<0.00001). Notably, the consistency in the direction of estimates favoring testicular sperm in all studies– adds confidence to these findings (Figure-1).

A study from our group, included in the meta-analysis mentioned above, compared DNA fragmentation rates between ejaculated and testicular sperm in 81 men with idiopathic oligozoospermia and elevated DFI (11). In our study, SDF rates by SCD using fluorescence microscopy were about 80% lower in testicular than ejaculated sperm (Figure-2) (Ejaculate: 40.7% ± 9.9%; Testis: 8.3% ± 5.3%, P<0.001). This study as well as others (12-15), included in that meta-analysis, provided data to answer the question of how often testicular specimens are better than ejaculated specimens concerning SDF (Table-1). The answer is that SDF is lower in testicular than ejaculated sperm in virtually all men with high SDF levels in semen, a reassuring data for the use of testicular sperm.

One of the main reasons why SDF is higher in semen than testis relates to the susceptibility of sperm chromatin to oxidative attack, particularly during epididymis transit (16). Apoptosis triggered by testicular conditions and by oxidative stress during sperm transit through the male reproductive tract can explain the high positivity of ejaculated sperm from infertile men for SDF, a phenomenon observed in both animal and human studies (17, 18). The source of the oxidative stress can be anything from a specific clinical condition such as a varicocele and a subclinical genital infection to age, obesity, smoking, and environmental exposure to toxicants (19). This oxidative-induced damage to sperm chromatin can be avoided in selected ICSI candidates provided the epididymis is bypassed.

Lastly, the existing evidence indicates that sperm retrieved from the testis of men with elevated SDF result in higher pregnancy rates when used for sperm injections. In the meta-analysis discussed above, we also looked at ICSI outcomes using testicular versus ejaculated sperm in men with confirmed elevated SDF in semen (10). Four studies provided this data, including 507 cycles and 3,840 injected oocytes (11, 15, 20, 21). In three of the four studies, elevated SDF was defined by a DNA
The odds ratio of achieving a clinical pregnancy using testicular sperm was 2.4 (95% CI 1.57-3.73, I²=34%, P<0.0001) and the results were conservative in subgroup analyses including couples with ICSI failure (OR 4.18, 95% CI 1.67-10.47, I²=36%, P=0.002) or first ICSI comers (OR 2.06, 95% CI 1.25-3.37, I²=39%, P=0.004). Furthermore, the OR of a live birth also favored testicular sperm (2.58, 95% CI 1.54-4.35, I²=0%, P=0.0003).

Importantly, the odds of a miscarriage were reduced by approximately 67% overall using testicular sperm (OR 0.28, 95% CI 0.11-0.68, I²=11%, P=0.005) (Figure-3). The conclusion was that ICSI with testicular sperm improves reproductive outcomes when compared with ejaculated sperm in men with high SDF.

A prospective, observational cohort study from our group (evidence level 2b), which had a substantial weight (59%) in the meta-analysis discussed above, included 147

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Figure 1 - Comparison of sperm DNA fragmentation rates in ejaculated and testicular sperm of 81 infertile men undergoing ICSI: (A) Use of testicular sperm for ICSI resulted in an absolute reduction of 32.6% (relative reduction of 79.7%) in SDF; (B) Sperm chromatin dispersion (SCD) test for assessing SDF in testicular sperm. A variant of the Halosperm test (Halotech DNA, Spain) that combines a dual fluorescent cocktail probe to discriminate somatic cells from spermatozoa was used. Spermatozoa and somatic cells exhibit differences in the wavelength emission associated with each fluorochrome (green for proteins and red for DNA). Spermatozoa exhibit only red fluorescence on the sperm head owing to protamine removal, while non-sperm cells fluoresce yellow as a result of the combined emission of both fluorochromes (A). Spermatozoa exhibiting red fluorescence with a green flagellum and no halo of chromatin dispersion represented those with fragmented DNA (arrow cap). In contrast, spermatozoa exhibiting red fluorescence with a green flagellum and haloes of chromatin dispersion represented those with non-fragmented DNA (arrow). A somatic cell with its typical high protein and DNA contents and a spermatozoon with its characteristic low protein remnant and high DNA content are seen in B and C, respectively, using a single channel fluorescence emission. After merging the information provided by protein and DNA selective staining, somatic cells and spermatozoa can be easily distinguished (d and d’). In addition, the sperm tail fluoresces in green, and this feature also helps to distinguish spermatozoa from other cell elements (a and d’). Adapted with permission from Esteves et al. (11).
Table 1 - Characteristics of studies comparing sperm DNA fragmentation rates between testicular and ejaculated sperm of the same men and how often SDF rates were lower in testis versus ejaculated sperm among men with high SDF in semen.

<table>
<thead>
<tr>
<th>Study</th>
<th>Infertile male population studied</th>
<th>No. patients</th>
<th>SDF assay</th>
<th>DFI cutoff (%)</th>
<th>No. patients (%) SDF lower in testicular sperm than ejaculated sperm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greco et al. 2005 (15)</td>
<td>Non-smokers; Mean sperm count: 26.8 M/mL; Sperm motility: 36.7%; Sperm morphology: 20.9%</td>
<td>18</td>
<td>TUNEL</td>
<td>15</td>
<td>17 (94.5%)</td>
</tr>
<tr>
<td>Moskovtsev et al. 2010 (13)</td>
<td>High DFI despite AOX</td>
<td>12</td>
<td>TUNEL</td>
<td>30</td>
<td>11 (91.7%)</td>
</tr>
<tr>
<td>Esteves et al. 2015 (11)</td>
<td>Idiopathic oligozoospermia (5-15 M/mL); high DFI despite AOX</td>
<td>81</td>
<td>SCD</td>
<td>30</td>
<td>81 (100.0%)</td>
</tr>
</tbody>
</table>

DFI = DNA fragmentation index; SDF = Sperm DNA Fragmentation; AOX = Oral antioxidant therapy; TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling; SCD = sperm chromatin dispersion.
Table 2 - Characteristics of studies comparing intracytoplasmic sperm injection (ICSI) outcomes using testicular versus ejaculated sperm in infertile men with high sperm DNA fragmentation (SDF) in semen.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>No. patients/cycles</th>
<th>SDF assay (cutoff)</th>
<th>ICSI Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greco et al. 2005 (15)</td>
<td>Case-control</td>
<td>ICSI failure (≥2); normozoospermia ¹</td>
<td>18</td>
<td>TUNEL (15%)</td>
<td>2PN, CPR</td>
</tr>
<tr>
<td>Esteves et al. 2015 (11)</td>
<td>Prospective</td>
<td>Non-ICSI failure; oligozoospermia ²</td>
<td>172</td>
<td>SCD (30%)</td>
<td>2PN, CPR, miscarriage, LBR</td>
</tr>
<tr>
<td>Pabuccu 2016 (20)</td>
<td>Retrospective</td>
<td>ICSI failure (≥2); normozoospermia ³</td>
<td>71</td>
<td>TUNEL (30%)</td>
<td>2PN, CPR</td>
</tr>
<tr>
<td>Bradley et al. 2016 (21)</td>
<td>Retrospective</td>
<td>Non-ICSI failure; oligozoospermia ¹</td>
<td>228</td>
<td>SCIT (29%)</td>
<td>2PN, CPR, miscarriage, LBR</td>
</tr>
</tbody>
</table>

¹ The studied populations of Greco et al. and Bradley et al. were classified as normozoospermic (>15 million/mL) or oligozoospermic (<15 million/mL) based on the calculated mean or median sperm concentration.

² The study by Esteves et al. and Pabuccu et al. included men with oligozoospermia (5-15 million/mL) and normozoospermia (>15 million/mL) based on the 2010 World Health Organization manual for semen analysis.

2PN = two-pronuclear zygote; TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling; SCD = sperm chromatin dispersion; SCIT = sperm chromatin integrity test, which is a variation of sperm chromatin sperm assay (SCSA); CPR = clinical pregnancy rate; LBR = live birth rate

Figure 3 - Forest plots showing odds ratios for (A) fertilization rates, (B) clinical pregnancy rates, (C) miscarriage rates, and (D) live birth rates with the use of intracytoplasmic sperm injection with testicular (Testi-ICSI) or ejaculated (Ejac-ICSI) sperm in men with high sperm DNA fragmentation, including subgroup analyses according to study population (repeated ICSI failure and non–ICSI failure) and semen analysis profile (oligozoospermia and normozoospermia).

A. Fertilization rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Testi-ICSI Events Total</th>
<th>Ejaculated Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fertilization - oligozoospermia / non-ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley 2016</td>
<td>553</td>
<td>975</td>
<td>347</td>
<td>521</td>
<td>28.7%</td>
</tr>
<tr>
<td>Pabuccu 2016</td>
<td>423</td>
<td>753</td>
<td>556</td>
<td>801</td>
<td>29.1%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>976</td>
<td>903</td>
<td>1322</td>
<td>57.7%</td>
<td>0.61 [0.52, 0.71]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>976</td>
<td>903</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity, Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.46 (P = 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fertilization - Normozoospermia / repeat ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greco 2005</td>
<td>110</td>
<td>187</td>
<td>131</td>
<td>185</td>
<td>20.7%</td>
</tr>
<tr>
<td>Pabuccu 2016</td>
<td>151</td>
<td>198</td>
<td>156</td>
<td>220</td>
<td>21.6%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>267</td>
<td>287</td>
<td>405</td>
<td>42.3%</td>
<td>1.20 [0.88, 1.65]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>267</td>
<td>287</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity, Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.16 (P = 0.25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2113</td>
<td>1727</td>
<td>100.0%</td>
<td></td>
<td>0.81 [0.58, 1.15]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>1263</td>
<td>1190</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity, Tau² = 0.10; Chi² = 15.82, df = 3 (P = 0.001); I² = 81%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.18 (P = 0.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 14.85, df = 1 (P = 0.0001), I² = 93.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours Ejaculated Favours Testi -ICSI

<table>
<thead>
<tr>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

671
B. Clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Test-ICSI</th>
<th>Ejaculated</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPR - oligozoospermia / non-ICSI failure</td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Bradley 2016</td>
<td>35</td>
<td>66</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Estes et al. 2015</td>
<td>77</td>
<td>35</td>
<td>97</td>
<td>52.1%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>143</td>
<td>129</td>
<td>82.7%</td>
<td>2.06 [1.25, 3.37]</td>
</tr>
<tr>
<td>Total events</td>
<td>75</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.65, df = 1 (P = 0.20); I^2 = 39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.86 (P = 0.004)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| CPR - normozoospermia / repeat ICSI failure | | | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Greco 2005 | 8 | 18 | 1 | 18 | 2.1% | 13.60 [1.48, 125.31] | | |
| Pollock 2016 | 13 | 31 | 8 | 40 | 15.2% | 2.89 [1.01, 8.28] | | |
| Subtotal (95% CI) | 49 | 58 | 17.3% | 4.18 [1.67, 10.47] | | |
| Total events | 21 | 9 | | | | |
| Heterogeneity: $\chi^2 = 1.56, df = 1 (P = 0.21); I^2 = 30% |
| Test for overall effect: $Z = 3.05 (P = 0.002)$ |

| Total (95% CI) | 192 | 187 | 100.0% | 2.42 [1.57, 3.73] | | |
| Total events | 96 | 55 | | | | |
| Heterogeneity: $\chi^2 = 4.52, df = 3 (P = 0.21); I^2 = 39% |
| Test for overall effect: $Z = 4.01 (P < 0.001)$ |
| Test for subgroup differences: $\chi^2 = 1.78, df = 1 (P = 0.18), I^2 = 43.7%$ |

C. Miscarriage rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Test-ICSI</th>
<th>Ejaculated</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage - oligozoospermia / non-ICSI failure</td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Bradley 2016</td>
<td>4</td>
<td>35</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Estes et al. 2015</td>
<td>4</td>
<td>40</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>75</td>
<td>46</td>
<td>73.6%</td>
<td>0.33 [0.12, 0.90]</td>
</tr>
<tr>
<td>Total events</td>
<td>8</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.82, df = 1 (P = 0.18); I^2 = 45%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.37 (P = 0.02)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Miscarriage - normozoospermia / repeat ICSI failure | | | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Greco 2005 | 0 | 8 | 1 | 1 | 13.3% | 0.02 [0.00, 1.43] | | |
| Pollock 2016 | 1 | 13 | 2 | 8 | 12.1% | 0.25 [0.02, 3.94] | | |
| Subtotal (95% CI) | 21 | 9 | 26.4% | 0.13 [0.02, 1.12] | | |
| Total events | 1 | 3 | | | | |
| Heterogeneity: $\chi^2 = 0.39, df = 1 (P = 0.52); I^2 = 0% |
| Test for overall effect: $Z = 1.85 (P = 0.06)$ |

| Total (95% CI) | 96 | 55 | 100.0% | 0.28 [0.11, 0.68] | | |
| Total events | 9 | 16 | | | | |
| Heterogeneity: $\chi^2 = 3.35, df = 3 (P = 0.39); I^2 = 11% |
| Test for overall effect: $Z = 2.03 (P = 0.045)$ |
| Test for subgroup differences: $\chi^2 = 6.55, df = 1 (P = 0.01), I^2 = 0%$ |

D. Live birth rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Test-ICSI</th>
<th>Ejaculated</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Birth Rates - oligozoospermia / non ICSI failure</td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Bradley 2016</td>
<td>31</td>
<td>66</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Estes et al. 2015</td>
<td>26</td>
<td>77</td>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>143</td>
<td>129</td>
<td>100.0%</td>
<td>2.58 [1.54, 4.35]</td>
</tr>
<tr>
<td>Total events</td>
<td>67</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.07, df = 1 (P = 0.79); I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 3.58 (P = 0.0003)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI) | 143 | 129 | 100.0% | 2.58 [1.54, 4.35] | | |
| Total events | 67 | 33 | | | | |
| Heterogeneity: $\chi^2 = 0.07, df = 1 (P = 0.79); I^2 = 0% |
| Test for overall effect: $Z = 3.58 (P = 0.0003)$ |
| Test for subgroup differences: Not applicable |

$CI =$ confidence interval; $IV =$ inverse variance.
Adapted with permission from Esteves et al. (10).
infertile couples (11). The men had idiopathic oligozoospermia (5-15 million/mL) and persistently elevated SDF (DFI>30% by SCD) despite taking oral antioxidant therapy. The women were aged <40 years and had no apparent fertility issues. The main outcome measures were clinical pregnancy rate (CPR), live birth rate (LBR), and miscarriage rate, and the study was powered (80%) to detect a 30% difference in LBR between the groups with a significance level of 5%. The clinical characteristics of the couples subjected to ICSI using testicular versus ejaculated sperm were not statistically different. In this study, we found that LBR was significantly higher (P=0.007) in the Testi-ICSI group (46.7%) than in the Ejac-ICSI group (26.4%). Moreover, miscarriage rates were lower in couples who used testicular versus ejaculated sperm for ICSI (10% vs. 34.3%, P=0.012). The relative risk of achieving a live birth by Testi-ICSI was increased by 76% (RR 1.76, 95% CI 1.15-2.70). This means that the number needed to treat by Testi-ICSI compared with Ejac-ICSI to achieve one additional live birth was 4.9 (95% CI 2.8-16.8), thus suggesting that one out of five oocytes pick-ups can be avoided if testicular sperm is used in preference over ejaculated sperm.

Although the current data supporting testicular sperm for selected non-azoospermic infertile men is reassuring, it is important to recognize the existence of gaps in knowledge and the risks of sperm retrieval, as discussed in detail elsewhere (1). Briefly, there is still limited evidence as regards the clinical efficacy of Testi-ICSI. Furthermore, there is a need to define the best candidates for Testi-ICSI and compare its cost-effectiveness with other laboratory methods of sperm selection. Also, sperm retrieval has potential hazards, although the overall risk is low (<5%) and the complications minor (22, 23). These shortcomings, however, should not refrain from offering testicular sperm for selected ICSI couples provided we discuss with our patients the limitations of SDF testing and the possible clinical benefits and risks of Testi-ICSI.

In my practice, I request SDF testing to selected ART candidates and recommend treatment of the underlying conditions associated with SDF (24). Varicocele, lifestyle factors (smoking, obesity, occupational exposure), and genital infections are potentially correctable factors that have been associated with SDF. Identification and treatment of these conditions may decrease SDF and enable the use of ejaculated sperm for ICSI or the application of less complex assisted reproduction methods (reviewed by Esteves et al. (25)). Testi-ICSI is reserved for cases with persistently elevated SDF after all possible measures were taken to reduce SDF, or when the clinical scenario does not allow treatment. Importantly, we do not recommend Testi-ICSI to unselected populations of infertile men with untested SDF, such as those with cryptozoospermia, as the current evidence remains equivocal concerning the potential benefit of Testi-ICSI to this subset of men (26).

We rely on testicular sperm instead of laboratory methods to select specimens with lower SDF levels because it allows for sperm acquisition before transiting through the epididymis, which is when SDF is thought to be acquired. Also, it has been shown that Testi-ICSI provides higher LBR when compared with laboratory methods such as physiological intracytoplasmic sperm injection (PICSI) and intracytoplasmic morphologically selected sperm injection (IMSI) in couples with high SDF in semen (21). In a 2016 study, Bradley et al. evaluated 448 cycles in which sperm injections were carried out with ejaculated and testicular sperm. In the former, PICSI and IMSI were used to select sperm with better chromatin integrity for ICSI. They found that LBR birth rates with Testi-ICSI (49.8%) were significantly higher than IMSI (28.7%) and PICSI (38.3%). The lowest live birth rates (24.2%) were achieved when no method was used to select sperm for ICSI (P = 0.020).

Lastly, as for the health of offspring resulting from Testi-ICSI in cases of high SDF, there is lack of published data. However, reports of ICSI using testicular sperm in azoospermia have been overall reassuring, as no major differences are noted in the short-term neonatal outcomes and congenital malformation rates among children from fathers with nonobstructive azoospermia or obstructive azoospermia (27, 28).

In conclusion, I first presented evidence confirming that SDF negatively impacts
ART pregnancy outcomes and is associated with pregnancy loss. Then, I provided data to substantiate the premise that SDF is lower in testicular than ejaculated sperm among infertile men with high SDF in semen. Lastly, I summarized the evidence supporting the proposition from which the use of testicular in preference over ejaculated sperm (therefore with lower SDF) is associated with improved ICSI pregnancy outcomes in couples whose male partners have high SDF in semen. These evidence-based premises make the argument stated at the beginning of this article “Infertile couples with ICSI failure should be offered Testi-ICSI if male partners have high SDF in the neat ejaculate” irrefutable. Therefore, Testi-ICSI should be considered in the treatment plan of infertile couples undergoing ICSI when the following conditions are met (i) Presence of high SDF levels in neat ejaculate, measured by a reliable assay with a validated threshold, and (ii) Persistence of elevated SDF levels despite treatment of the underlying condition causing SDF (if correctable). A failed ICSI cycle using ejaculated sperm with no other obvious reasons explaining that failure should reinforce consideration for the use of Testi-ICSI, provided the conditions mentioned above are met.

**DISCLOSURE**

Expanded from an invited talk by the author delivered at the American Society for Reproductive Medicine (ASRM) Annual Meeting, San Antonio, USA, October 2017.

**REFERENCES**

Testicular versus ejaculated sperm should be used for intracytoplasmic sperm injection (ICSI) in cases of infertility associated with sperm DNA fragmentation | Opinion: No

Mark Sigman 1

1 Department of Urology Brown University and The Miriam Hospitals, RI 02906, EUA

The argument for the use of testicular sperm instead of ejaculated sperm for infertility due to sperm DNA fragmentation (SDF) relies on several assumptions. When each assumption is examined, it becomes clear that the assumptions are either unproven, due to insufficient data, or just plain wrong. These assumptions are: 1) sperm DNA fragmentation assays are good diagnostic tests; 2) IVF/ICSI failed because of elevated SDF; and 3) testicular sperm will result in pregnancy or live birth when ejaculated sperm will not. It has been demonstrated that when comparing populations, SDF is greater in infertile than in fertile populations. In addition, SDF is negatively associated with pregnancy rates by IVF/ICSI with an odds ratio of 1.68 (1). However, these population associations are insufficient to rely on SDF assays to direct patient management. There are a multitude of SDF assays, some such as TUNEL, directly measure the presence of sperm DNA fragmentation, while others such as SCSA, alkaline COMET, and Sperm Chromatin Dispersion (SCD) only indirectly measure fragmentation. There remains poor standardization of techniques and even variable protocols of the same assays between different laboratories. These problems have lead the American Society of Reproductive Medicine Practice Committee report to state that “existing data relating to relationship between DNA fragmentation and reproductive outcomes too limited to routinely use” Their most favorable conclusion is that the effect of SDF on IUI, IVF, and ICSI may be clinically informative – hardly an overwhelming endorsement (2). While odds ratios are useful for describing associations in populations, they are not proper statistical metrics by which diagnostic tests are judged. The results of individual patient’s SDF assays are used to direct those individual’s therapy, the assays are being used as diagnostic tests. The metrics by which diagnostic tests are evaluated are sensitivity, specificity, and the area under the Receiver Operating Characteristic (ROC) curves. The relationship between SDF and ART outcomes have been evaluated by at least 7 prior meta-analyses – all of which used odds ratios or relative risk ratios. Overall the results have been inconclusive. Li et al. reported that SDF was associated with IVF pregnancy rates but not with ICSI outcomes (3). Collins reported that sperm DNA damage predicts ART outcome, but the results of testing would not necessarily affect the decision to proceed with ART because the effects were likely clinically insignificant (4). Most recently, Simon determined that the association depends on the type of assay used. There was no association of SCSA and ART outcomes while there was a ne-
gative relationship between SDF and IVF and/or ICSI outcomes. When proper ROC analysis is performed, the assays perform either mediocre or no better than flipping a coin. For example, the TUNEL has an AUC of 0.71, a sensitivity of 0.84 but a specificity of 0.24. This means that there is a high false positive rate – patients with elevated SDF still become pregnant. This makes it inaccurate to use the results to inform patients that they will not achieve pregnancy by ART using ejaculated sperm if their SDF by TUNEL is elevated. In comparison, the SCSA and SCD had AUC’s of 0.49 – no better than using a coin flip to determine the result and make clinical recommendations (5). It is clear that recommending testicular sperm retrieval (TESE) for couples with high SDF is based on a test that needs improvement in testing characteristics, validation in clearly defined populations, and standardization of protocols and thresholds.

The use of testicular sperm instead of ejaculated sperm assumes that testicular sperm is of better quality. In comparing testicular to ejaculated sperm in the same patients, testicular sperm has been found to have lower SDF, however, sperm aneuploidy was increased in the testicular sperm - certainly a worrisome finding (6). To justify TESE instead of ejaculated sperm, we must be assured that testicular sperm are healthier sperm, not just sperm with lower SDF values. Regardless of the biology of the sperm, testicular sperm should yield better pregnancy rates than ejaculated sperm. A recent meta-analysis found no statistically significant improvement in ICSI pregnancy rates in cryptozoospermic men when comparing testicular sperm to ejaculated sperm (7).

Many studies arguing for TESE report pregnancy after TESE/ICSI cycles in couples that have failed prior ejaculated sperm ICSI cycles. The assumption is that the pregnancies in subsequent ICSI cycles were due to the use of testicular sperm, not due to just repeating the IVF/ICSI cycle. These studies ignore the fact that pregnancy and live birth rates are substantial with further ejaculated sperm IVF/ICSI cycles. Luke et al. utilizing SART data calculated estimated optimal cumulative live birth rates of approximately 30% after 1 cycle growing to over 60% by the 3rd cycle with further increases with additional cycles (8). Simply put, couples that fail an IVF/ICSI cycle, may become pregnant by just pursuing additional ejaculated sperm cycles without resorting to TESE. The argument for utilizing TESE sperm for couples that have failed IVF/ICSI relies on studies reporting better pregnancy rates with this approach. It is quite informative to examine the studies and the study designs supporting this approach. There are three types of study designs that can evaluate ejaculated vs. testicular sperm. Case series are the most frequently published manuscripts. These papers report pregnancy rates in couples that utilized testicular sperm after they failed ejaculated sperm cycles. It is obvious that since the initial ejaculated sperm cycles failed to achieve pregnancy that pregnancy rates in subsequent cycles will be better if they occur at all. All couples who achieved pregnancy with ejaculated sperm are excluded from these reports. Thus, this study design cannot demonstrate that the cause of subsequent successful cycles was due to the source of the sperm or just from repeating the cycles. A second study design reported are cohort studies in which couples that choose TESE are compared to those that refused TESE. While this study design is superior to case study designs, the one study utilizing this approach proceeded to TESE based on SDF results without having the couples under an initial ejaculated sperm ICSI cycle. Thus, we don’t know that the couples in the TESE arm would have failed ICSI with ejaculated sperm. In addition, since patients chose which treatment they wanted, the door is open to biasing factors that are not accounted for (9). The ideal study design is a randomized controlled trial of couples that failed IVF/ICSI, including groups with normal and elevated SDF in both arms that are randomized to either ejaculates sperm ICSI or testicular sperm ICSI. It is important to include subgroups of normal SDF since the argument for TESE in these cases is that the ejaculated sperm have high SDF and the testicular sperm have lower SDF and that outcomes from testicular sperm are limited to those with high SDF. Without
examining couples with low ejaculated sperm SDF, any demonstrated improvement in pregnancy rates may be due to just using testicular sperm – not due to lower SDF in testicular sperm. Review of these randomized studies is easy because there are none, not a single one. All reports are either case series or observational cohort designs, and only include couples with high SDF. Up through the end of 2017, there are five reports (four published articles, and one abstract) comparing pregnancy rates from testicular and ejaculated sperm in couples with elevated SDF. All report better pregnancy or live birth rates from testicular sperm. While a superficial review suggests the superiority of testicular sperm, an evaluation of the study designs suggests otherwise. Three publications are case series that compared subsequent testicular sperm cycles to prior failed cycles in the same patients (10-12). As discussed, results can only be better in subsequent cycles, and as demonstrated by the SART data analysis, repeated cycles are often successful. Two cohort studies compared two different patient groups, all of whom had elevated SDF – ejaculated sperm couples and testicular sperm couples. In one study, couples went to TESE based on elevated SDF without having had any prior ICSI cycles (9). The second only included couples that failed prior IVF/ICSI cycles (13). Since these two studies utilized completely different study designs addressing different questions, they cannot but combined to address this issue.

Examining the characteristics of subjects included in the various studies is critical to allow generalizations that we may make to apply the findings to our own patients. Populations consisted of only patients with sperm densities of less than 5 million sperm per mL (11), sperm densities of 5 – 15 million/mL (9), normal sperm densities (13), while some contained subjects with wide ranges of semen parameters (10, 12). These differences between subject populations makes it difficult to compare studies. Further difficulties arise when examining what level of sperm DNA fragmentation was considered elevated in these studies. Of the studies utilizing TUNEL assays, thresholds were >30% (13), >15% (10), and >7% (11). Of those that used the SCD, thresholds were 30% but the assay techniques were different (9, 12). Therefore, some studies classified patients as abnormal while those same patients would have been classified as normal by other investigators. Outcomes that may be examined include fertilization rates, pregnancy rates, miscarriage rates, and live birth rates. Most studies reported no difference in fertilization rates between TESE and ejaculated groups while one reported worse rates in the TESE group (9). While four of the studies reported better pregnancy rates and one reported no change, because of the study design limitations, the cause of the better pregnancy rates cannot be attributed to the source of sperm. Similarly, live birth rates were reported as better with testicular sperm (one study did not report live birth rates), the study designs limit conclusions about the cause of the differing rates. Most recently, a study presented in May 2018 examined couples with elevated SDF that failed an ejaculated sperm ICSI cycle who subsequently choose either TESE or a second ejaculated sperm ICSI cycle. The authors found no statistical difference in pregnancy or live birth rates when comparing the testicular sperm to the ejaculated sperm group (14). Of interest, in the two studies reporting miscarriage rates, both found lower rates in the testicular groups (9, 10). This raises the possibility that better live birth rates may be due to lower miscarriage rates from testicular sperm and that what we should study is not infertility couples, but recurrent miscarriage couples.

This methodical analysis of the published data demonstrates that SDF tests fail as diagnostic tests to direct therapy. The assays need standardization and validation. In addition, the published studies do not utilize one of the most commonly ordered and commercially available assays, the SCSA. Therefore, clinicians should not extrapolate their patient’s SCSA results to determine whether to use TESE for ICSI cycles. Elevated SDF has not been shown to be the cause of failed ART cycles due to flaws in study designs and the lack of data on low SDF couples in these trials. Testicular sperm has not been shown...
to result in better outcomes than ejaculated sperm since the level of evidence is poor – ranging from 2b (cohort studies) to 4 (case series). The included subjects are not comparable with greatly variable sperm densities in different studies. The practice of testicular sperm retrieval for couples with elevated SDF and failed IVF/ICSI should be considered experimental - randomized controlled trials are greatly needed. In addition, the potential genetic and epigenetic risks of testicular sperm should not be ignored. Finally, it is important to remember that we physicians have taken an oath to do no harm.

REFERENCES


Review of post bariatric surgery effects on common genitourinary physiology

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ABSTRACT

**Background:** Obesity is a worldwide challenging health problem. Weight loss through medical management of obesity has not always been successful, thus, giving rise to the need for surgical intervention. Bariatric surgery has been shown to be helpful for morbidly obese patients. However, studies have also shown the effect of surgery on stone formation, fertility and erectile function. This review summarizes the main findings of several studies that analyze stone formation and fertility in men as well as erectile function post bariatric surgery. The underlying pathophysiologic alterations post bariatric surgery include increased absorption of oxalate leading to hyperoxaluria, hypocitraturia and increased urinary calcium oxalate supersaturation. Contradicting data exist on the effect of bariatric surgery on fertility and erectile function. Further studies are needed to analyze the mechanisms.

INTRODUCTION

Obesity is a public health concern with increased prevalence in the past two decades (1). The highest peak is in women and men aged between 20 and 40 years (2). In adults aged 20 years and above, it is defined as body mass index (BMI) equal to or greater than 30 kg/m² (3). Obesity affects more than one third of adults in the United States (US) (4). The 2011-2012 National Health and Nutrition Examination Survey (NHANES) conducted on 9120 individuals in the US showed that 31.8% of the 584 youth (youth defined as those from birth until two years of age) were either overweight or obese, while 16.9% of the youth were obese (3). Obesity causes several health risks such as diabetes, hypertension, dyslipidemia, cardiovascular disease, sleep apnea, etc. (5). It can even affect reproductive functions in both sexes and lead to pregnancy/perinatal or offspring adverse effects (1). In men, it may cause oligozoospermia and asthenozoospermia (1), erectile dysfunction (2) and subfertility (6). The estimated annual medical costs of illness pertinent to adult obesity exceed 200 US billion (5). This implies that 20.6% of the US national health expenditures are spent on obesity-linked illnesses (5).

Bariatric surgery is an alternative for patients with BMI ≥40 kg/m² or BMI ≥35 kg/m² and who suffer from coexisting morbidities linked
to obesity (6). The currently performed bariatric surgeries are either restrictive such as sleeve gastrectomy (SG) and laparoscopic adjustable gastric band (LAGB) or combined restrictive/mal-absorptive like Roux-en-Y gastric bypass (RYGB) (1). In 2011, around 340,000 bariatric surgeries were performed across the globe and RYGB was the most common procedure (47%), followed by SG (28%) and LAGB (18%) (1). The number of bariatric surgeries rose to 468,609 in 2013 worldwide (7) and 196,000 procedures were performed in the US alone in 2015 (8). Although bariatric surgery can lead to weight reduction and decrease of the above mentioned health problems, it leads to numerous physiological alterations that are not just restricted to the gastrointestinal tract (4). Clinical data propose that bariatric surgery is linked to nephrolithiasis due to variations in urinary volume, oxalate and citrate (9). However, other studies show conflicting effect on fertility in men and erectile function (10, 11).

OBJECTIVES

This review addresses the physiological alterations of bariatric surgery on the genitourinary system.

MATERIALS AND METHODS

We comprehensively searched the databases of Pubmed on March 21 and 22 and August 31, 2017 for clinical trials, review papers and meta-analyses focusing on the effect of bariatric surgery on the incidence of stone formation, pathophysiology of stone risk and fertility in men as well as erectile function. The inclusion criteria were based on the most relevant, most recent and most cited studies about clinical and experimental literature that discuss pathophysiology of stone risk and mechanism of sexual and erectile dysfunction in men after bariatric surgery. The summary table of studies about changes in genitourinary system, fertility and sexual function in humans after bariatric surgery is presented in Table-1 and of animal studies in Table-2 and arranged by type of study (retrospective, prospective, cross-sectional and case reports respectively).

RESULTS & DISCUSSION

Bariatric surgery and nephrolithiasis

Bariatric surgery causes higher incidence of nephrolithiasis (7, 8, 12). The risk of kidney stone formation after RYGB has been studied over the last decade (9). One study reported that the incidence of stone among 4639 patients post RYGB was 7.65% vs. 4.63% of obese controls (p<0.0001) (13). The person-time stone incidence was projected to be 16.62 stones per 1000 person-years for RYGB (13). A meta-analysis of four articles (1 randomized trial and 3 cohort studies) showed that the incidence of kidney stone formation depends on the type of procedure (7). Patients who have undergone RYGB had an overall increased risk of 1.73 vs. those who have not undergone any procedure, while patients who have undergone laparoscopic banding or SG had a decreased risk of 0.37 (7). In a population-based study with 762 co-morbidity-matched patients vs. 759 controls, the incidence of stone formation was more common in patients who underwent bariatric surgery vs. controls (p<0.01) (12). The risk was highest among those who underwent mal-absorptive procedures, followed by RYGB and restrictive procedures (12).

The mechanism for nephrolithiasis post bariatric surgery is complex, but involves different pathologies such as hyperoxaluria, hypocitraturia and aciduria (8). Hyperoxaluria is common in patients who have undergone RYGB because of changes in intestinal microbial flora that lead to increased oxalate absorption (8). The relationship between hyperoxaluria and stone formation was firstly investigated by Nelson et al. in a study on 23 patients (14 men and 9 women; mean age = 45 years) (14). There were 21 patients who developed nephrolithiasis and 2 developed oxalate nephropathy (14). Prospective studies on non-stone formers showed hyperoxaluria in 45 patients (15), doubling of urinary oxalate excretion in 21 patients (16), increase in urine oxalate and decreased urine volume in 11 patients (17) and increased urine oxalate in 13 patients after patients underwent RYGB (18). Another study among 151 patients followed up for a year after RYGB showed significant higher urinary oxalate (24 vs. 41 mg; p<0.001) and urinary uric acid (545 vs. 645 mg;
Table 1 - Human studies about physiological alterations of bariatric surgery on the genitourinary system arranged by study type.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>Surgery type</th>
<th>Sample size</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al. (14)</td>
<td>2005</td>
<td>Retrospective study</td>
<td>RYGB</td>
<td>23 patients</td>
<td>Calcium oxalate nephrolithiasis in 21 patients. Enteric hyperoxaluria with oxalate nephropathy in 2 patients. Increased 24-hour excretion of urinary oxalate and calcium oxalate supersaturation.</td>
</tr>
<tr>
<td>Matlaga et al. (13)</td>
<td>2009</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>4693 patients vs. 4693 controls</td>
<td>In operated group: Increased risk of kidney stone.</td>
</tr>
<tr>
<td>Park et al. (15)</td>
<td>2009</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>45 patients</td>
<td>Increased urinary oxalate and calcium oxalate supersaturation. Decreased urinary citrate and total urinary volume.</td>
</tr>
<tr>
<td>Penniston et al. (20)</td>
<td>2009</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>39 patients</td>
<td>Decreased urinary volume in RYGB and gastric banding. Decreased urinary calcium in RYGB. Decreased urinary citrate in 14 RYGB patients and 1 gastric binding patient. Increased urinary oxalate in RYGB.</td>
</tr>
<tr>
<td>Dufey et al. (16)</td>
<td>2010</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>21 patients</td>
<td>Increased urinary oxalate excretion. <em>De novo</em> hyperoxaluria. Increased hypocitraturia.</td>
</tr>
<tr>
<td>Reis et al. (24)</td>
<td>2010</td>
<td>Prospective study</td>
<td>Gastric bypass</td>
<td>20 patients 20 cohorts</td>
<td>In operated group: Increased International Index of Erectile Function score, total testosterone, and follicle-stimulating hormones. Decreased prolactin level.</td>
</tr>
<tr>
<td>Kumar et al. (17)</td>
<td>2011</td>
<td>Prospective study</td>
<td>RYGB 2 biliopancreatic diversion-duodenal switch</td>
<td>11 patients</td>
<td>Increased urine oxalate excretion. Increased plasma oxalate and urine calcium oxalate supersaturation. Increased fecal fat excretion. Decreased total urine volume.</td>
</tr>
<tr>
<td>Valezi et al. (19)</td>
<td>2013</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>151 patients</td>
<td>Increased urinary oxalate. Increased urinary uric acid. Decreased urinary volume.</td>
</tr>
<tr>
<td>Rosenblatt et al. (28)</td>
<td>2013</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>23 patients 14 obese controls 14 lean controls</td>
<td>In operated group: Improved erectile dysfunction and overall satisfaction.</td>
</tr>
<tr>
<td>Agrawal et al. (18)</td>
<td>2014</td>
<td>Prospective study</td>
<td>RYGB</td>
<td>11 patients</td>
<td>Increased urinary oxalate. Decreased citrate. Decreased urine volume.</td>
</tr>
</tbody>
</table>
Bariatric surgery effects

Lieske et al. (12) 2015 Prospective study RYGB 591 patients vs. 762 controls
105 Mal-absorptive procedure
56 restrictive
7 other

In operated group: Risk of stones.

Sarwer et al. (25) 2015 Prospective study RYGB 32 patients
Increased total testosterone and sex hormone binding globulin.

Goiten et al. (26) 2015 Prospective study 36 laparoscopic sleeve gastrectomy
48 patients
Improved general satisfaction, desire and erection.

El Bardisi et al. (27) 2016 Prospective study SG 46 patients
Increased serum testosterone.

Samavat et al. (23) 2017 Prospective study 23 RYGB 23 patients
Increased gonadotropins, total testosterone, sex-hormone-binding-globulin and calculated free testosterone.
Decreased estradiol.
Increased semen volume and viability.
Improved progression and total motility and total sperm number.
In both groups: Worsened sperm morphology.

Maalouf et al. (22) 2010 Cross-sectional study RYGB 19 patients
Increased urine oxalate.
Decreased urine citrate.
Decreased urine calcium.

di Frega et al. (11) 2005 Case reports RYGB 6 patients
Non-obstructive azoospermia.
Spermatogenesis arrest.

Sermondade et al. (10) 2012 Case reports 1 SG 2 RYGB 3 patients
Extreme oligoasthenoteratozoospermia.
No azoospermia.

Calcium oxalate stones are more common after bariatric surgery. In a comorbidity-matched study of 762 patients who underwent surgery vs. 759 controls (mean age = 45 years), patients with history of stone were more likely to form stones after surgery (p<0.001) (12). Urine oxalate excretion increased after bariatric surgery (<8 months vs. >8 months, p<0.001) in 55 patients with follow-up stones, in 248 patients without follow-up stones and in 20 obese controls with follow-up stones (12). Moreover, mal-absorptive bariatric surgery causes hyperoxaluria by the absorption of fatty acids and/or bile salts followed by the saponification of calcium ions and fat-soluble vitamins (9). This saponification leads to decreased calcium in the intestinal lumen, decreased calcium-oxalate as well as increased free oxalate in the small and large intestine (9). By this way, dietary oxalate...
becomes available for absorption by the gut and excretion by the kidneys (20). Another possible mechanism for the cause of hyperoxaluria is the colonization of bowel bacteria called *Oxalobacter formigenes* that metabolize intestinal oxalate after surgery (19). In an animal study, 16 diet induced obese rats underwent sham surgery as controls and 19 RYGB rats were introduced to a normal calcium, high fat (40%) diet (with or without 1.5% potassium oxalate) for five weeks and then given a normal (10%) fat diet for two weeks (21). RYGB rats had eightfold higher fecal fat excretion (p<0.001), heavier stools (p=0.02) and fivefold increase in urine oxalate excretion (p<0.001) (21).

Another reason for nephrolithiasis is hypocitraturia, which is less common than hyperoxaluria (8). Citrate is the dissociated anion of citric acid that is utilized due to acidosis (8). This acidosis increases renal citrate reabsorption and reduces excretion in urine (8). It is known to inhibit calcium oxalate and calcium phosphate precipitation through formation of soluble complexes with calcium (8). Prospective studies with non-stone formers had decreased urinary citrate, calcium and total urine volume in 45 patients (15), decreased urinary citrate excretion in 21 patients (16) and decreased urine volume and decreased citrate volume in 13 patients (18) after RYGB. A study including 151 patients post RYGB showed that urinary volume (1310 vs. 930mL, p<0.001), citrate (268 vs. 170 mg, p<0.001) and calcium (195 vs. 105 mg, p<0.001) decreased significantly postoperatively (preoperative vs. postoperative, respectively) (19). In a retrospective study among 39 non-stone formers (28 females and 11 males, mean age = 51.2 years), 52% of RYGB patients had urinary citrate value of <370 mg/day vs. 9% of patients with gastric band but both had decreased urine volume (20). Another retrospective study had similar results in 38 patients wherein around 50% had lower urinary citrate levels (22). A previously mentioned study that included 55 patients with follow-up stones, 248 patients without follow-up stones and 20 obese controls with follow-up stones showed that urine citrate was lower in the group with stones vs. the group without stones (p<0.001) (12).

### Infertility and Erectile Function

There is scarce data about the effect of bariatric surgery on fertility and sperm production (6), but rising evidence has shown an association between bariatric surgery and subfertility (10). It has been proposed that excess bodyweight

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### Table 2 - Animal studies about changes in urinary profile after bariatric surgery.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study type</th>
<th>Surgery type</th>
<th>Sample size</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canales et al. (21)</td>
<td>2013</td>
<td>Prospective</td>
<td>RYGB</td>
<td>19 rats/16 controls</td>
<td>In operated group: Increased urinary volume. Increased urine pH. Increased urine oxalate excretion.</td>
</tr>
<tr>
<td>Choi et al. (29)</td>
<td>2014</td>
<td>Prospective</td>
<td>Gastric bypass</td>
<td>15 subject rats/10 control rats</td>
<td>In operated group: Increased intracavernous pressure/mean arterial pressure ratio. Increased cavernosum smooth muscle/collagen ratio. Increased endothelial nitric oxide synthase and neuronal nitric oxide synthase. Decreased expression of Rho kinase and of 8-hydroxy-2-deoxyguanosine levels.</td>
</tr>
</tbody>
</table>
affects sperm production, but it is still not explained if weight loss through operation can reverse this effect (10). Multiple case reports have shown that bariatric surgery affects fertility: six patients (mean age=38 years) with a previous child who underwent RYGB presented with secondary infertility/azoospermia after surgery (11). These patients with azoospermia who had testicular biopsy showed spermatogenesis arrest at the spermatogonium stage (11). In another study, three patients had worsened semen parameters during the first year post RYGB such as oligoasthenoteratozoospermia, but none had azoospermia (10). A prospective study on 31 patients (23 RYGB and 8 controls) evaluated seminal parameters six months post-surgery (23). There was a statistically significant increase in gonadotropins (follicle-stimulating hormone and luteinizing hormone), total testosterone, sex-hormone-binding-globulin, calculated free testosterone, increase in semen volume and semen viability and decrease in estradiol (23). There are several explanations for subfertility post-surgery. Undernutrition and disruption of normal pulsatile gonadotrophin-releasing hormone secretion, nutritional deficiencies and release of such liposoluble toxic substances can negatively impact spermatogenesis (10). Other mechanisms include insufficient absorption of nutrients needed for spermatogenesis (11). However, the reversibility of spermatogenesis might indicate that correction of nutritional deficiencies and removal of exposure to toxic substances may be helpful (10).

Many studies have investigated the effect of bariatric surgery on erectile function. A prospective randomized controlled long-term trial compared surgical and non-surgical weight loss impact on erectile function and sexual hormones in morbidly obese men (10 patients and 10 controls) (24). The International Index of Erectile Function (IIEF), total testosterone and free testosterone increased significantly in the intervention group (p=0.0224, p=0.0043 and p=0.0149, respectively) two years after the procedure (24). A prospective study on 32 patients who underwent RYGB and undertook the IIEF showed that these patients had significant increase in total testosterone and sex hormone binding globulin (p<0.001) during the fourth year post operation (25). Similarly, a study targeting 14 males who completed the questionnaire also showed that the male brief sexual function inventory increased after six months from surgery but failed to reach significance (26). A prospective study including 46 patients who underwent sleeve gastrectomy and had semen analysis after a year showed that serum testosterone and sperm concentration increased significantly (p<0.001) in patients with azoospermia (p=0.02) and oligospermia (p=0.001) (27). A prospective study on 51 patients (23 RYGB, 14 overweight and obese controls and 14 lean controls) showed that erectile functions scores were better than those of the obese controls (p=0.015) but lower than those of the lean controls (p=0.028) (28). A study randomized 10 rats into control group and 15 into bypass surgery and showed that the operated group had an increase in the ratio of intracavernosal pressure over mean arterial pressure (p=0.021) which was used to determine erectile function. The authors suggested that glucose homeostasis recovery causes metabolic and biochemical restoration (29). This restoration leads to functional recovery in the corpus cavernosum and results in improved erectile dysfunction (29).

The prevalence of obesity and related morbidities has recently risen across the globe (24). Bariatric surgery has been shown to be favorable in this case (26). However, complications have been observed over the past few years as result of bariatric surgery specifically RGYB (9, 12). The effects of weight loss through bariatric surgery on fertility and erectile dysfunction have not been studied well and results are still controversial. Limitations of the above reviewed studies include low response rate (20, 26) and loss to follow-up and patient burden for collecting tests such as urine specimen and semen samples (20). Some studies did not have randomization (12), while some had very small sample sizes (10, 11, 29) which does not help in stratifying data according to many important factors especially age (26). As for the investigations on sexual behavior to assess the effect of surgery on subfertility, some assessments that were utilized did not include quality of life and relationship satisfaction (25), while others may have had selection bias (26). Another important element to consider is that the underlying mechanism for sexual dysfunction,
infertility and nephrolithiasis related to obesity is multifactorial (26). This may lead to higher incidence of stones and decline in sexual function after bariatric surgery. Finally, it is important to note the possibility of relapsing obesity and recurrence of co-morbidities post-surgery (28).

CONCLUSIONS

Bariatric surgery has proven to be effective and beneficial in the management of obesity (19) and obesity related complications (1, 5, 6). However, the severe decrease in the absorption of nutrients after RYGB may cause short-term and long-term problems such as infertility as depicted by some studies (10, 11). Further elucidation of the pathophysiological mechanism for stone formation and negative effect on fertility and spermatogenesis post-surgery remains an active domain for research (8, 11) in this area.

Urologists should take into account the risk of calcium oxalate stone formation post RYGB in order to provide preventive measures such as increased fluid intake and appropriate dietary measures to protect against renal stone formation (4). A metabolic assessment for nephrolithiasis is suggested for patients who undergo RYGB (19). Additionally, preoperative assessment of patients’ nutritional status and micronutrient supplementation should be taken into account (1). Prospective studies are warranted to confirm the possible benefit of restrictive bariatric procedures on the decreased risk of stone formation in addition to the effect on fertility and erectile function.

CONFLICT OF INTEREST

None declared.

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Diagnostic accuracy of multiparametric magnetic resonance imaging in detecting extracapsular extension in intermediate and high-risk prostate cancer

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ABSTRACT

Objectives: To evaluate the diagnostic performance of preoperative multiparametric magnetic resonance imaging (mp-MRI) as a predictor of extracapsular extension (ECE) and unfavorable Gleason score (GS) in patients with intermediate and high-risk prostate cancer (PCa).

Materials and Methods: Patients with clinically localized PCa who underwent radical prostatectomy (RP) and had preoperative mp-MRI between May-2011 and December-2013. Mp-MRI was evaluated according to the European Society of Urogenital Radiology MRI prostate guidelines by two different readers. Histopathological RP results were the standard reference.

Results: 79 patients were included; mean age was 61 and median preoperative prostate-specific antigen (PSA) 7.0. On MRI, 28% patients had ECE evidenced in the mp-MRI, 5% seminal vesicle invasion (SVI) and 4% lymph node involvement (LNI). At RP, 39.2% had ECE, 26.6% SVI and 12.8% LNI. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of mp-MRI for ECE were 54.9%, 90.9%, 76%, 81% and 74.1% respectively; for SVI values were 19.1%, 100%, 77.3%, 100% and 76.1% respectively and for LNI 20%, 98.4%, 86.7%, 66.7% and 88.7%.

Conclusions: Major surgical decisions are made with digital rectal exam (DRE) and ultrasound studies before the use of Mp-MRI. This imaging study contributes to rule out gross extraprostatic extension (ECE, SVI, LNI) without competing with pathological studies. The specificity and NPV are reasonable to decide surgical approach. A highly experienced radiology team is needed to provide accurate estimations of tumor extension and aggressiveness.

INTRODUCTION

Risk stratification for localized PCa is a combination of multiple clinical and laboratory parameters, none of which includes an imaging test providing adequate anatomical detail. These parameters are used to classify patients into risk groups along with nomograms that predict outcomes such as pathological staging, biochemical recurrence, clinical progression and cancer specific survival. More than a third of patients are misclassified with clinical staging, PSA and
transrectal ultrasound-guided (TRUS) prostate biopsy (1). Recently, additional parameters such as MRI and the percentage of positive biopsy cores have been added into risk classification methods, both with promising results (2).

Traditionally, RP and radiotherapy have been considered the reference standard treatment for patients with localized PCa (3) both achieving long-term disease control. High rates of erectile dysfunction and incontinence are related to surgical techniques and difficult preservation of the neurovascular bundles. Therefore, accurate preoperative knowledge of tumor stage and possible ECE is crucial in achieving the best surgical, oncological and functional results (4).

Recent findings support the use of mp-MRI of the prostate, combining T2-weighted imaging with diffusion-weighted imaging (DWI) and perfusion imaging, as the most sensitive and specific imaging tool for different clinical scenarios in patients with PCa such as detection, staging, and follow-up (5-13). Nonetheless, its routine use is still a topic of debate given the high variability among studies regarding the diagnostic accuracy of mp-MRI in staging and prediction of ECE (14).

The aim of this study was to evaluate diagnostic accuracy of a 1.5 tesla mp-MRI in detecting ECE, SVI, LNI and unfavorable GS in patients with intermediate and high-risk PCa.

**MATERIALS AND METHODS**

After approval from our hospital review board and ethics committee, clinical records were reviewed retrospectively. Patients with clinically localized PCa, who underwent RP and extended lymph node dissection between May 1st 2011 and December 31st 2013 at our institution, and had preoperative mp-MRI, were identified. Inclusion criteria comprised intermediate or high-risk cancer patients as defined by D’Amico classification (intermediate risk: clinical stage T2b or PSA levels between 10.1 and 20ng/mL or GS 7; high risk: clinical stage ≥T2c or PSA levels >20ng/mL or GS 8-10). Finally, the diagnostic accuracy of mp-MRI in detecting ECE, SVI, LNI and unfavorable GS (equal or greater than 8) was analyzed.

**Multiparametric MRI and Image analysis**

Preoperative mp-MRI was performed with a 1.5 tesla Siemens system. Patient should wait 6 weeks after biopsy for MRI study; no rectal preparation nor endorectal coil were used in any patient. Studies included T2-weighted imaging, dynamic contrast-enhanced imaging and diffusion-weighted imaging. Mp-MRI results were assessed and reported according to the European Society of Urogenital Radiology (ESUR) MRI prostate guidelines from 2012 by two different radiologists with different years of experience (14 and 8 years of experience). Readers knew diagnosis and initial PSA level but were blinded to details of histopathological report. They adopted one of the following image signs to subjectively classify ECE: 1) bulging of prostatic contour; 2) irregularity of prostatic contour; 3) neurovascular bundle thickening; 4) loss or discontinuity of prostatic contour line; 5) measurable extra-capsular disease. The sum of three of the previously mentioned signs were considered positive for ECE. Tumor contact length (TCL) to the prostate contour was also measured and a 12mm-threshold was used as an additional sign of ECE and independently analyzed as a different variable. For SVI, the subjective image signs adopted were: 1) expansion; 2) low T2 signal; 3) filling in of angle; 4) enhancement and restricted diffusion. The sum of two signs were considered positive for SVI. For LNI, size criteria were used and a short axis >10mm was considered positive (15). For case examples, see Figure-1 and Figure-2. Apparent diffusion coefficient (ADC) is the measure of the magnitude of diffusion of water molecules within tissue. These values were obtained by positioning the region of interest (ROI) in the index lesion (defined as the largest lesion) and a threshold of less than 0.87x10-3mm2/s was considered indicative of unfavorable GS.

**Histopathological evaluation**

RP specimens were macroscopically marked with ink and fixed in formalin. The specimen was serially sectioned at 3mm thickness. Perpendicular cuts were done for the first portion of the apex and base, the remaining prostate was then cut in the sagittal plane and, posteriorly, in quadrants from apex to base. Slices were further cut into
microscopic sections of 3–5μm and stained with Haematoxylin and Eosin. ECE was defined as tumor cell growth into the extraprostatic tissue and subclassified as: 1) focal ECE when involving only a few glands or a tumor involving less than one high power (40X) field in one or two sections or 2) established ECE when a more extensive spread was seen beyond the prostatic edge (16). SVI was defined as tumor infiltration of the muscular wall of the seminal vesicles. Lymph nodes were processed as a whole with posterior differentiation of nodules from fat. The pathological T-stage (pT) was defined according to the TNM classification.

Statistical analysis

Socio-demographic characteristics were described. A descriptive analysis was conducted and the measures of central trend and variability were reported. Median or mean for continuous variables and absolute or relative frequencies for categorical variables were calculated. Contingency tables (using most experienced radiologist data) were used to calculate overall diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value of mp-MRI in predicting ECE, SVI, LNI and GS greater or equal to 8. Finally, a receiver operating characteristic curve (ROC curve) with an area under the curve (AUC) values were generated to analyze predictive accuracy of ADC in detecting unfavorable GS, and Spearman correlation was used. Inter-reader reliability was calculated using kappa statistics (0–0.2 none, 0.21–0.39 minimal, 0.4–0.59 weak, 0.6–0.79 moderate, 0.8–0.9 strong, above 0.9 almost perfect). A p-value below 0.05 was considered significant. The analysis was performed using STATA 13.1 software.

RESULTS

Seventy-nine patients were eligible for the study; patient and disease characteristics are
shown in Table-1. 36.7% of the patients had a PSA >10ng/mL. Mp-MRI quality was adequate for interpretation; seven subjects had more than 50% hemorrhage image changes from prior biopsy without significant implications for reading. 21 (28%) patients had ECE evidenced by the mp-MRI, 4 (5.3%) patients had SVI and 3 (4%) patients had LNI. RP specimen analysis reported 31 (39.2%) patients with ECE, 21 (37.5%) patients with SVI and 10 (12.9%) with LNI. Measurement of diagnostic agreement between both radiologists for ECE, SVI and LNI reported kappa values of 0.287, 0.5726

Table 1 - Patient and disease characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age (years)*</td>
<td>61.1 (39-78, SD±7.50)</td>
</tr>
<tr>
<td>PSA Level (ng/mL)^</td>
<td>7.0 (0.02-31, SD±7.25)</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>57 (74.0%)</td>
</tr>
<tr>
<td>T2a</td>
<td>17 (22.1%)</td>
</tr>
<tr>
<td>T2b</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>T3a</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>D’Amico classification</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>51 (65.4%)</td>
</tr>
<tr>
<td>High risk</td>
<td>27 (34.6%)</td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>46 (58.2%)</td>
</tr>
<tr>
<td>pT3a</td>
<td>13 (16.5%)</td>
</tr>
<tr>
<td>pT3b</td>
<td>20 (25.3%)</td>
</tr>
<tr>
<td>Biopsy Gleason Score</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6 (7.7%)</td>
</tr>
<tr>
<td>7</td>
<td>46 (59%)</td>
</tr>
<tr>
<td>8</td>
<td>20 (25.6%)</td>
</tr>
<tr>
<td>9</td>
<td>5 (6.4%)</td>
</tr>
<tr>
<td>10</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Pathology Gleason Score</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>7</td>
<td>53 (67.1%)</td>
</tr>
<tr>
<td>8</td>
<td>14 (17.7%)</td>
</tr>
<tr>
<td>9</td>
<td>10 (12.7%)</td>
</tr>
</tbody>
</table>

*mean and (range, standard deviation); ^median and (range, standard deviation); npatient number
and 0.380 respectively, demonstrating minimal and weak agreement when two radiologists with different years of experience assessed all three variables.

Mp-MRI findings were compared to final pathology. Results of accuracy, sensitivity, specificity, PPV and NPV of mp-MRI in detecting ECE, SVI and LNI in comparison to histopathological results are summarized in Table-2. AUC for ECE was 0.7 (95% CI 0.6-0.8), for SVI 0.6 (95% CI 0.5-0.7) and for LNI 0.6 (CI 0.5-0.7) (Figure-3).

When focal and established ECE were considered separately, accuracy, sensitivity, specificity, PPV and NPV were 73%, 53.9% (95% CI 42.6-65.1), 77.4% (95% CI 68-86.9%), 33.3% (95% CI 22.7-44), 88.9% (95% CI 81.8-96) for focal ECE, and 73%, 52.6% (95% CI 41.3-63.9), 80.4% (95% CI 71.3-89.4), 47.6% (95% CI 36.3-58.9), 83.3% (95% CI 74.9-91.8) for established ECE.

With mp-MRI tumor contact length (TCL) threshold of 12mm for the diagnosis of ECE, we found accuracy, sensitivity, specificity, PPV and NPV values of 52.7%, 69.2% (95% CI 58.7-79.8), 49.2% (95% CI 37.8-60.6), 22.5% (95% CI 13-32) and 82.4% (95% CI 80.9-95.6) for focal ECE, and of 55.4 %, 68.4% (95% CI 57.8-79), 50.9% (95% CI 39.5-43.1), 32.5% (95% CI 21.8-43.2) and 82.4% (95% CI 73.7-91) for established ECE, respectively.

Finally, when ADC values were compared to pathological results, mp-MRI accuracy, sensitivity, specificity, PPV and NPV in predicting unfavorable GS were 69.3%, 13% (95% CI 5.4-20.7), 94.2% (95% CI 88.9-99.5), 50% (95% CI 38.7-61.3) and 71% (95% CI 60.8-81.3), respectively. When

### Table 2 - Comparison of operative characteristics of mp-MRI in high risk PCa for ECE, SVI, LNI compared to pathology results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (n)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeong et al. (13)^</td>
<td>922</td>
<td>43</td>
<td>84</td>
<td>61</td>
<td>79</td>
<td>52</td>
</tr>
<tr>
<td>ECE</td>
<td></td>
<td>35</td>
<td>94</td>
<td>81</td>
<td>62</td>
<td>83</td>
</tr>
<tr>
<td>SVI</td>
<td></td>
<td>14</td>
<td>97</td>
<td>92</td>
<td>23</td>
<td>95</td>
</tr>
<tr>
<td>LNI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lista et al. (24)*</td>
<td>85</td>
<td>58</td>
<td>98</td>
<td>-</td>
<td>95</td>
<td>75</td>
</tr>
<tr>
<td>ECE</td>
<td></td>
<td>75</td>
<td>96</td>
<td>-</td>
<td>80</td>
<td>94</td>
</tr>
<tr>
<td>SVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinaquy et al. (25)*</td>
<td>47</td>
<td>72</td>
<td>77</td>
<td>-</td>
<td>86</td>
<td>59</td>
</tr>
<tr>
<td>ECE</td>
<td></td>
<td>73</td>
<td>95</td>
<td>-</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td>SVI</td>
<td></td>
<td>33</td>
<td>91</td>
<td>-</td>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>LNI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerantola et al. (26)T</td>
<td>60</td>
<td>35</td>
<td>90</td>
<td>62</td>
<td>79</td>
<td>57</td>
</tr>
<tr>
<td>ECE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boesen et al. (4)T</td>
<td>87</td>
<td>74</td>
<td>88</td>
<td>83</td>
<td>77</td>
<td>86</td>
</tr>
<tr>
<td>ECE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somford et al. (16)T</td>
<td>183</td>
<td>64.9</td>
<td>72.7</td>
<td>-</td>
<td>88.9</td>
<td>38.1</td>
</tr>
<tr>
<td>ECE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1.5T MRI scanner; T 3.0T MRI scanner; ^ Overall using both 1.5T and 3.0T MRI scanner
ADC values were considered as a continuous variable, AUC was 0.622 (95% CI 0.5-0.8) (Figure-1) and the Spearman’s Rho was -0.34 (p<0.001).

**DISCUSSION**

Identification of occult ECE, SVI and LNI is of critical importance for prognosis and treatment selection of patients with intermediate and high-risk disease PCa. Clinical staging in this study was predominantly T1c and T2a (74% and 22.1%) the remaining being classified as T2b and T3a. Pathological staging reported pT2 in 58.2% of the cases, pT3a in 16.5% and pT3b in 25.3%. Pathological ECE was reported on 39.2% of the cases and 30.4% had an unfavorable GS (≥8). Understaging is frequent with only clinical assessment (15), therefore, it underscores the importance of a correct staging and identification of intermediate and high-risk patient preoperatively, which may lead to improved decision-making regarding treatment and surgical approach.

Operative characteristics of mp-MRI for the detection of ECE, SVI and LNI, differ among published studies and are highly influenced by the use of endorectal coil (er), MRI parameters and clinical interpretation (16). Recent reports are focused on improving er-MRI imaging technology and functional imaging techniques (dynamic contrast enhancement and diffusion weighted imaging) to optimize accuracy in staging suspicious lesions (17). These advances lead to the use of combined mp-MRI with anatomic T2-weighted imaging, with promising results for PCa detection and extension. One meta-analysis (18) determined diagnostic accuracy of mp-MRI for PCa detection using anatomic T2-weighted imaging combined with two functional techniques (DWI and DCE-MRI). Pooled data of seven studies (526 patients) showed sensitivity of 0.74 (95% CI, 0.66-0.81),
specificity of 0.88 (95% CI, 0.82-0.92) for PCa detection, with NPVs ranging from 0.65 to 0.94.

Our results are consistent with those reported in the literature. For ECE detection, mp-MRI has a reported sensitivity between 35-62.5% and specificity of 89-92% (Table-2). Our study showed sensitivity of 55% and specificity of 91%, both within the range of the literature. Feng et al. (15) sought to evaluate mp-MRI ability to detect focal or established ECE reported by pathology. When considered separately, mp-MRI had a low performance in identifying focal ECE, with a sensitivity of 14.3% and a PPV of 5.6%. However, mp-MRI was accurate in predicting established ECE, with a sensitivity of 73% and a PPV of 57%. Our study reported a sensitivity of 53% and a PPV of 48% for established ECE, and for focal ECE performance was poor. Mp-MRI is unable to identify and localize focal ECE, which accounts for a large majority of the cases (18). Nerve-sparing RP requires of mp-MRI to provide a high NPV in detecting ECE. Our results for SVI and LNI are also comparable to literature (Table-2). SVI detection has been reported with PPVs of 62% to 95% and NPVs of 73% to 83%. Sensitivity and specificity for LNI is between 14-33% and 91-97%, respectively (19).

Measurement of diagnostic agreement between radiologists in our study for ECE, SVI and LNI demonstrated minimal and weak. It has been demonstrated in literature that inter-reader reproducibility tend to be higher for relatively experienced readers. This can be explained due to study complexity, different reading scales used such as the PI-RADS of Likert scale and interpretation sensibility may be affected by lesion location, volume and tumor aggressiveness (20, 21).

Furthermore, TCL parameter has also shown correlation with pathologically confirmed microscopic ECE. Baco et al. (22) documented accuracy of 82%, 79% sensitivity, 85% specificity, 76% PPV and 88% NPV when using a 20mm TCL threshold. Our study evaluated the differences in predictive values by using a 12mm threshold when comparing established and focal microscopic ECE, both with acceptable NPVs when evaluating these parameters. Other studies have concluded that a higher length of contact between tumor margin and prostatic capsule is associated with an increased risk of ECE.

In general, literature concludes that mp-MRI has a fair performance capacity for predicting unfavorable GS. Hegde et al. (12) conducted a retrospective study with 118 patients, demonstrating that ECE or SVI findings on mp-MRI are associated with a higher risk of identifying previously undetected GS 8-10 disease. In our study, mp-MRI evidenced low power either to confirm or rule out unfavorable GS. Other studies have evidenced that a high percentage of patients have GS ≥7 at non-index tumors and mp-MRI has low power for the detection of these lesions (23). Also, the diffusion coefficient ADC allows for quantitative and qualitative assessment of tumor aggressiveness and has positive correlation with GS (24). In this study, ADC as binary variable when compared to GS ≥8 had high specificity and NPV, low AUC and its values are inversely correspondent to GS as reported with Spearman rho, although it shows a low negative correlation. Mp-MRI has shown to be useful in identifying PCa extension and especially in ruling in locoregional extension.

The limitation of this study is its retrospective nature and small sample size leading to large confidence intervals. Also, operative characteristics depend on how the presence of ECE, SVI and LNI are defined. For our study, the presence of locally advanced disease consisted of binary variables (yes or no), and the data would be improved by using ordinal scales such as prostate imaging reporting and a standardized data system (PIRADS) for extension evaluation. According to the magnetic field strength, the 3T magnet increases signal to noise ratio therefore increases resolution. However, both 1.5T and 3.0T can provide accurate and reliable diagnostic exam when technical parameters are properly used (23). Although members of the PIRADS steering committee prefer the use of 3T, 1.5T magnets are more widely available and our study reflects the practice of most of the devices currently installed worldwide. Finally, both radiologists had a 10-year experience difference which makes data heterogeneous and consequently the low inter-rater reliability.
CONCLUSIONS

Major surgical decisions are made with DRE and ultrasound studies before the use of Mp-MRI. This imaging study contributes to rule out gross extraprostatic extension (ECE, SVI, LNI) without competing with pathological studies. The specificity and NPV are reasonable to decide surgical approach. A highly experienced radiology team is needed to provide accurate estimations of tumor extension and aggressiveness. Moreover, it is necessary to carry out prospective and multicenter studies in order to achieve higher consensus regarding MRI use in PCa assessment in developing countries.

ABBREVIATIONS

RP = Radical prostatectomy
PSA = Prostate specific antigen
Pca = Prostate cancer
GS = Gleason score
TRUS = Transrectal ultrasound-guided MRI = Magnetic resonance imaging
TCL = Tumor contact length
AUC = Area under the curve
cT = Clinical tumor stage
Mp-MRI = Multiparametric MRI
PIRADS = Prostate imaging reporting and data system
T2W = T2-weighted
DWI = Diffusion-weighted imaging
DCE-MRI = Dynamic contrast-enhanced MRI
ADC = Apparent diffusion coefficient
DCE = Dynamic contrast-enhanced
ECE = Extracapsular extension
SVI = Seminal vesicle invasion
LNI = Lymph node involvement

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CONFLICT OF INTEREST

None declared.

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Changes observed in prostate biopsy practices in an inner city hospital with a high risk patient population following the 2012 USPSTF PSA screening recommendations

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ABSTRACT

Introduction: We compared characteristics of patients undergoing prostate biopsy in a high-risk inner city population before and after the 2012 USPSTF recommendation against PSA-based prostate cancer screening to determine its effect on prostate biopsy practices.

Materials and Methods: This was a retrospective study including patients who received biopsies after an abnormal PSA measurement from October 2008-December 2015. Patients with previously diagnosed prostate cancer were excluded. Chi-square tests of independence, two sample t-tests, Mann-Whitney U tests, and Fisher’s exact tests were performed.

Results: There were 202 and 208 patients in the pre-USPSTF and post-USPSTF recommendation cohorts, respectively. The post-USPSTF cohort had higher median PSA (7.8 versus 7.1ng/mL, p=0.05), greater proportion of patients who were black (96.6% versus 90.5%, p=0.01), and greater percentage of biopsy cores positive for disease (58% versus 29.5%, p<0.001). Multivariable analysis supported that the increase in PSA was independent of the increase in the proportion of patients who were black. The proportion of patients who were classified as D’Amico intermediate and high-risk disease increased in the post-USPSTF cohort and approached statistical significance (70.1% versus 58.8%, p=0.12).

Conclusions: Our study suggests that the USPSTF recommendations may have led to an increase in pre-biopsy PSA as well as greater volume of disease. Also, a greater proportion of patients were being classified with intermediate or high risk disease. While the clinical significance of these findings is unknown, what the data suggests is somewhat troubling. Future research should further examine these changes in a larger cohort as well as resultant long-term outcomes.

INTRODUCTION

In May 2012, the United States Preventative Services Task Force (USPSTF) issued a recommendation against prostate specific antigen (PSA)-based prostate cancer screening for men in the general United States population (1). This recommendation was rooted in two studies, the Prostate,
Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC), neither of which reported a significant African American or Afro-Caribbean cohort (2, 3). The USPSTF acknowledges that the results of PLCO and ERSPC are difficult to generalize to the black population, and yields in suggesting that this high-risk population be evaluated under separate guidelines. Similarly, the National Comprehensive Cancer Network (NCCN) acknowledges that African Americans “have a higher incidence of prostate cancer, increased prostate cancer mortality, and earlier age of diagnosis compared to Caucasian-American men. However, the effects of earlier or more intensive screening on cancer outcomes and on screening-related harms in African-American men remain unclear” (4). It is uncertain how to best apply screening recommendations in a high-risk population such that the harms of overscreening are balanced with the benefits of early detection of clinically significant disease.

Given the increased risk for disease as well as predisposition for more aggressive disease in African Americans (4-8), we hypothesize that prostate biopsy practices in an inner-city hospital serving a predominately black population were not changed in response to the USPSTF guidelines. Thus, we sought to characterize prostate biopsy patterns in a single academic institution where the patients mostly identify as Caribbean, Caribbean American, African, and African American.

MATERIALS AND METHODS

After obtaining IRB approval (#793946-1) we performed a retrospective chart review of patients who received initial prostate biopsies at a single institution from October 27, 2008 to December 15, 2015. All patients received a 12-core systematic transrectal ultrasound guided biopsy. The primary population was divided into patients biopsied prior to May 22, 2012 and patients biopsied on or after that date. History of prostate cancer and absence of data on age, PSA, race, specialty of provider that initiated PSA screening, or results of prostate biopsy were excluded. We collected age, race, PSA prior to biopsy, provider specialty who initiated screening, and biopsy results (Gleason score, number of cores positive). PSA values were unadjusted for finasteride use. Digit rectal exam findings were unavailable for a significant portion of our population, and so were excluded from our analysis.

Chi-square tests of independence, two sample t-tests, and Mann-Whitney U tests were performed to compare patient demographic and clinical factors in both cohorts. Analysis included age, race, PSA level, whether a primary care physician (PCP) or urologist initiated PSA screening, and diagnosis of biopsy. Subsequently, a conditional multivariable logistic regression model was built to characterize the independent effect of each factor on undergoing a biopsy in the pre-recommendation period (group-1) versus the post-recommendation period (group-2). The model estimated odds ratios and 95% confidence intervals for each predictive factor. Standard regression assumptions were verified graphically. More specifically, plots were used to confirm that independent variables were linear with the log odds; variable transformations were not necessary. Regarding missing data, 1% of patients had a missing data point that was used for analysis. Imputation of missing data was achieved using multivariate imputation by chained equations (9).

Among patients who had a positive biopsy, the percent cores positive, Gleason score, and D’Amico Risk Group (low vs. intermediate vs. high) were compared between the two time periods using a chi-square test of independence, Mann-Whitney U test, and Fisher’s exact test. All analyses were conducted using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall, 202 patients underwent prostate biopsy prior to the USPSTF recommendation (group-1) and 208 patients underwent prostate biopsy after the USPSTF recommendation (group-2). Of note, MRI and fusion biopsy are not used in the diagnosis of prostate cancer in this institution, and as so these are unlikely to serve as a confounder. In univariate analysis, there was no
significant difference in the mean age, whether a PCP or urologist initiated PSA-based screening, or the percentage of positive biopsies between groups 1 and 2 (Table-1). Group-2 had a significantly greater proportion of patients who were of African-American descent (96.6% versus 90.5%, \( p=0.01 \)) (Table-1). Yet, the absolute difference in the number of African Americans biopsied is small (\( n=199 \) versus \( n=181 \)) and has limited clinical significance. Additionally, median PSA was significantly greater in group-2 compared to group-1 (7.8 nanograms/milliliter (ng/mL) vs. 7.1 ng/mL, \( p=0.05 \)) (Table-1). These results remained statistically significant in multivariable analysis (Table-2). Patients biopsied in the post-USPSTF period were 2.14 times more likely to be of African-American descent as compared to patients biopsied in the pre-USPSTF period (OR=2.14, 95% CI=1.05, 3.55). For every 1ng/mL increase in PSA in the post-USPSTF group, the odds of being biopsied increased 67% (OR=1.67, 95% CI=1.02, 2.38) relative to patients biopsied in the pre-USPSTF period.

In a subset analysis, characteristics were compared among patients who had a positive biopsy in the pre and post-USPSTF period (\( n=107 \) and \( n=100 \), respectively) (Table-3). Our data showed that the median percentage of positive cores in group-2 was significantly greater than in group-1 (58% versus 29.5%, \( p<0.001 \)). Though the analysis is underpowered, the data suggests that patients in group-2 exhibited worse D’Amico risk classification relative to patients in group-1. In the pre-USPSTF cohort, 44.1% and 58.8% of patients had low-risk and clinically significant disease respectively. In comparison, the post-USPSTF cohort exhibited 29.9% and 70.1% of patients with low-risk and clinically significant disease respectively.

Table 1 - Characteristics of All Patients, Pre and Post USPSTF Guidelines.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-USPSTF</th>
<th>Post-USPSTF</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±sd)</td>
<td>64.6±8.3</td>
<td>64.1±7.7</td>
<td>0.51</td>
</tr>
<tr>
<td>PSA Level (Median , IQR)*</td>
<td>7.1 (8.8)</td>
<td>7.8 (9.1)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Black</td>
<td>181 (90.5%)</td>
<td>199 (96.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21 (9.5%)</td>
<td>9 (3.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Decision to Screen PSA</strong></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>PCP</td>
<td>82 (41.2%)</td>
<td>90 (45.0%)</td>
<td></td>
</tr>
<tr>
<td>Urologist</td>
<td>117 (58.8%)</td>
<td>110 (55.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Positive Biopsies</strong></td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>No</td>
<td>95 (47.0%)</td>
<td>106 (51.5%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107 (53%)</td>
<td>100 (48.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - Multivariable Analysis.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2.14 (1.05, 3.55)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>PSA Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 point increase</td>
<td>1.67 (1.02, 2.38)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
patients with low-risk and clinically significant disease, respectively (p=0.12).

**DISCUSSION**

The demographics of our study population lend insight on the effect of the USPSTF recommendation in a high-risk population. Previous literature has attempted to characterize the effect of the recommendation on screening and biopsy practices, but did so without a significant black population (10, 11). There is strong evidence to suggest that blacks are more likely to develop prostate cancer in their lifetime and that their disease tends to progress more quickly as well (6-8, 12, 13). Given these considerations, we sought to determine whether practice patterns have changed since May 2012.

In the study period following the publication of the recommendation, group-2 was significantly more likely to harbor a higher volume of disease, and was near-significantly more likely to harbor clinically significant D’Amico-classified intermediate or high-risk disease. Most strikingly, patients in group-2 with positive biopsies had almost double percentage of positive cores. This trend cannot be explained by the use of MRI or fusion guided biopsy as these technologies are not used at our institution. Similar results have been shown in the literature. Banerji et al. conducted a similar study, which evaluated 448 patients with prostate needle biopsies 30 months before and 310 patients with prostate needle biopsies 30 months after the USPSTF issued their recommendation. Their data showed that patients biopsied after the recommendations were more likely to have clinical T2b and T2c-T3a disease (adjusted p=0.012 and adjusted p=0.017, respectively). In addition, the post-USPSTF population was more likely to have D’Amico-classified high-risk prostate cancer (34% vs. 46%, adjusted p=0.027). Furthermore, the pre-USPSTF recommendation group was more likely to have a lower volume of disease: 22% of patients in the pre-recommendation group had less than 34% of biopsy cores showing cancer, whereas 29% of the post-recommendation group had less than 34% of biopsy cores showing cancer (unadjusted p=0.031) (10). Similar to our findings, their study suggests that since the USPSTF issued their recommendation, there has been an increase in the incidence of higher-risk and higher volume disease. Notably, the authors did not report on demographics and therefore it is difficult to confidently apply such findings to an innately high-risk population such as the one featured in our study.

There appears to be an interesting trend when considering the demographics of the two groups. Group-2 displayed an increase in the proportion of patients receiving a biopsy who were
black, despite comparable age and number of patients receiving biopsy in the two cohorts. There was also a significant increase in the median PSA of biopsied individuals in the post-USPSTF recommendation group. The mechanism of this difference may be at the level of PSA screening, with provider focus on the high-risk population, or at the level of biopsy, with providers having a higher PSA threshold for biopsy. Another possibility is that unrecognized cultural influences, such as increased awareness of prostate cancer in the black community, has resulted in patients taking a more proactive role in screening for prostate cancer, with more patients asking to undergo PSA screening. Alternatively, these findings may be explained by shifts in the ethnic distribution of our hospital’s catchment area over time. Of note, though the increase in proportion of black men amongst those undergoing prostate biopsy reached statistical significance, the increase in absolute number of black men undergoing prostate biopsy between the two groups was small (n=181 vs. n=199, pre-USPSTF recommendation group and post-USPSTF recommendation group respectively). Given the >90% black demographics in both groups, this significance and true mechanism of this finding remain unclear and require further research. In review, Perez et al. reported no significant differences between cohorts in the mean PSA and proportion of patients undergoing biopsy who were African American despite large differences in reported values (11). Perez et al. reported the mean PSA in the pre-USPSTF recommendation group as 7.7 ng/mL while the post-USPSTF recommendation group was 11ng/mL (p=0.31), and the proportion of patients who were African American in the pre-USPSTF recommendation group was 11.9 while in the post-USPSTF recommendation group was 18.8 (p=0.34). However, their study population was small, with 201 patients in the pre-USPSTF recommendation cohort and 212 in the post-USPSTF recommendation cohort. Nevertheless, the authors reported that on multivariable analysis, African Americans in the post-USPSTF cohort were nearly five times more likely to undergo biopsy when compared to African Americans in the pre-USPSTF cohort (OR 6.31, 95% CI 1.65-24.23; p=0.007) (11). The congruence of this data with ours is limited by the small African American cohort of their population. Regardless, there appears to be a focus on high-risk populations following the USPSTF recommendation.

Notably, there was no difference between the two groups in regards to the specialty of the provider who initiated PSA screening. As such, it is unlikely that recommendations from specialist groups such as the 2013 updated screening recommendations released by the American Urologic Association, would have had a major impact on screening practices. Prior to the USPSTF recommendation statement, slightly more patients received their initial PSA screening test from a urologist, which maintained true following the recommendation statement as well. This finding is somewhat expected, being that the USPSTF’s recommendation was issued to the general public and not specialty focused. The stance on PSA-based screening has always mixed throughout the medical field, thus it is unexpected that urology practices differ greatly from non-urologists.

Our results must be considered through the scope of our limitations. We conducted a retrospective study, which is inevitably confounded by selection bias. In addition, our sample size may have been too small to lend significance to some of the trends revealed in our analysis. In particular, the difference in the proportion of patients in each D’Amico risk group trended towards significance. However, given that we collected data from only approximately 100 patients in each group, the presence or absence of a true difference remains unclear. Furthermore, our study assessed biopsy frequency on the basis of total biopsies performed. This metric is influenced by several factors including hospital resources. The rate of biopsy for patients with elevated PSA would strengthen out conclusions and should be a point of further study. Additionally, we were unable to sub-stratify patients by nationality as this data was unavailable in our chart review. Thus, we could not perform nationality or region-specific analyses on our diverse population, which is primarily composed of people from various countries in the Caribbean region and Africa. Of note, we selected the date of USPSTF guideline publication to stratify our two groups. This does not take into
account a potential lag that may have occurred from the dissemination of the recommendations to their implementation. Despite these limitations, we feel that our study adds to the growing body of literature on the role of PSA screening and prostate biopsy in high-risk individuals, particularly black men.

We recommend further examination of practice patterns in order to determine whether the changes observed occurred due to provider selection of higher-risk patients for PSA screening or due to an increased PSA threshold to initiate biopsy. Additionally, we recommend research into outcome measures following the USPSTF recommendations to further understand the clinical implications of the USPSTF recommendations. We are aware that these recommendations are dynamic and that the USPSTF continues to work alongside the American Urologic Association and American Cancer Society to revise their proposals. In the most recent 2017 update, the USPSTF has recently relabeled PSA testing in men ages 55-69 years a grade “C” or recommended to be offered selectively to patients (14). Specifically, they recommend that the decision to receive PSA-based screening should be both individualized and shared between the clinician and patient. The risks and benefits of testing should be well understood by the patient before undergoing screening. Presently, USPSTF continues to recommend against PSA testing in males 70 years or older. With successful characterization of the trends in prostate biopsy practice patterns, we hope to guide practice patterns in the high-risk population with hopes of reducing overtreatment of clinically insignificant disease while continuing to aggressively treat clinically significant disease.

CONCLUSIONS

In summary, we found that in the time since the USPSTF issued their recommendation against PSA-based prostate cancer screening, there has been a significant increase in the PSA of patients who have undergone prostate biopsy in our study population. Additionally, these patients were more likely to be black in comparison to the pre-recommendation cohort. Lastly, patients with a positive biopsy had higher volume of disease and were near-significantly more likely to have D’Amico-classified intermediate and high risk disease. More research is needed to identify the mechanisms underlying these observations. We also suggest further research into long-term outcomes in black men who are not undergoing PSA-based prostate cancer screening as per the USPSTF recommendations.

ABBREVIATIONS

USPSTF = United States Preventative Services Task Force
PSA = Prostate specific antigen
NCCN = National Comprehensive Cancer Network
PLCO (Cancer Screening Trial) = Prostate, Lung, Colorectal, Ovarian
ERSPC = European Randomized Study of Screening for Prostate Cancer
PCP = Primary care physician

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Johnathan Khusid contributed similarly as first author

CONFLICT OF INTEREST

None declared.

REFERENCES


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Polygamy, sexual behavior in a population under risk for prostate cancer diagnostic: an observational study from the Black Sea Region in Turkey

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1 Department of Urology, Ordu University, Faculty of Medicine, Ordu, Turkey

ABSTRACT

Aim: Although prostate cancer (PCa) is the most common cancer type in men, a replaceable risk factor has not yet been established. In our study, we assessed the relationship between the number of sexual partners, age of first sexual experience and age of first masturbation and prostate cancer incidence.

Materials and Methods: In Ordu University Department of Urology between January 2013 and September 2016, in PSA elevation and rectal examination, patients with prostate biopsy were evaluated due to nodule palpation in the prostate. At younger ages and at present, their first masturbation ages, first sexual debut ages, and total sexual partner numbers were recorded. The correlation between the obtained data and PCa frequency was evaluated.

Results: The study included 146 patients with PCa identified on biopsy and 171 patients with benign biopsy results who answered the questions. 66.7% of the ones whose biopsy results were benign and 40.6% of cancer suspects had only one sexual partner. The median number of sexual partners was 1±4 (1-100) in the benign group and 2±6 (1-500) in the malignant group (p=0.039). There was a negative correlation between age of first sexual debut and number of partners (r: -0.479; p <0.001).

Conclusion: In our study, it appears that there may be an association between the number of sexual partners and prostate cancer in the patient group with PSA level above 4ng/mL. Avoidance of sexual promiscuity or participation in protected sex may be beneficial to protect against prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer type in males and in second place in terms of cancer-linked deaths (1). Though this is a very common cancer, the etiology is only partly understood. Age, ethnicity and family history are known to be important for the etiology (2). Studies of migrants have reported environmental factors and lifestyle factors may be important (3). However, the majority of these factors cannot be changed. A variable risk factor for PCa has still not been definitely determined. Studies have related PCa risk with factors linked to more active sexual life (4). Sexual activity include various dimensions like sex of the partners, number of sexual partners, frequency of ejaculation and age of first sexual debut. It is thought that all of these may affect
PCa development in negative or positive ways to varying degrees. Some studies have reported that sexual behavior and sexually transmitted disease may play a role in the etiology of prostate cancer (5). In our study, we aimed to assess the correlation between number of sexual partners, monthly frequency of sexual relations, age of first sexual debut and age of first masturbation with the incidence of prostate cancer.

MATERIALS AND METHODS

Patients undergoing prostate biopsy at Ordu University Medical Faculty Urology Clinic from January 2013 to September 2016 were assessed. Patients with PSA>4 or nodule felt during digital rectal examination were referred for biopsy. All biopsies were completed in 12 quadrants with TRUS guidance. All patients provided information to a doctor during an interview. Informed consent forms have been obtained as the patients have been informed that their data would be kept confidential and used for research purposes. The answers to questions about frequency of sexual relations when young and currently, age of first masturbation, age of first sexual experience and total numbers of sexual partners were recorded. The correlation of the obtained data with the incidence of PCa was assessed. Patients who did not wish to answer the questions were excluded from the study. The study included 146 patients with PCa identified on biopsy and 171 patients with benign biopsy results. The mean age of patients in the benign group was 64.38±8.20 (41-92) years and in the malignant group was 67.39±9.34 (43-97) years. The median PSA values were 6.55±4.86 (2.28-42.00) in the benign group and 8.60±13.15 (3.26-934.30) in the malignant group. In terms of sexual partners, 66.7% of the benign group and 40.6% of the malignant group had only one sexual partner. Median number of sexual partners was 1±4 (1-100) in the benign group and 2±6 (1-500) in the malignant group. The difference in numbers of sexual partners was found to be statistically significant between the groups (p=0.039). There was no statistically significant difference between the two groups in terms of number of relations per month when young and currently, first masturbation age and first sexual debut age. Details of data and p values are shown in Table-1. There was a negative correlation identified between age of first sexual debut and number of partners (r: -0.479; p<0.001).

DISCUSSION

Our study found an association between the number of sexual partners over life and positive biopsy for PCa among patients at risk of PCa diagnosis. It is thought that sexually transmitted infections (STI) are a significant factor for the link with PCa. A study by Rosenblatt et al. identified a positive correlation between the number of female sexual partners and PCa risk (6). Studies related to this topic have found that syphilis identified by serologic tests increases the risk of prostate cancer by 1.8 times and this increase is correlated with the number of sexual partners (7). Two meta-analyses published in 2002 and 2005 identified...
that sexually transmitted infections increased the risk of PCa (4, 8). It is thought that factors like bacteria and fungus causing infections and injury to the prostate stimulate inflammasome-mediated proinflammatory cytokines beginning tumor progression (9). The role of inflammation in PCa development has been known for a long time. It is thought that inflammation encourages angiogenesis and DNA damage causing carcinogenesis (10-12). A PCPT study showed that inflammation observed in prostate biopsy specimens is related to high grade cancer developing in advanced periods (13). Proinflammatory cytokines and chemokines released from immune cells aid the formation of neoplastic cells (9). In our study, we believe the relationship between number of partners and incidence of PCa may be due to sexually transmitted infections and prostatic inflammation linked to these infections.

There are studies showing that age of initial sexual activity and frequency of ejaculation are effective in development of PCa. The increase in frequency of ejaculation reduces the carcinogenic material concentration within prostatic fluids and intraluminal prostatic crystalloid accumulation and thus it is reported that frequency of ejaculation may be protective against cancer (14-16). In our study, we identified that both groups were similar in terms of the markers of ejaculation frequency of first masturbation age, first sexual debut age and frequency of sexual relations when young and currently. Among data assessing sexual life, a significant difference was only found for the number of sexual partners. The median number of sexual partners and the number of those with more than one sexual partner in the malignant group were identified to be statistically significantly higher compared to the benign group.

In our study, we identified that as the age of first sexual debut reduced, the number of partners increased. There are different interpretations in the literature related to the effect of age of first sexual debut and number of partners on PCa development. Rotkin et al. reported that early age of first sexual debut increased the risk of prostate cancer (17). Rosenblatt et al. proposed that rather than an early start to sexual relations, the number of partners was important (6). In fact, the study by Rotkin did not assess the effect of number of sexual partners. Ahmadi et al. reported that the risk of prostate cancer was lower for males who married at a young age (18). The study by Ahmadi was based in Iran. Iranian Muslims are explicitly different to Western societies as a result of tight governmental restrictions on open sexual relationships and prostitution as well as cultural and religious fixation on avoiding premarital and extramarital sexual activity. In our study, as the age of sexual debut reduced, the number of partners increased and we found the number of partners

<table>
<thead>
<tr>
<th>Variables</th>
<th>Benign</th>
<th>Malign</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients age</td>
<td>63.03±8.07(a)</td>
<td>66.24±7.73(a)</td>
<td>0.002**</td>
</tr>
<tr>
<td>PSA (ng/dL)</td>
<td>6.40±3.83 (3.60-25.20)(b)</td>
<td>8.6±10.16 (0-330)(b)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Number of sexual partners</td>
<td>1±4 (1-100)(b)</td>
<td>2±6 (1-500)(b)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Monthly sexual intercourse frequency in youth</td>
<td>10±7 (3-30)(b)</td>
<td>10±6 (2-24)(b)</td>
<td>0.236</td>
</tr>
<tr>
<td>Current monthly sexual intercourse frequency</td>
<td>4±5 (0-22)(b)</td>
<td>4±6 (0-17)(b)</td>
<td>0.957</td>
</tr>
<tr>
<td>First masturbation age</td>
<td>15±15 (0-18)(b)</td>
<td>12±16 (0-35)(b)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Age of first sexual debut</td>
<td>20±6 (14-27)(b)</td>
<td>18±6 (13-52)(b)</td>
<td>0.137</td>
</tr>
</tbody>
</table>

\(a\) = mean±SD; \(b\) = median±IQR (min-max); * = p<0.05; ** = p<0.01
was related to incidence of prostate cancer. When all this data is assessed with our results, it appears that the number of sexual partners is important for PCa development.

Our study group comprises a homogeneous group living in a small geographical area. The study region does not have inward migration and is a relatively small area. As the region is small, it may not be possible to generalize our results to the whole population. However, it is considered that genetic factors, nutritional habits and environmental factors are effective in the etiology of PCa. An advantage of our study is that the study group comprises people living in the same geographic region, with similar life styles, nutritional forms and genetic characteristics. In both our patient groups, the effects of these factors may be accepted as being similar. Additionally, in our country, society avoids open conversation related to sexuality. It is very difficult to obtain information about previous sexual experience from males of adult age. There is a risk that information given on the question forms and in interviews is deficient or wrong. In our clinic, a single doctor works with patients to resolve concerns of patients worried due to the possibility of prostate cancer and to ensure compliance with testing and follow-up during this process. More time is allotted to patients and confidence is given that the information that they provide will remain confidential. The diagnosis, treatment and process after treatment for these patients is performed by the same doctor. Due to the trust built up in this environment, we believe the information given is accurate. Thus, it is very hard to record data for this number of patients from a small region. As a result, our study is the first study to investigate this data in Turkey.

There are some limitations of our study. The first is that serologic testing was not completed to assess our patients for STI. As a result, we do not have clear results in terms of previous STI history. However, as the number of partners increase, an increase in incidence of STI is expected. Studies have shown that experiencing STI clearly increases the chances of PCa. In our study, as the number of sexual partners increased, there was an increase observed in the incidence of prostate cancer. Another limitation is that though biopsy was benign in the group with high PSA, there is a chance of occurrence on 2nd and 3rd biopsies. Although, the number of patients with a single sexual partner was higher in the group with benign biopsy results, there was a considerable number of patients with multiple sexual partners in both groups. As the size of groups was limited in our study, further studies with larger sample size can give different results. Since both of the groups consisted of patients with high PSA values, some of the patients with benign biopsy result may develop prostate cancer later in their life and diagnosed by a second or third biopsy. Therefore, it is better to say “there was a significant relationship between number of sexual partners and prostate cancer detection by first biopsy”. We believe it will be beneficial to perform a similar comparison with a control group with low PSA levels and hence a low risk of PCa.

**CONCLUSIONS**

In our study, it appears that there may be an association between the number of sexual partners and prostate cancer in the patient group with PSA level above 4ng/mL. There was no association found between frequency of sexual relations in youth and at present, first age of masturbation and first age of sexual experience with PCa. Though not clearly revealed by our study, when the literature and our results are assessed together, we hypothesize that avoidance of sexual promiscuity or participation in protected sex may be beneficial to protect against prostate cancer. However, there is a need for more comprehensive studies to confirm this.

**CONFLICT OF INTEREST**

None declared.

**REFERENCES**


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Impact of PSA density of transition zone as a potential parameter in reducing the number of unnecessary prostate biopsies in patients with PSA levels between 2.6 and 10.0 ng/mL

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ABSTRACT

Purpose: To assess the accuracy of prostate-specific antigen (PSA) adjusted for the transition zone volume (PSATZ) in predicting prostate cancer by comparing the ability of several PSA parameters in predicting prostate cancer in men with intermediate PSA levels of 2.6 – 10.0 ng/mL and its ability to reduce unnecessary biopsies.

Materials and Methods: This study included 656 patients referred for prostate biopsy who had a serum PSA of 2.6 – 10.0 ng/mL. Total prostate and transition zone volumes were measured by transrectal ultrasound using the prolate ellipsoid method. The clinical values of PSA, free-to-total (F/T) ratio, PSA density (PSAD) and PSATZ for the detection of prostate cancer were calculated and statistical comparisons between biopsy-positive (cancer) and biopsy-negative (benign) were conducted.

Results: Cancer was detected in 172 patients (26.2%). Mean PSA, PSATZ, PSAD and F/T ratio were 7.5 ng/mL, 0.68 ng/mL/cc, 0.25 ng/mL/cc and 0.14 in patients with prostate cancer and 6.29 ng/mL, 0.30 ng/mL/cc, 0.16 ng/mL/cc and 0.22 in patients with benign biopsies, respectively. ROC curves analysis demonstrated that PSATZ had a higher area under curve (0.838) than F/T ratio (0.806) (P<0.001) and PSAD (0.806) (P<0.001). With a cut-off value of 0.22 ng/mL/cc, PSATZ had 100% of sensitivity and could have prevented 24% of unnecessary biopsies.

Conclusions: PSATZ may be useful in enhancing the specificity of serum PSA. Compared to other PSA related parameters, it was better in differentiating between prostate cancer and benign prostatic enlargement. Also, PSATZ could reduce a significant number of unnecessary biopsies.

INTRODUCTION

According to the World Health Organization, prostate cancer (PC) is the second most common cancer and the sixth leading cause of death among males worldwide (1). In 2015, an estimated 27,540 PC-related deaths are anticipated in the United States (1). According to the Brazilian National Cancer Institute (INCA), approximately 68,800 new cases were diagnosed in Brazil in 2014 (2).
Determination of serum levels of prostate-specific antigen (PSA) has been used in clinical practice since 1988, and has become the most valuable tumor marker widely used in screening for prostate cancer. It is considered to be responsible for 45-70% of decreased PC-related deaths reported since 1990 (3). The production of PSA occurs mainly in epithelial cells located in the transition zone (TZ), which makes it organ-specific, but not cancer-specific. Therefore, a multi-parameter approach is essential, given that PSA value taken singularly is not sufficiently accurate, due to the interference of age and frequently coexisting conditions, such as benign prostate hyperplasia (BPH) and prostatitis (4). It seems to be difficult to discriminate between prostate cancer and benign conditions especially among patients with intermediate PSA levels between 2.6 and 10 ng/mL (5). Within this range, there is a trade-off between specificity and sensitivity, a significant degree of the former being lost in the interest of achieving an acceptable degree of the latter (6). In other words, many patients are submitted to unnecessary biopsies because it is important to maintain acceptable diagnosis rates. Therefore, approximately 70% of prostate biopsy results are negative in this group (7). Different PSA parameters such as PSA velocity (6), age specific reference ranges (7), PSA density (PSAD) (8), PSA density adjusted by transition zone (PSATZ) (9) and the correlations between its molecular forms, have been introduced to improve the diagnostic accuracy of serum PSA. However, it remains unclear which method is superior in routine use. Recent studies like PROMIS (10) showed that multiparametric MRI as a first strategy to diagnose PC is effective and cost effective; however, in developing countries such as Brazil, this is not a reality in the great majority of our public health system. Therefore, simpler and most available approaches to evaluate PSA parameters and PC screening are warranted.

The prostate volume (PV) and transition zone volume (TZV) can be determined by transrectal ultrasound (TRUS) using the ellipsoid formula (11). It is known that BPH increases PSA levels by increasing the TZV (4). The ratio between the absolute value of PSA and PV is designated PSA density (PSAD), and the ratio between the absolute value of PSA and TZV is designated PSA density of the transitional zone (PSATZ). The rationale is that by adjusting PSA values for PV or TZV, the influence related to the nonmalignant portion of the gland, which is believed to account for most of the physiological PSA increase, ought to be reduced (8, 9). Some studies have suggested that PSATZ is more specific than PSAD and its use could, therefore, reduce the number of unnecessary biopsies (12, 13).

In this study, we compared PSA and its parameters to evaluate the accuracy of PSATZ in predicting prostate cancer in patients with total PSA levels between 2.6 and 10.0 ng/mL, and whether it could reduce the number of unnecessary biopsies in this group, without missing positive cases.

**MATERIALS AND METHODS**

We prospectively included a total of 656 consecutive patients who presented with PSA levels between 2.6 and 10.0 ng/mL and were referred to the University Hospital São Paulo, from January 2014 to December 2016, of the Federal University of São Paulo, Brazil (HSP/UNIFESP) for prostate biopsy. University Hospital São Paulo is a public hospital, responsible for the assistance of nearly six millions people, almost 35% of São Paulo city population. Information regarding clinical and epidemiological characteristics and PSA levels were retrieved after a thorough chart review. Patients with previous history of prostate cancer, hormonal manipulation, documented urinary tract infection, acute or chronic bacterial prostatitis, previous prostate surgery, recent 5-alpha-reductase inhibitors use and any condition that may affect serum PSA level were not included. This study design was approved by the Research Ethics Committee of our Institution, according to the Declaration of Helsinki. All patients included in this study signed an informed consent.

Serum total PSA concentration and free PSA were determined by an enzyme immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA).

Transrectal ultrasonography of the prostate was performed by experienced staff using
an EnVisor ultrasound system (Philips Healthcare, Eindhoven, The Netherlands) with a 9 MHz endocavity transducer. The prostate was scanned in multiple transverse and sagittal planes. Triaxial distances at the maximal length, width and height of the prostate and the TZ were measured as previously described (4, 13). Both PV and TZV were calculated using the prolate ellipsoid formula (volume=length x width x height x \(\pi/6\)). PSAD and PSATZ were calculated by dividing the PSA value by the PV and TZV, respectively.

Transrectal ultrasound-guided core biopsies of the prostate were performed using an 18-gauge cutting needle in a spring-loaded biopsy gun (Bard Urological, Covington, GA, USA). All biopsies were performed by experienced physicians. Randomly, 20% of our ultrasound measurements results were compared to MRI results, showing a high concordance rate between the two methods. Systematic sextant biopsies with a total of 12 samples were taken from the peripheral zone comprising six peripheral zone biopsies. When ultrasound revealed focal changes, additional samples were taken and sent for analysis. All specimens were adequate for pathologic diagnosis. Prostate intraepithelial neoplasm or atypia were defined as no malignancy.

The results for the quantitative variables are presented as the mean values ± standard error. Variables of different groups were compared using the Mann-Whitney U test. In order to draw comparisons between the patients with cancer and those without, we analyzed the following variables: age; PSA; PV; TZV; PSAD and PSATZ. The Student’s t-test for independent samples was used in order to compare the two groups of patients with cancer (positive biopsy) and those without (negative biopsy). The significance of the parameters (PSA, PSAD, PSATZ and F/T ratio) for predicting prostate cancer were assessed based on receiver operating characteristic (ROC) curves, which are plots of the true positive rates (sensitivity) versus the false positive rates (1-specificity), using all different possible cut-off values. The software IBM SPSS - Statistical Package for the Social Sciences, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA) was used in this study.

RESULTS

Mean patient age was 67.8 (range 46 to 87 years old). Of 656 patients, 172 (26.2%) had a positive biopsy for prostate cancer and 484 (73.8%) had negative biopsies. Table-1 summarizes the features of the distribution of quantitative variables: age, prostate volume; TZ volume; total PSA levels; F/T ratio; PSAD; and PSATZ for patients with positive or negative biopsies. All patients with prostate cancer had significantly higher levels of total PSA, PSAD and PSATZ and significantly lower F/T ratios, PV and TZV when compared to patients with negative biopsies.

Sensitivity, specificity, positive and negative predictive values and the number of potentially reducible biopsies of each PSA-related parameter were calculated for all 656 patients at different cut-off values (Table-2). A PSAD with a cut-off value of 0.15 ng/mL/cc had a sensitivity of 91%
Table 2 - Sensitivity, specificity and reducible biopsies for different PSA, PSAD, F/T ratio and PSATZ values in 656 patients.

<table>
<thead>
<tr>
<th>PSA (ng/mL) greater than</th>
<th>Number of biopsies</th>
<th>Number of cancer</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Reducible biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>656</td>
<td>172</td>
<td>1.000</td>
<td>0.017</td>
<td>0.265</td>
<td>1.000</td>
<td>1.22%</td>
</tr>
<tr>
<td>4.0</td>
<td>567</td>
<td>168</td>
<td>0.977</td>
<td>0.176</td>
<td>0.265</td>
<td>0.955</td>
<td>13.5%</td>
</tr>
<tr>
<td>5.0</td>
<td>523</td>
<td>154</td>
<td>0.895</td>
<td>0.238</td>
<td>0.294</td>
<td>0.865</td>
<td>20.2%</td>
</tr>
<tr>
<td>6.0</td>
<td>406</td>
<td>128</td>
<td>0.744</td>
<td>0.426</td>
<td>0.315</td>
<td>0.824</td>
<td>38.1%</td>
</tr>
<tr>
<td>7.0</td>
<td>301</td>
<td>118</td>
<td>0.686</td>
<td>0.622</td>
<td>0.392</td>
<td>0.848</td>
<td>54.1%</td>
</tr>
<tr>
<td>8.0</td>
<td>179</td>
<td>76</td>
<td>0.442</td>
<td>0.787</td>
<td>0.425</td>
<td>0.799</td>
<td>72.7%</td>
</tr>
<tr>
<td>9.0</td>
<td>74</td>
<td>40</td>
<td>0.233</td>
<td>0.930</td>
<td>0.541</td>
<td>0.773</td>
<td>88.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F/T ratio less than</th>
<th>Number of biopsies</th>
<th>Number of cancer</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Reducible biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>82</td>
<td>74</td>
<td>0.430</td>
<td>0.983</td>
<td>0.902</td>
<td>0.829</td>
<td>87.5%</td>
</tr>
<tr>
<td>0.12</td>
<td>146</td>
<td>101</td>
<td>0.587</td>
<td>0.907</td>
<td>0.692</td>
<td>0.861</td>
<td>77.7%</td>
</tr>
<tr>
<td>0.14</td>
<td>237</td>
<td>121</td>
<td>0.703</td>
<td>0.760</td>
<td>0.511</td>
<td>0.878</td>
<td>63.8%</td>
</tr>
<tr>
<td>0.15</td>
<td>275</td>
<td>135</td>
<td>0.785</td>
<td>0.711</td>
<td>0.491</td>
<td>0.903</td>
<td>58.0%</td>
</tr>
<tr>
<td>0.18</td>
<td>303</td>
<td>145</td>
<td>0.843</td>
<td>0.674</td>
<td>0.479</td>
<td>0.924</td>
<td>53.8%</td>
</tr>
<tr>
<td>0.20</td>
<td>367</td>
<td>149</td>
<td>0.866</td>
<td>0.550</td>
<td>0.406</td>
<td>0.920</td>
<td>44.0%</td>
</tr>
<tr>
<td>0.22</td>
<td>384</td>
<td>155</td>
<td>0.901</td>
<td>0.527</td>
<td>0.404</td>
<td>0.938</td>
<td>41.4%</td>
</tr>
<tr>
<td>0.25</td>
<td>472</td>
<td>161</td>
<td>0.936</td>
<td>0.357</td>
<td>0.341</td>
<td>0.940</td>
<td>28.0%</td>
</tr>
<tr>
<td>0.31</td>
<td>603</td>
<td>172</td>
<td>1.000</td>
<td>0.110</td>
<td>0.285</td>
<td>1.000</td>
<td>8.0%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PSAD (ng/mL per mL) greater than</th>
<th>Number of biopsies</th>
<th>Number of cancer</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Reducible biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>603</td>
<td>172</td>
<td>1.000</td>
<td>0.110</td>
<td>0.285</td>
<td>1.000</td>
<td>8.0%</td>
</tr>
<tr>
<td>0.11</td>
<td>570</td>
<td>169</td>
<td>0.983</td>
<td>0.171</td>
<td>0.296</td>
<td>0.965</td>
<td>13.1%</td>
</tr>
<tr>
<td>0.13</td>
<td>479</td>
<td>165</td>
<td>0.959</td>
<td>0.351</td>
<td>0.344</td>
<td>0.960</td>
<td>26.9%</td>
</tr>
<tr>
<td>0.15</td>
<td>397</td>
<td>158</td>
<td>0.919</td>
<td>0.506</td>
<td>0.398</td>
<td>0.946</td>
<td>39.4%</td>
</tr>
<tr>
<td>0.17</td>
<td>336</td>
<td>138</td>
<td>0.802</td>
<td>0.591</td>
<td>0.411</td>
<td>0.894</td>
<td>48.7%</td>
</tr>
<tr>
<td>0.18</td>
<td>309</td>
<td>125</td>
<td>0.727</td>
<td>0.620</td>
<td>0.405</td>
<td>0.865</td>
<td>52.9%</td>
</tr>
<tr>
<td>0.20</td>
<td>214</td>
<td>124</td>
<td>0.721</td>
<td>0.814</td>
<td>0.579</td>
<td>0.891</td>
<td>67.3%</td>
</tr>
<tr>
<td>0.22</td>
<td>161</td>
<td>91</td>
<td>0.529</td>
<td>0.855</td>
<td>0.565</td>
<td>0.836</td>
<td>75.4%</td>
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</table>

<table>
<thead>
<tr>
<th>PSATZ (ng/mL per mL) greater than:</th>
<th>Number of biopsies</th>
<th>Number of cancer</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Reducible biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>599</td>
<td>172</td>
<td>1.000</td>
<td>0.118</td>
<td>0.287</td>
<td>1.000</td>
<td>8.7%</td>
</tr>
<tr>
<td>0.22</td>
<td>494</td>
<td>172</td>
<td>1.000</td>
<td>0.334</td>
<td>0.348</td>
<td>1.000</td>
<td>24.7%</td>
</tr>
<tr>
<td>0.25</td>
<td>452</td>
<td>162</td>
<td>0.942</td>
<td>0.401</td>
<td>0.358</td>
<td>0.951</td>
<td>31.1%</td>
</tr>
<tr>
<td>0.30</td>
<td>340</td>
<td>151</td>
<td>0.878</td>
<td>0.610</td>
<td>0.444</td>
<td>0.934</td>
<td>48.1%</td>
</tr>
<tr>
<td>0.33</td>
<td>286</td>
<td>138</td>
<td>0.802</td>
<td>0.694</td>
<td>0.483</td>
<td>0.908</td>
<td>56.4%</td>
</tr>
<tr>
<td>0.35</td>
<td>262</td>
<td>131</td>
<td>0.762</td>
<td>0.729</td>
<td>0.500</td>
<td>0.896</td>
<td>60.0%</td>
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<tr>
<td>0.37</td>
<td>243</td>
<td>128</td>
<td>0.744</td>
<td>0.762</td>
<td>0.527</td>
<td>0.893</td>
<td>62.9%</td>
</tr>
<tr>
<td>0.40</td>
<td>230</td>
<td>128</td>
<td>0.744</td>
<td>0.789</td>
<td>0.557</td>
<td>0.897</td>
<td>64.9%</td>
</tr>
<tr>
<td>0.46</td>
<td>195</td>
<td>107</td>
<td>0.622</td>
<td>0.818</td>
<td>0.549</td>
<td>0.859</td>
<td>70.2%</td>
</tr>
<tr>
<td>0.55</td>
<td>148</td>
<td>94</td>
<td>0.547</td>
<td>0.888</td>
<td>0.635</td>
<td>0.846</td>
<td>77.4%</td>
</tr>
</tbody>
</table>

F/T ratio = free-to-total PSA ratio; PSA = prostate-specific antigen; PSAD = PSA density; PSATZ = PSA density of the transition zone.
and a specificity of 50%. A PSATZ with a cut-off value of 0.33 ng/mL/cc detected 138 of 172 cancers (80.2%) with a specificity of 69.4%. A F/T ratio with a cut-off value of 0.15 detected 135 of 172 patients (78.5%) with a specificity of 71.1%. In this group, PSATZ provided better results concerning sensitivity, specificity and positive predictive values than PSA, PSAD, PSATZ and F/T ratio. Using a cut-off value for PSATZ of 0.33 ng/mL/cc, we found a sensitivity of 80.2% and a specificity of 69.4%. The maximal cut-off values that preserved 100% of sensitivity, in which no cancer would be missed, were 0.10 ng/mL/cc for PSAD, with a positive predictive value of 0.285; 0.22 ng/mL/cc for PSATZ, with a positive predictive value of 0.348; and 0.31 for F/T ratio with a positive predictive value of 0.285. Of all these parameters, at 100% sensitivity, PSATZ had the highest specificity (33.4%) and the highest positive predictive value (0.348).

ROC curves analyses were performed in all patients for PSA, PSAD, F/T ratio and PSATZ (Figure-1). At the level of 100% sensitivity, the curve of PSATZ shows better specificity than the others. The AUCs were 0.683 for PSA, 0.806 for PSAD, 0.838 for PSATZ and 0.832 for F/T ratio (Table-3). The AUC of PSATZ was the highest among all of these parameters. Figure-1 was the highest among all of these parameters. Figure-1 demonstrates ROC curves of total PSA, F/T ratio, PSAD and PSATZ.

**DISCUSSION**

The role of transrectal prostate biopsy (TRUS-Bx) has changed over time. Its importance has evolved from pure cancer detection to assisting clinical patient management such as active surveillance; however, it is associated with significant morbidity and increased level of anxiety (14). Therefore, maximum efforts should be concentrated to reduce biopsy adverse effects, to improve selection for TRUS-Bx using novel cancer-specific biomarkers and imaging, in an effort to reduce the number of unnecessary biopsies. To address these issues highlighted above, our study underscores the importance of PSATZ as a reliable predictor of prostate cancer for patients with PSA in intermediate levels and its ability to reduce a significant number of unnecessary biopsies. To date, this is the largest Brazilian study addressing these issues.

Determination of serum PSA levels is the most useful available screening test for prostate cancer (6). However, in cases of intermediate PSA levels, it is difficult to discriminate between prostate cancer and BPH, particularly in patients with PSA levels between 2.6 and 10.0 ng/mL, in which there is an overlap between the two conditions (5). To increase the PSA specificity and reduce the number of unnecessary biopsies, which can occur in approximately 70% of the cases, many authors have proposed alternative PSA parameters, such as PSAD (8), PSATZ (9) and the F/T ratio (10). However, there is still some controversy of the use of these PSA parameters in routine use. In this study, we compared some PSA parameters in order to find the most sensitive and specific method to diagnose prostate cancer.

The majority of PSA in serum is bound to protease inhibitors such as ACT (α-1-antichymotripsin) and only a minority exists in the unbound or free form. The proportion of free PSA (fPSA) is lower in men with prostate cancer than in men with BPH (10). Therefore, investiga-
tors proposed the concept of free-to-total PSA ratio for the detection of prostate cancer, in order to differentiate prostate cancer from BPH, especially in patients with intermediate PSA levels (10). Early studies showed that a combination of PSA and F/T ratio improved the specificity from 55% to 73% at a sensitivity level of 90% (15). Using a F/T ratio cut-off value of 0.28, Catalona et al. reported a 90% detection of prostate cancers and a 12% reduction of biopsies (16). In our study, F/T ratio with a cut-off value of 0.15 we had a sensitivity of 78.5% and a specificity of 71.1% and could reduce unnecessary biopsies by 58%. For a screening test, at 100% sensitivity, PSA with a cut-off value of 0.10 ng/mL/cc could reduce unnecessary biopsies by 8.0%.

It is well recognized that benign prostatic enlargement can result in serum PSA elevation in the absence of prostate carcinoma (4). Benson et al. (8) introduced the concept of PSAD, which is calculated by dividing the total PSA value by the prostate volume. A PSAD with a cut-off 0.15 ng/mL/cc provided a more reliable indication for ultrasound-guided biopsy of the prostate than PSA alone without significantly compromising cancer detection (8). Although some authors have reported that PSAD is useful in differentiating between prostate cancer and BPH (7, 8, 16), others have questioned its validity (17). Therefore, it is not clear whether PSAD is of real help when deciding if a patient with intermediate levels of PSA must undergo a prostate biopsy. In our study, PSAD with a cut-off value of 0.15 ng/mL/cc had a sensitivity of 78.5% and a specificity of 71.1%, and was inferior to PSATZ. For a screening test, at 100% sensitivity, PSAD with a cut-off value of 0.10 ng/mL/cc could reduce unnecessary biopsies by 8.0%.

It is known that most cases of BPH result from an increase TZV and most PSA leakage from the prostate into the serum comes from the TZ (5, 18). Some studies of correlation between PSA and zonal volume have revealed that the best predictor of serum PSA level is not total prostate volume but TZV, especially TZ epithelial volume (19). Also, ultrasonography has revealed major differences in the proportion of the TZV compared with PV in men with or without BPH per se, implying significant differences between PSAD and PSATZ (11). They also reported a clear correlation between age and TZV. Therefore, adjusting the PSA density for TZV could be a more valuable method than calculating PSAD. Kalish et al. (9) introduced the concept of total PSA adjusted for TZV and suggested that compared with total PSA and PSAD, it was the only significant multivariate predictor using stepwise logistic regression analysis. However, different from our study, they did not adopt ROC analyses as a statistical method, their biopsies were directed at sonographically suspicious areas and they did not include sextant biopsies. Zlotta et al. (20) have also shown that PSATZ was superior to PSAD using ROC analysis, but their study, with fewer patients, was not prospective. They reported the superiority of PSATZ with a cut-off value of 0.35 ng/mL/cc over PSAD and F/T ratio in predicting prostate cancer. In a study involving 281 patients, Kikuchi et al. (21)
classified PSATZ as the best method, improving the accuracy of PSA test when compared to total PSA, PSAD and its molecular forms, including fPSA. However, Kobayashi et al. (22) evaluated patients with PSA levels between 2.6 and 4.0 ng/mL and reported no significant difference between PSAD and PSATZ in terms of their accuracy in detecting prostate cancer. In a recent study, Amini et al. (23) studied the predictability of PSATZ in the diagnosis of prostate cancer among patients with chronic inflammation of prostate and showed a strong correlation between a low PSATZ and the absence of prostate malignancy in this group.

In our study, PSATZ was compared with total PSA, PSAD and F/T ratio in a group of 656 men with PSA levels of 2.6 - 10.0 ng/mL. The AUC of PSATZ was the greatest among all AUCs. The ROC curve of PSATZ deviated to left side, especially at the level of 100% sensitivity, compared with other PSA related parameters. It means that PSATZ could be used as a good screening test. With a cut-off value of 0.22 ng/mL/cc, we had 100% sensitivity and could have avoided 24.7% of unnecessary biopsies. Therefore, it is reasonable to suggest that PSATZ is, in this study, superior to PSAD and F/T ratio in distinguishing benign from malignant cases, and could be used as an additional PSA parameter to our Brazilian prostate cancer screening program. According to our results, patients with low PSATZ values could possibly be followed less frequently and less aggressively treated.

It is not entirely clear the reasons for the variance in PSATZ reports, but some limitations may include the difficulty of accurate TZV measurement by transrectal ultrasound (TRUS), variability of PSA with aging and variable distribution of glandular and stromal components in BPH (5, 18). The accuracy of TZV measurement is ultrasonographer dependent, which may influence the reproducibility of PSATZ. It is sometimes difficult to assess the TZV measurement in patients with a very small or very large prostate or with diffuse calcifications, because TZ borders can be less clear in these patients. However, Zlotta et al. (24) showed that, in patients with BPH, when the TZ was measured by an experienced ultrasonographer, there was little difference between the PV and TZV estimated by preoperative transrectal ultrasound and the actual volume of the surgical specimen after prostatectomy. In our study, all TRUS were performed by experienced staff in order to increase inter-operator reliability.

In our data, PSATZ performance results were very similar to F/T ratio. However, the measurement of F/T ratio requires 2 tests and therefore, also increases the sources of bias. Another critical issue relates to the weak stability of fPSA as a protein and results may vary if the samples are not stored at -80°C and/or if they are not analyzed shortly after venipuncture. Djavan et al. detected an intertest variability of >72% when fPSA values from the same patient were drawn in different departments of the same institution (25).

CONCLUSIONS

In this study, PSATZ was the most reliable test to discriminate between patients with and without prostate cancer compared to other PSA related parameters in patients with intermediate PSA levels. Therefore, PSATZ could be used as a valuable test for biopsy candidates, reducing the number of unnecessary biopsies, therefore improving the cost effectiveness for detecting prostate cancer.

CONFLICT OF INTEREST

None declared.

REFERENCES


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E-mail: wagneriared@gmail.com
Comparing the short–term outcomes and complications of monopolar and bipolar transurethral resection of bladder tumors in patients with coronary artery disease: a prospective, randomized, controlled study

Deniz Bolat 1, Bülent Guñlusoy 1, Özgür Aydoğdu 1, Mehmet Erhan Aydin 1, Cetin Dincel 1

1 Department of Urology, Bozyaka Training and Research Hospital, Izmir, Turkey

ABSTRACT

Introduction: To compare the perioperative outcomes and complications of monopolar and bipolar transurethral resection of bladder tumors (TURBT) in patients with coronary artery disease (CAD).

Materials and Methods: A total of 90 CAD patients with newly diagnosed bladder cancer who underwent TURBT were randomized into monopolar TURBT (M-TURBT) and bipolar TURBT (B-TURBT) groups. Primary outcome was safety of the procedures including obturator jerk, bladder perforation, clot retention, febrile urinary tract infection and TUR syndrome. The secondary outcome was the efficacy of TURBT procedures, including complete tumor resection, sampling of the deep muscle tissue and sampling of the qualified tissues without any thermal damage.

Results: Mean ages of the patients in M-TURBT and B-TURBT groups were 71.36±7.49 and 73.71±8.15 years, respectively (p=0.157). No significant differences were found between M-TURBT and B-TURBT groups regarding complete tumor resection (76.2% vs. 87.5%, p=0.162) and muscle tissue sampling rates (71.4% vs. 64.6%, p=0.252). Obturator jerk was detected in 16.7% of the patients in M-TURBT group and 2.1% in B-TURBT group (p=0.007). No statistically significant differences were found between the groups regarding intraoperative and postoperative complications.

Conclusions: Both monopolar and bipolar systems can be used safely and effectively during TURBT procedure in CAD patients. Due to the more frequently seen obturator jerk in M-TURBT than B-TURBT, careful surgical approach is needed during M-TURBT.

INTRODUCTION

Transurethral resection (TUR) is the cornerstone of diagnosis and initial therapy of the bladder tumors (1). The aim of the transurethral resection of bladder tumors (TURBT) is to reach a definitive diagnosis and to remove all visible lesions, including part of the underlying muscle tissue (2). Traditionally, TURBT has been performed with monopolar cautery. The potential hazards of this modality include hypotonic fluid absorption and the resultant electrolyte imbalance (3). Recently, the bipolar resectoscope used for TUR of the prostate (TURP) was introduced for the treatment of bladder tumors (2). Bipolar technologies allow the electric current to complete the circuit without passing through the patient (4). By this way, saline solution can be used instead of glycine...
for irrigation during resection. Initial studies of bipolar TURBT (B-TURBT) were promising with fewer fluid and electrolyte abnormalities, and a decreased incidence of obturator jerk (5-7).

With the progressive aging of the population, the prevalence of vascular diseases is increasing (8). In their study, Lucia et al. reported that TURP had low risk for severe complications, but cardiovascular events in elderly patients undergoing this surgical operation were more common than in general population (9). With an increase in the number of elderly population that requires surgical procedures and anticoagulant/antiaggregant therapy, these patients need great concern for possible complications related to accompanied comorbidities (10). Patients with bladder tumors are as older as patients with benign prostatic hyperplasia (BPH). An important feature of these patients is coronary artery disease (CAD) requiring anticoagulant/antiaggregant therapy and thus having serious risk factors for possible perioperative bleeding complications. No consensus exists among urologists regarding the pre-, intra-, and postoperative management of patients taking anticoagulant/antiaggregant medications such as acetylsalicylic acid (ASA), warfarin, or clopidogrel were stopped before 7 days of the procedure and, if necessary, replaced by low-molecular-weight heparin.

Exclusion criteria: Patients without CAD were excluded. Also, patients with acute urinary tract infection, absence of urethelial cancer on pathology report after TURBT, who underwent TURBT for residual tumors, re-staging or recurrent bladder tumors and who were not suitable for spinal anesthesia were excluded.

Randomization: The patients were equally randomized, by means of sealed envelopes, for monopolar TURBT (M-TURBT) or bipolar TURBT (B-TURBT). Patients were blinded to the allocated group.

Technique of M-TURMT and B-TURMT: At dorsal lithotomy position, perineal skin was cleaned with the antiseptic solution. No obturator nerve block was performed before the procedure. Under spinal anesthesia, after a routine cystourethroscopy, M-TURMT was performed with an U-shaped cutting loop, 26Fr continuous flow resectoscope (Karl Storz Endoskope, Tuttlingen, Germany) with 30-degree telescope, and an electrosurgical generator (Valleylab Force FX, Boulder, CO, USA) with power settings of 120W for cutting and 80W for coagulating using mannitol irrigation. Differently, in patients who underwent B-TURBT, an ESG-400 bipolar generator (Olympus Europe, Hamburg, Germany) with power settings of 200W for cutting and 120W for coagulating with saline irrigation was used. At the end of the operation 22Fr 3-way Foley catheter was placed in all patients, and if indicated, continuous irrigation saline was maintained until the urine efflux was completely clean. In uncomplicated cases at the postoperative 24 to 48 hours, Foley catheter was removed and the patient was discharged.

Outcomes: Primary outcome of this study was the safety of the procedures including obturator jerk, bladder perforation, clot retention, febrile urinary tract infection and TUR syndrome. Severity of obturator jerk was classified based on our previous study (12). If the adductor spasm was
severe enough to disturb the surgeon’s resection, it was deemed as a severe obturator jerk. However, if there was an adductor spasm, but not severe enough to disturb the surgeon, it was deemed as a moderate obturator jerk. Bladder perforation was defined as subserosal injury if the perivesical fatty tissue was seen and as complete perforation if drainage tube or surgical repair was required. TUR syndrome was defined as serum sodium level <125mmol/L and one or more circulatory and/or neurological symptoms.

The secondary outcome was the efficacy of both TURBT procedures, including complete tumor resection, sampling of the deep muscle tissue and sampling qualified tissues without any thermal damage. All resections were performed under the supervision of a senior urologist and resection completeness and complications were noted intraoperatively. Thermal damage was classified into 2 groups depending on the quantity of cautery artifacts: mild cautery artifact was defined as cautery artifacts involving less than 50% of entire specimen, and severe cautery artifact was defined as cautery artifacts involving more than 50% of entire specimen (1).

Pathological examination: A single uropathologist, blinded for the allocation, evaluated the resected specimens. Tumor stage, tumor grade, presence of muscularis propria, invasion of the muscle tissue, and presence of thermal tissue damage were reported (13, 14).

Statistical analysis: Data was analysed using the Statistical Package for Social Sciences (SPSS 17.0 for Windows, Chicago, IL, USA). Power calculations were performed with minitab 17 software. Data was expressed as mean±standard deviation, number and percentage according to the type of variables. Numeric variables were tested using independent sample T test, and categorical variables were tested using chi-square or Fisher’s exact test. Values of p <0.05 were accepted as statistically significant.

RESULTS

A total of 120 patients was enrolled in the study. Twenty patients were excluded from the study prior to the randomization. Of the excluded patients, 12 of them were unfit for spinal anesthesia and 8 of them were unfit for TURBT operation due to the priority requirement of coronary artery stenting or by-pass surgery. A total of 100 patients were equally randomized to M-TURBT and B-TURBT groups. After randomization, 10 patients were excluded because of active urinary tract infection, absence of urethelial cancer, and TURBT for residual or recurrent bladder cancer. Finally, 42 patients in M-TURBT group and 48 patients in B-TURBT group were analyzed (Figure-1).

Of the patients, 42 in M-TURBT group and 48 in B-TURBT group had only CAD or CAD and concomitant diseases, such as hypertension (HT) and/or diabetes mellitus (DM). No statistically significant differences were observed in the baseline characteristics of 2 groups. Mean ages in M-TURBT and B-TURBT groups were 71.36±7.49 and 73.71±8.15 years, respectively (p=0.157). Mean tumor sizes were 3.1±2.4cm in M-TURBT group and 3.0±2.9cm in B-TURBT group (p=0.875). Mean tumor numbers were 1.8±1.4 and 2.0±1.6 in M-TURBT and B-TURBT groups, respectively (p=0.556). Patient’s characteristics are shown in Table-1.

The operation time was not significantly different between M-TURBT and B-TURBT groups (34.6±18.7min vs. 34.3±21.2min; p=0.955). Obturator jerk was detected in 16.7% of the patients in group 1 and 2.1% in group 2, and this difference was statistically significant (p=0.007). No significant differences were found between M-TURBT and B-TURBT groups regarding complete tumor resection rates (76.2% vs. 87.5%, p=0.162) and muscle tissue sampling rates (71.4% vs. 64.6%,p=0.252). There were only two patients with thermal tissue damage in M-TURMT group and 1 patient in B-TURBT group. Mean catheterization time (days) was 1.7±1.4 and 1.5±1.3 in M-TURBT and B-TURBT groups, respectively (0.948). Intraoperative and postoperative outcomes are displayed in Table-2.

Subserosal bladder injury was detected in 6 patients (14.3%) in M-TURBT and 4 patients (8.3%) in B-TURBT groups (p=0.505). Complete bladder perforation was not detected in any of the groups. No significant differences were observed between the groups regarding clot retention, re-
Monopolar and bipolar transurethral resection of bladder tumors in patients with coronary artery disease

There was no patient with TUR syndrome in each group. Mean hemoglobin (Hb) and sodium (Na) decreases in the postoperative period were comparable between the groups. Postoperative complications and adverse events are displayed in Table-3.

In the peri- and postoperative periods, there was no death in both groups.

DISCUSSION

Uncomplicated surgery is especially important in urology clinics, which assist an elderly patient population. Even a small complication that develops in this patient group can lead to serious consequences due to accompanying comorbidities. The most common deadly comorbidity in the elderly patient group is CAD with or without comorbidities such as HT and DM. Overall, urological surgery is associated with a 2% risk of postoperative myocardial infarction and cardiac-related mortality, with TURBT considered as a low risk operation (15). In this comparative study, we aimed to analyze the results of monopolar and bipolar TURBT in patients who had CAD with or without other comorbidities.

Transurethral resection is integral to the management of bladder neoplasms (1). In recent years, as their experience with bipolar resection systems increases, urologists have begun to prefer...
### Table 1 - Preoperative patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M-TURBT</th>
<th>B-TURBT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. patients</strong></td>
<td>42</td>
<td>48</td>
<td>0.173*</td>
</tr>
<tr>
<td>Male</td>
<td>37 (88.1)</td>
<td>37 (77.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (11.9)</td>
<td>11 (22.9)</td>
<td></td>
</tr>
<tr>
<td>Mean±SD age (years)</td>
<td>71.36±7.49</td>
<td>73.71±8.15</td>
<td>0.157†</td>
</tr>
<tr>
<td>Mean±SD BMI (kg/m²)</td>
<td>25.14±4.80</td>
<td>26.13±4.82</td>
<td>0.336†</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>42</td>
<td>48</td>
<td>0.173*</td>
</tr>
<tr>
<td>Only CAD</td>
<td>18</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>CAD+HT</td>
<td>16</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>CAD+DM</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CAD+HT+DM</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>No. NYHA score</strong></td>
<td></td>
<td></td>
<td>0.955*</td>
</tr>
<tr>
<td>2</td>
<td>19 (45.2)</td>
<td>22 (45.8)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>23 (54.8)</td>
<td>26 (54.2)</td>
<td></td>
</tr>
<tr>
<td><strong>No. ASA score</strong></td>
<td></td>
<td></td>
<td>0.426*</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21 (50)</td>
<td>19 (39.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21 (50)</td>
<td>28 (58.3)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Mean±SD preop Hb (g/dL)</td>
<td>13.3±1.8</td>
<td>13.0±1.9</td>
<td>0.143†</td>
</tr>
<tr>
<td>Mean±SD preop Na (mmol/L)</td>
<td>137.6±2.2</td>
<td>137.8±3.1</td>
<td>0.736†</td>
</tr>
<tr>
<td>Mean±SD tumor size (cm)</td>
<td>3.1±2.4</td>
<td>3.0±2.9</td>
<td>0.875†</td>
</tr>
<tr>
<td>Mean±SD tumor number</td>
<td>1.8±1.4</td>
<td>2.0±1.6</td>
<td>0.556†</td>
</tr>
<tr>
<td>No. orifice involvement</td>
<td>10 (23.8)</td>
<td>14 (29.2)</td>
<td>0.566*</td>
</tr>
<tr>
<td><strong>No. stage</strong></td>
<td></td>
<td></td>
<td>0.473*</td>
</tr>
<tr>
<td>Ta</td>
<td>24</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>12</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>6</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>No. grade</strong></td>
<td></td>
<td></td>
<td>0.530*</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

BMI = Body mass index; CAD = Coronary artery disease; HT = Hypertension; DM = Diabetes Mellitus; ASA = American Society of Anesthesiologists; NYHA = New York Heart Association; Hb = Hemoglobin; Na = Sodium

† Independent sample t test, * Chi-square
these systems in the treatment of bladder tumors. A bipolar current has better hemostatic capacity compared with a monopolar current because it allows deep coagulation and has a cut and seal effect (16). Sugihara et al. found a similar incidence of postoperative hemostatic procedures and transfusion rates in a comparative study between monopolar and bipolar TURBT (16). In another study, Zhao et al. reported that bleeding was not a severe risk factor during TURBT to the urologists in the current approaches, and the established blood loss between both groups was not significantly different (17). Based on the prostatic experience, bipolar resection was believed to induce better hemostasis as the deep coagulation and the cut and seal property of the bipolar current contribute to augment the ability to control bleeding points (18, 19). In the current study, mean Hb and

Table 2 - Intraoperative and postoperative outcomes.

<table>
<thead>
<tr>
<th></th>
<th>M-TURBT (Mean±SD)</th>
<th>B-TURBT (Mean±SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD operation time (min.)</td>
<td>34.6±18.7</td>
<td>34.3±21.2</td>
<td>0.955†</td>
</tr>
<tr>
<td>Mean±SD resected tissue (cc)</td>
<td>3.77±4.47</td>
<td>5.55±9.52</td>
<td>0.251†</td>
</tr>
<tr>
<td>Obturator jerk (%)</td>
<td></td>
<td></td>
<td>0.007*</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (11.9)</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (4.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. complete tumor resection</td>
<td>32 (76.2)</td>
<td>42 (87.5)</td>
<td>0.162*</td>
</tr>
<tr>
<td>No. early postop instillation</td>
<td>14 (33.3)</td>
<td>8 (16.7)</td>
<td>0.074**</td>
</tr>
<tr>
<td>No. thermal tissue damage (%)</td>
<td></td>
<td></td>
<td>1.000*</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1(2.4)</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (2.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. muscle tissue sampling (%)</td>
<td>30 (71.4)</td>
<td>31 (64.6)</td>
<td>0.252*</td>
</tr>
<tr>
<td>Means±SD catheterization time (day)</td>
<td>1.7±1.4</td>
<td>1.5±1.3</td>
<td>0.948†</td>
</tr>
<tr>
<td>Mean±SD hospitalization time (day)</td>
<td>2.8±2.1</td>
<td>2.4±2.1</td>
<td>0.456†</td>
</tr>
</tbody>
</table>

† Independent sample t test; * Chi-square; ** Fisher’s exact

Table 3 - Postoperative complications and adverse events.

<table>
<thead>
<tr>
<th></th>
<th>M-TURBT (Mean±SD)</th>
<th>B-TURBT (Mean±SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. bladder perforation (%)</td>
<td></td>
<td></td>
<td>0.505*</td>
</tr>
<tr>
<td>Subserosal injury</td>
<td>6 (14.3)</td>
<td>4 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Complete perforation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. febrile urinary tract infection (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. clot retention (%)</td>
<td>1 (2.4)</td>
<td>0</td>
<td>0.461**</td>
</tr>
<tr>
<td>No. blood transfusion (%)</td>
<td>2 (4.8)</td>
<td>0</td>
<td>0.215**</td>
</tr>
<tr>
<td>No. TUR syndrome (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. recoagulation (%)</td>
<td>1 (2.4)</td>
<td>0</td>
<td>0.461**</td>
</tr>
<tr>
<td>Mean ± SD Hb decrease (g/dL)</td>
<td>-0.66±0.66</td>
<td>-0.72±1.24</td>
<td>0.307†</td>
</tr>
<tr>
<td>Mean ± SD Na decrease (mmol/L)</td>
<td>-0.40±2.64</td>
<td>-0.43±3.40</td>
<td>0.051†</td>
</tr>
</tbody>
</table>

TUR=Transurethral resection, Hb=Hemoglobin, Na=Sodium
† Independent sample t test; * Chi-square; ** Fisher’s exact
sodium decreases in the postoperative period were not different between the two groups. This can be explained by three facts: Firstly, bleeding in TURBT was not severe as that in TURP, secondly the amount of tissue resected in bladder tumors was much less than in prostate operations, and lastly the operation time of TURBT is shorter than TURP. When we examined postoperative complications, blood transfusion was performed in 2 patients and clot retention was seen in one patient in M-TURBT group. None of the patients had blood transfusion and clot retention in B-TURBT group. In our series, the mean catheterization time and hospitalization time were also similar in both groups.

A major concern for most urologists is to achieve complete removal of the bladder tumor without any complications (20). An incidence of obturator jerk during TURBT is variable according to the type of anesthesia employed and the site of the tumor (21). Reporting the incidence and the difference between both techniques in inducing obturator reflex is the subject of debate (21). Some reports described obturator reflex occurred in nearly half of the patients and others reported an incidence around 1% (2, 22). Aggressive, deep resection or obturator nerve reflex that results in violent adduction of the leg during the resection may cause the injury or even perforation of the bladder wall (23). In the current study, the incidence of obturator reflex was significantly different in each group and found as 16.7% in group 1 and 2.1% in group 2 (p=0.007). Spinal anesthesia without obturator block carries higher risk than general anesthesia for obturator jerk. Although it is rare, bladder perforation is a major complication that worries urologists. Real incidence of bladder perforation might be possibly underestimated because of underreporting, and it ranges from 1.7 to 5% (6, 24). Similar to obturator reflex debate, the value of bipolar resection in decreasing the incidence of bladder perforation is yet to be confirmed (21). Gupta et al. reported a significant rate of obturator jerks and subsequent perforation in their first 10 patients when the power setting of the bipolar machine was adjusted for 160 and 80W for cutting and coagulation, respectively (25). But, they showed that such complications had been eliminated by using a lower power setting of 50 and 40W (25). In another study, Golan et al. reported an incidence of 0.36% for bladder perforation in an analysis of 4.144 TURBT procedures and concluded that severe bladder injury was more likely to occur in elderly patients with large tumors located on the posterior wall, and that it did not appear to increase the risk of extravesical seeding (26). In this study, none of the patients in both groups had complete perforation of bladder.

None of our patients died from cardiovascular disease. Undoubtedly, this can not be solely attributed to the success of the surgical procedure. It is important to evaluate these patients carefully and rigorously for the last cardiac status in the preoperative period. The operation may be delayed temporarily in patients who require urgent coronary stenting or have severe arrhythmia, except those who need immediate surgical intervention. Preoperative withdrawal of anticoagulant/antiaggregant drugs to reduce the risk of regional or neuraxial blockade is another important point. The interruption of long-term acetyl salicylic acid (ASA) treatment for elective urologic procedures creates a management dilemma due to the competing risks of recurrent ischemic events and hemorrhage (10). In a meta-analysis of 50.279 patients treated with ASA for secondary prevention of CAD, Eisenstein et al. showed that the cardiac complication rate increased threefold after withdrawal of ASA and that the rate was even higher for patients with coronary stents (27). Despite being controversial, our clinical approach is to stop anticoagulant/antiaggregant medicines before 7 days and give low-molecular-weight heparin for prophylaxis. Our results support that this clinical approach is feasible for these group of patients. To the best of our knowledge, the recent study represents the first trial comparing the safety and efficacy of monopolar and bipolar TURBT in patients with CAD.

Our study has some limitations. Firstly, the present study has relatively small sample size. The low number of the patients can be explained by our exclusion criteria. We excluded patients who were not suitable for spinal anesthesia and unfit for surgery due to previous coronary artery stenting or by-pass surgery. We also excluded patients who were treated with anticoagulant/antiaggregant
medication. Since most of the patients with CAD had to use anticoagulant/antiaggregant drugs, our final patient number was 90. Secondly, we had supposed that anticoagulant/antiaggregant medication could potentially effect the outcomes of this prospective study and excluded these patients to have a more homogenous group of patients.

CONCLUSIONS

Both monopolar and bipolar systems can be used safely and effectively during TURBT procedure in patients with CAD. Obturator jerk was more frequently seen in M-TURBT and a careful surgical approach is needed during M-TURBT.

CONFLICT OF INTEREST

None declared.

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18. Mamoulakis C, Skolarikos A, Schulze M, Scoffone


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Telephone: +90 505 638-3010
E-mail: drbolat@hotmail.com
Acute kidney injury following radical cystectomy and urinary diversion: predictors and associated morbidity


1 Urology and Nephrology Center, Mansoura University, Egypt

ABSTRACT

Introduction: Acute kidney injury (AKI) after major surgeries is associated with significant morbidity and mortality. We aim to report incidence, predictors and associated comorbidities of AKI after radical cystectomy in a large cohort of patients.

Materials and Methods: We conducted a retrospective analysis of 1000 patients who underwent open radical cystectomy in a tertiary referral center. Perioperative serum creatinine measurements were used to define AKI according to the RIFLE criteria (as Risk, Injury and Failure). The predictors of AKI after surgery were determined using univariate and multivariate analyses.

Results: Out of 988 evaluable patients, AKI developed in 46 (4.7%). According to RIFLE criteria; AKI-Risk, AKI-Injury and AKI-Failure occurred in 26 (2.6%), 9 (0.9%) and 11 (1.1%) patients, respectively. Multivariate analysis showed that performing nephroureterectomy with cystectomy (Odds ratio [OR]: 4.3; 95% Confidence interval [CI]: 1.3-13.6; p=0.01) and the development of high grade complications (OR: 3.8; 95% CI 1.9-7.2; p<0.0001) were independently associated with AKI.

Conclusions: AKI is a significant morbidity after radical cystectomy and the term should be included during routine cystectomy morbidity assessment.

INTRODUCTION

Radical cystectomy and urinary diversion continue to be the basic modality for treatment of localized muscle invasive bladder cancer in both genders (1). Following surgery, a wide scale of diversion-related complications have been described and extensively analyzed including gastro-intestinal, urinary and renal function complications (2).

Acute kidney injury (AKI) is a devastating co-morbidity that is commonly encountered in critically ill patients and after major surgeries and is associated with severe morbidity and mortality (3). It has been shown that patients who partially recovered from an episode of AKI are at higher risk of long-term mortality (4) and those who completely recovered from an episode of AKI are more likely to develop incident chronic kidney disease (CKD) (5) or even end-stage renal disease (6, 7). The incidence and predictors of AKI after major urologic surgeries are poorly studied in the literature and limited mainly to cardiothoracic and orthopedic surgeries (8-10). This study was conducted to investigate the incidence and predictors of AKI in a large cohort of patients undergoing radical cystectomy and urinary diversion.
MATERIALS AND METHODS

Study Design

A retrospective cohort study was conducted in 1000 patients underwent radical cystectomy and urinary diversion at our tertiary referral center between January 2004 and September 2009. The study received our internal review board approval with informed consent waived because of the retrospective nature of the study. Patients with missed data about serum creatinine (SCr) measurements were excluded (n=12). All patients underwent open radical cystectomy with standard pelvic lymphadenectomy up to the level of the common iliac artery and followed by urinary diversion. During the postoperative period, all ureters were stented for 11-to-13 days after orthotopic bladder substitution and 9 days after ileal conduit urinary diversion. Patients were kept in the hospital until catheter free; 21 days and 11 days for orthoptic and ileal conduit diversions, respectively.

Data Collection and Measurements

Data were collected from a prospectively maintained electronic database at our institution. Demographics included age, gender, body mass index (BMI) with obese patients defined as BMI >30, and the presence of diabetes mellitus or hypertension. Patient’s co-morbidities were assessed using age-adjusted Charlson Co-morbidity index (CCI) as previously described (11). The presence of CKD was diagnosed as proposed by the National Kidney Foundation by having estimated glomerular filtration rate (eGFR) <60mL/min/1.7m² (12). Baseline GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) (13). In patients presented with oliguria or anuria, measurements were obtained after decompressing the pelvicalyceal system by percutaneous nephrostomy tube and SCr measures had stabilized.

Recorded laboratory values included hemoglobin (anemia was defined as <10gm/dL) and albumin (hypoalbuminemia was defined as serum albumin <3.5gm/dL). The rate of blood loss was described as hemoglobin deficit and was calculated by the difference between preoperative and the lowest value of postoperative hemoglobin. Operative data included performing nephroureterectomy with cystectomy or not and type of the urinary diversion. The operating time was not reported in all patients; therefore, this item was eliminated from the analysis.

Postoperative complications were classified and graded according to the proposed modification of the Dindo-Clavien system (14) and grade I and II were considered minor and grades III to IV were considered major.

Outcome Assessment

The primary outcome of the study is the development of AKI. Three SCr measurements were used to define AKI. Baseline SCr is the nearest value before or at time of surgery. During the postoperative period, the peak SCr elevations and SCr at discharge were recorded. Patients with persistent rise of SCr at time of discharge were included. Patients with temporary transient rise were excluded from the study. Based on these readings, AKI was defined according to the RIFLE criteria by a persistent (till time of discharge) increase of SCr measurements 1.5 times the baseline value (15). Acute kidney injury was further classified into AKI-Risk (SCr increases >1.5 times the baseline value), AKI-Injury (SCr increased >2 times the baseline value) and AKI-Failure (SCr increased >3 times the baseline value). As the scope of this study was limited to the perioperative period, AKI categories Loss of function and End-stage renal disease were not evaluated.

Statistical analysis

Continuous variables were described as mean±SD for parametrically-distributed variables and median (interquartile range [IQR]) for non-parametric variables and nominal variables as frequencies (percentages) in each category. Age and BMI were described as continuous and nominal variables. We determined the incidence of AKI after radical cystectomy and urinary diversion. Continuous variables were compared between the two groups by student t test and categorical variables by Chi-square test. Patient’s demographics, operative and postoperative data were tested for
association with the occurrence of AKI. Significant factors were entered into a binary logistic regression model to determine the independent factors associated with AKI. Further sub-analysis of the cohort was performed excluding patients underwent nephroureterectomy with cystectomy, to account for a more homogenous study population.

**RESULTS**

**Patient’s Characteristics**

A total of 988 patients (82.1% males) were eligible for the perioperative assessment of AKI. Of our study population, 72.9% were considered to have normal preoperative renal function (eGFR ≥60mL/min./m²). Ileal orthotopic bladder substitution was the most popular type of diversion and urothelial carcinoma was the most common histopathological type. Patient’s demographics are displayed in Table-1.

**Incidence and independent variables associated with AKI after radical cystectomy**

Acute kidney injury developed in 46 (4.7%) patients after radical cystectomy. According to RIFLE criteria; AKI-Risk, AKI-Injury and AKI-Failure occurred in 26 (2.6%), 9 (0.9%) and 11 (1.1%) patients, respectively.

Table-2 presents the association between the development of AKI and various study population characteristics. Comparing patients with and without AKI, there was no significant difference regarding age, gender, presence of DM, CKD or hypertension, BMI or preoperative SCr measurements. Similarly, type of urinary diversion did not attain significant association with the development of AKI after surgery.

The mean±SD age-adjusted CCI was 2.8±0.9 for patients developing AKI after cystectomy vs. 2.4±1 for patients without AKI, a difference with statistical significance (p=0.017). Furthermore, AKI developed in 14.3% of patients undergoing nephroureterectomy at time of radical cystectomy vs. 4.4% in patients undergoing radical cystectomy without nephroureterectomy (p=0.014). Similarly, the development of high grade postoperative complications was significantly associated with the development of AKI after radical cystectomy (12.2% vs. 3.4% in patients with and without high grade complication; p<0.0001). The relationship between different grades of complications and the subcategories of AKI are shown in Table-3.

The three significant variables were entered into multivariate binary logistic regression analysis for determining independent variants associated with the development of AKI after radical cystectomy (Table-4). Only two variables remained statistically significant; performing nephroureterectomy with radical cystectomy had 4.3 times risk of development of AKI (p=0.01) and the de-

<table>
<thead>
<tr>
<th>Table 1 - Demographics for patients undergoing radical cystectomy and urinary diversion.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr, mean, (SD)</strong></td>
</tr>
<tr>
<td><strong>Gender, no. (%)</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Urinary diversion, no. (%)</strong></td>
</tr>
<tr>
<td>Orthotopic</td>
</tr>
<tr>
<td>Ileal conduit</td>
</tr>
<tr>
<td>Continent cutaneous/rectal</td>
</tr>
<tr>
<td><strong>Histopathology, no. (%)</strong></td>
</tr>
<tr>
<td>TCC</td>
</tr>
<tr>
<td>SCC</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td><strong>Tumor stage, no. (%)</strong></td>
</tr>
<tr>
<td>T₁ or less</td>
</tr>
<tr>
<td>T₂</td>
</tr>
<tr>
<td>T₃</td>
</tr>
<tr>
<td>T₄</td>
</tr>
<tr>
<td>Tx</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
</tr>
<tr>
<td>N₀</td>
</tr>
<tr>
<td>N₁</td>
</tr>
<tr>
<td>N₂</td>
</tr>
<tr>
<td>N₃</td>
</tr>
</tbody>
</table>

SD = Standard deviation; CKD = Chronic kidney disease; TCC = Transitional cell carcinoma; SCC = Squamous cell carcinoma
Table 2 – Demographics for Patients with and Without Acute Kidney Injury after Radical Cystectomy.

<table>
<thead>
<tr>
<th></th>
<th>AKI, no. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Scale variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>57.9 (8.3)</td>
<td>60 (7.1)</td>
</tr>
<tr>
<td>Age adjusted CCI, mean (SD)</td>
<td><strong>2.4 (1)</strong></td>
<td><strong>2.8 (0.9)</strong></td>
</tr>
<tr>
<td>SCr, basal, mg/dL, mean (SD)</td>
<td>1.3 (0.5)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.4 (4.9)</td>
<td>27.1 (4.7)</td>
</tr>
<tr>
<td>HB, deficit, gm/dL, median (IQR)</td>
<td>3.3 (2.5)</td>
<td>3.3 (2.3)</td>
</tr>
<tr>
<td>Albumin, gm/dL, mean (SD)</td>
<td>3.5 (0.4)</td>
<td>3.4 (0.4)</td>
</tr>
<tr>
<td><strong>Nominal variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>775 (95.6)</td>
<td>36 (4.4)</td>
</tr>
<tr>
<td>Female</td>
<td>167 (94.4)</td>
<td>10 (5.6)</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>798 (95.6)</td>
<td>37 (4.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>144 (94.1)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>811 (95.6)</td>
<td>37 (4.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>131 (93.6)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>538 (95.9)</td>
<td>23 (4.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>404 (94.6)</td>
<td>23 (5.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>889 (95.3)</td>
<td>44 (4.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>53 (96.4)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>680 (94.4)</td>
<td>40 (5.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>262 (97.8)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>668 (95.4)</td>
<td>32 (4.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>274 (95.1)</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>644 (95.1)</td>
<td>33 (4.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>298 (95.8)</td>
<td>13 (4.2)</td>
</tr>
<tr>
<td>Nephroureterectomy with cystectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>918 (95.6)</td>
<td>42 (4.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>24 (85.7)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Type of diversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthotopic</td>
<td>543 (94.6)</td>
<td>31 (5.4)</td>
</tr>
<tr>
<td>Loop</td>
<td>372 (96.1)</td>
<td>15 (3.9)</td>
</tr>
<tr>
<td>Others</td>
<td>27 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative high grade complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td><strong>818 (96.7)</strong></td>
<td><strong>28 (3.3)</strong></td>
</tr>
<tr>
<td>Yes</td>
<td><strong>124 (87.3)</strong></td>
<td><strong>18 (12.7)</strong></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ confined</td>
<td>701 (94.7)</td>
<td>39 (5.3)</td>
</tr>
<tr>
<td>Extravesical</td>
<td>241 (97.2)</td>
<td>7 (2.8)</td>
</tr>
</tbody>
</table>

CCI = Charlson Comorbidity index; SCr = serum creatinine; BMI = body mass index; HB = hemoglobin; DM = Diabetes mellitus; CKD = Chronic kidney disease

* analysis excluded patients with Tx
Acute kidney injury following radical cystectomy

Development of high-grade postoperative complications had 3.8 times risk of the development of AKI (p<0.0001). Furthermore, sub-analysis of the cystectomy cohort performed without nephroureterectomy during surgery, yielded orthotopic urinary diversion (Odds ratio (OR): 2.5; 95% Confidence interval (CI): 1.1-4.9; p=0.018), in addition to the development of high-grade postoperative complications, was significantly associated with 2.5 times rise in the likelihood of the development of AKI.

**DISCUSSION**

Acute kidney injury is a well-studied co-morbidity after major surgical trauma notably cardiac surgeries (8, 9, 16). Radical cystectomy is a major surgical trauma by definition and urinary diversion is a well-known risk factor for renal function deterioration especially with ureteroileal anastomosis (UIA) obstruction (17). Therefore, incorporation of urinary diversion after radical cystectomy gives a special importance for studying AKI because of the increased burden on kidneys in such patients.

Early renal function changes after radical cystectomy were described in many reports in terms of acute renal failure. Schiavina et al. reported acute renal failure in 18 (4.4%) of their patients (18). Takada et al., in a multi-institutional study from Japan, reported an incidence of 0.5% of renal failure (19). Yuh and associates reported an overall incidence of 7.1% (14 out of 196 patients) that developed renal failure after robot-assisted radical cystectomy. The authors subcategorized the renal failure into 12 and 2

---

**Table 3 – Association between postoperative complications and the various stages of acute kidney injury after radical cystectomy.**

<table>
<thead>
<tr>
<th>Postoperative Complications*</th>
<th>Acute kidney injury classification, no. (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk</td>
<td>Injury</td>
</tr>
<tr>
<td>I-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20 (2.4)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (4.4)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (2.4)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (4.6)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (2.6)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (4.2)</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

* Complications are categorized according to the modified Clavien system: I, II = minor; III = required intervention either by regional or general anesthesia; IV = single or multiorgan failure requiring intensive care unit admission

**Table 4 – Univariate and Multivariate Analyses for Factors Predicting Acute Kidney Injury after Radical Cystectomy.**

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age-CCI</td>
<td>1.424</td>
<td>1.065-1.905</td>
</tr>
<tr>
<td>NU</td>
<td>3.643</td>
<td>1.209-10.974</td>
</tr>
<tr>
<td>High grade complications</td>
<td>3.940</td>
<td>2.102-7.384</td>
</tr>
</tbody>
</table>

CCI = Charlson comorbidity index; NU = nephroureterectomy with cystectomy; OR = odds ratio; CI = Confidence interval
patients with minor and major complications, respectively (20). In the previous studies, the definition of postoperative renal failure is not clear, highlighting the lack in reporting AKI in the literature after radical cystectomy.

In this study, 46 (4.7%) of our patients developed persistent AKI at time of discharge. This incidence is relatively lower than reported after other major surgeries. After cardiac surgery, the incidence ranged from 8.9% up to 42% (8, 21) while after orthopedic surgery it was 16.8% (10). The probable higher risk of bleeding with its subsequent impact is anticipated in both cardiac and orthopedic surgeries. The use of cardiopulmonary bypass technique is a possible added factor in cardiac patients.

Many studies have described the association between various preoperative predictors and the occurrence of AKI after major surgeries (8, 16, 22). It has been shown previously that low eGFR is a significant predictor of AKI after major surgery (10, 22). However, this cannot be proved in our report probably because of the follow-up was limited to the peri-operative period. It has been shown that patients who experienced AKI were significantly associated with the development of later CKD on the long-term. Jones et al. showed that after a median follow-up of 2.5 years, 15% of patients with AKI, who were completely recovered at time of discharge, developed CKD with 5.9 folds increase in risk than those without AKI (5). Coca and associates in their systematic review about the incidence of CKD after AKI reported that patients with AKI had 8.8 and 3.1 folds increased risk for the development of CKD and ESRD, respectively (23). Therefore, the impact of AKI on the development of CKD on the long-term in this patient population is awaited.

Age-adjusted CCI is a cumulative score of multiple co-morbidities including diabetes mellitus, hypertension, cardiac and renal problems. These factors are known to affect renal function and therefore, patients with higher age-adjusted CCI are more likely to develop AKI in context of major surgical trauma as radical cystectomy. Nevertheless, our data failed to provide such evidence on multivariate analysis as an independent predictor. Generally, CCI is accepted as a mortality rather than a morbidity predictor (24). Although obesity was also shown to be associated with the development of AKI via oxidative stress mechanisms (25), BMI failed to predict AKI occurrence after radical cystectomy in this series probably because patients with morbid obesity are referred to radiotherapy as the primary modality of treatment in our practice.

In this contribution, performing nephroureterectomy with cystectomy was identified as a risk factor for the development of AKI irrespective of the type of urinary diversion. Probable explanations for these patients include possible prolongation of the operative time with subsequent increase in blood loss, hypotension and hypothermia as well as loss of functioning renal mass in patients performing nephrectomy for associated upper urothelial malignancy. Novara et al. reported significantly poor cancer-specific survival in patients with combined radical cystectomy and nephroureterectomy compared with isolated nephroureterectomy based on multi-institutional study (26). Conversely, in attempt to homogenize the cohort, we performed a sub-analysis excluding patients underwent nephroureterectomy with cystectomy, in this context, orthotopic substitution came into focus. It has been reported that the link between orthotopic substitution and renal function deterioration was attributed to the development of UIA stricture and to a less extent, pyelonephritis (27). Recently, there has been a focus on the effect of urinary diversion type on renal function. Gondo et al. has found that the type of urinary diversion was significantly correlated with renal function three months after surgery (28). Although this correlation was not maintained on multivariate analysis, this particular study is underpowered as smaller number of patients were included (164 patients). On the other hand, in a propensity matched analysis, the type of urinary diversion did not show an independent association with the development of CKD after surgery (29). Likewise, in patients with preoperative impaired renal function, continent diversion did not confer a risk for further renal function deterioration (30). It has to be noted that these two reports evaluated the long-term renal functional outcomes, and neither any of both had evaluated the develop-
ment of AKI in the early postoperative period and its long-term effects. Therefore, a more in-depth look is essential to delineate this issue.

Higher grade complications were proved to be independent predictors for the development of AKI. Whether these complications are the cause or an effect of AKI is debatable and further analysis of the timing of the occurrence of AKI would provide us with more precise conclusion. Finally, the significant association between AKI and early post-operative mortality is one of the most important data derived from this work.

To the best of our knowledge, this work is the first to categorize the incidence and predictors of AKI after radical cystectomy. The results of the study highlight the importance of reporting such significant complication in a standardized fashion. In addition, it appears mandatory to counsel the patient preoperatively for the risk of development of AKI. Finally, we invite all authors to report their incidence and predictors of AKI and the further impact on CKD on the long-term. Nevertheless, this study has several limitations that might interfere with accurate data interpretation. The retrospective nature of the study prevented incorporation of various potentially modifiable risk factors in the analysis as smoking history, the rate of blood transfusion, operative time, the use of nephrotoxic drugs, perioperative medications and anesthesia management that had been shown to affect the occurrence of AKI after major surgeries (8, 16, 31). Furthermore, we admit the relative low number of AKI incidents that underpowered the statistical analysis; therefore, multi-institutional studies are highly recommended.

CONCLUSIONS

We conclude that AKI is a significant morbidity after radical cystectomy that is associated with higher mortality rate. Patients with nephroureterectomy and those with high grade complications are more liable to develop AKI. Impact of AKI on the development of CKD on the long-term in this patient population is awaited. We believe this term is to be included during routine morbidity assessment of patients with radical cystectomy and urinary diversion.

CONFLICT OF INTEREST

None declared.

REFERENCES


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The diagnostic value of FNDC5/Irisin in Renal Cell Cancer

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ABSTRACT

Purposes: The aim of this study was to determine the diagnostic significance of fibronectin type III domain containing protein 5 (FNDC5)/Irisin levels in the sera of patients with renal cell cancer.

Materials and Methods: In the study, 48 individuals were evaluated. The patient group included 23 subjects diagnosed with renal tumor, and the control group of 25 healthy individuals. Patients diagnosed with renal tumor received surgical treatment consisting of radical or partial nephrectomy. Blood specimens were collected and serum FNDC5/Irisin and carcinoembryonic antigen (CEA) levels were determined using enzyme-linked immunosorbent assay (ELISA).

Results: FNDC5/Irisin and CEA levels in renal cancer patients were significantly higher compared with the control group (p=0.0001, p=0.009, respectively). Also, FNDC5 levels was more sensitive and specific than CEA levels. The best cut-off points for FNDC5/Irisin were >105pg/mL and CEA were >2.67ng/mL for renal cancer.

Conclusions: FNDC5/Irisin may be used as a diagnostic biomarker for renal cancer.

INTRODUCTION

Type-1 membrane protein FNDC5 contains 212 amino acids (aa). The N-terminal of FNDC5 contains the signal peptide (1-31aa) followed by the “Irisin,” which is 112 amino acids long (32-143aa). The length of the transmembrane domain is 21 amino acids and that of the cytoplasmic domain 48 amino acids (1). FNDC5 is proteolytically cleaved from the N-terminal domain, and a newly identified hormone, irisin, is then formed and released into blood. This hormone is known to act via cell surface receptors, although no such receptor has yet been identified (2). FNDC5 genes are present in humans, mice and rats. Expression of FNDC5 is stimulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α), which is a transcriptional co-activator of the peroxisome proliferator-activated receptor gamma nuclear receptor (PPARγ) (3). Serum FNDC5/irisin levels have previously been investigated in obesity, chronic kidney disease, type 2 diabetes mellitus (3-7) and various types of cancer (16-20).

Urological cancers are comprised of bladder, prostate, renal and testis cancers, which are among the 10 most frequent cancers in man except testis cancer. So far, the gold standard diagnosis of urological cancer is pathological diagnosis, and early screening methods are rare. Bladder...
cancer and kidney cell carcinoma lack specific predictive biomarkers and only some symptoms, for instance, hematuria, might have some effects in finding the existence of cancer (8).

Renal cancers amounts to 2% of the total human cancer burden, with approximately 190,000 new cases diagnosed each year. Although renal tumors can be completely removed surgically, hematogenous metastasis is frequent and may occur already at an early stage of the disease. Approximately, 85% of renal cancer is renal cell mediated. Renal cell carcinoma is a group of malignancies arising from the epithelium of the renal tubules. The most common type of renal cancer is clear cell renal cell carcinoma, which constitutes 60% to 70% of renal cell carcinomas (9). Clear cell renal cell carcinoma (CCRCC) is the most common type of cancer found in the kidney accounting for ~90% of all kidney cancers. In 2012, there were ~337,000 new cases of RCC diagnosed worldwide with an estimated 143,000 deaths, with the highest incidence and mortality in North America and Europe (10). Several studies have been performed with the aim of developing a biomarker with a high predictive value in renal tumors (11-13).

Carcinoembryonic antigen, first described by Gold and Freedman (1965), is a tumor-associated antigen characterised as a glycoprotein of approximately 180kDa molecular weight. CEA serum levels are known to be elevated in patients with a variety of neoplasms derived from the endoderm and ectoderm. Another studies showed CEA levels increased in renal cancer (11-13).

Based on the objective of developing a biomarker capable of use in renal tumors, we investigated FNDC5/irisin, a marker that has not previously been studied in patients with renal tumor. We compared FNDC5/irisin, with CEA, previously investigated marker in renal tumors.

**MATERIALS AND METHODS**

**Study population**

This retrospective study involved 23 renal cell cancer patients and 25 healthy controls. Informed consent was obtained from all patients and controls, and approval for the study was given by the local ethics committee of the Karadeniz Technical University Faculty of Medicine. Patients were selected from individuals presenting to the Karadeniz Technical University Medical Faculty Urology clinics. All of the patients were evaluated clinically and they were also previously biochemical and radiologically investigated. Surgical treatment in the form of radical or partial nephrectomy was performed in all cases of diagnosed renal tumor.

Five milliliter (5ml) blood samples for each subject were collected and kept for approximately 30 min in Vacutainer® tubes. These were taken from the peripheral vein and stored at 4°C. Serum specimens were obtained by centrifuging the blood samples at 3000rpm for 10 min. Serum specimens were then stored at ~80°C until biochemical analysis.

**Determination of FNDC5/irisin and CEA Levels**

FNDC5/irisin levels were determined using an enzyme linked immunosorbent assay (ELISA) kit (USCN, Life Science Inc., Catalog No.USCN-E82576Hu, P.R. China) in line with the manufacturer’s instructions. Absorbance of samples was measured at 450nm using a VERSA max tunable microplate reader (designed by Molecular Devices, California, USA). Results were expressed as pg/mL.

**Human (CEA) ELISA Kit**

CEA levels were determined using an ELISA kit (Sunred, Ref: DZE201121715, Lot: 201601, Shanghai, PRC) in line with the manufacturer’s instructions. Absorbance of samples was measured at 450nm using a VERSA max tunable microplate reader (designed by Molecular Devices, California, USA). Results were expressed as ng/mL.

**Statistical Analysis**

The test results were analyzed on SPSS (Statistics Program for Social and Science) 13.0.1 (license number: 9069772) statistical software. Data were shown as mean±standard deviation for normal distributed and median (interquartile range) for non-normal distributed variables. The distribution of FNDC5, CEA levels in each group...
were calculated by Kolmogorov-Smirnov test. Comparisons of the renal cancer’s and control groups were done by Student’s t-test for normal distribution and by Mann-Whitney U-test for non-normal distribution. Statistical significance was accepted as p<0.05.

RESULTS

Twenty-three patients were enrolled in the study. The renal tumor group consisted of 17 (73.91%) male and 6 (26.08%) female patients with a mean age of 58.5±15.7 years (range 25 to 80). The healthy control group consisted of 17 (49.1%) male and 8 (50.9%) female, with a mean age of 55.0±13.0 (range 40 to 66).

Distribution of biochemical parameters in the renal cancer and control groups is shown in Table-1. Comparison of two groups revealed significantly elevated FNDC5/Irisin levels and CEA in the patients with renal tumor (p=0.0001, p=0.009, respectively). Optimum diagnostic FNDC5/Irisin and CEA cutoff point, AUC according to the receiver operator characteristic (ROC) curve data are shown in Table-2. The pathological distribution of the tumors (pathological type, Fuhrman’s nuclear grade, pathological stage) in patients is shown in Table-3. The cases were classified according to the histological type, and clear cell RCC cases were also graded according to the Fuhrman system. There were also no significant difference between groups in terms of pathological type and stage and the Fuhrman’s grade (p>0.05). Spearman correlation analysis results of FNDC5/Irisin and CEA in patient, and control groups is shown in Figure-1. In addition, FNDC5 levels showed higher sensitivity and specificity indexes when compared to CEA levels, as observed in Figure-1. There was correlation between biochemical parameters in patient and control group (p=0.0001, r=0.636) (Figure-2).

DISCUSSION

Substantial promotions have been made in recent years in the diagnosis of renal cancers. But, there is still a need for a marker capable of use in the diagnosis and in determining prognosis of renal cancers.

Several studies have been performed with the aim of developing a biomarker with a high predictive value in renal tumors. Chu et al. found an overall increase of plasma CEA in 56% of the 23 patients studied (11), while Guinan et al.

Table 1 - FNDC5/Irisin and CEA levels.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Renal Cancer Group (n:23)</th>
<th>Control Group (n:25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNDC5/Irisin (pg/mL)</td>
<td>208±97</td>
<td>110±79</td>
<td>0.0001</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>4.08 (2.99-21.9)</td>
<td>3.36 (2.54-5.21)</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

Data were expressed as: mean ± SD, median (inter quarter range for 25-75%)

p shows differences between Control and Cancer according to student t test,

*p shows differences between Control and Cancer according to Mann Whitney U test

Table 2 - Optimum diagnostic FNDC5/Irisin and CEA cutoff point, AUC according to the receiver operator characteristic (ROC) curve.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>95% CI</th>
<th>Cutoff Point</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNDC5/Irisin (pg/mL)</td>
<td>0.768</td>
<td>0.658-0.856</td>
<td>&gt;105.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>0.666</td>
<td>0.558-0.763</td>
<td>&gt;2.67</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Table 3 - The pathological distribution of the tumors in patients.

<table>
<thead>
<tr>
<th>Pathological type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear Cell RCC</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>4 (17.3)</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>2 (8.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fuhrman’s nuclear grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>11 (47.8)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 (8.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1a</td>
<td>10 (43.4)</td>
</tr>
<tr>
<td>pT1b</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>pT2a</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>pT2b</td>
<td>2 (8.6)</td>
</tr>
<tr>
<td>pT3a</td>
<td>1 (4.3)</td>
</tr>
</tbody>
</table>

RCC = Renal cell cancer

Figure 1 - ROC curve analysis of renal cancer patient FNDC5/irisin and CEA values.

Figure 2 - FNDC5/irisin and CEA correlation.

found similar (41%) CEA positivity in their 23 patients with renal-cell carcinoma (12). Cases et al. (1991) showed that CEA, CA-50 and CA-125 levels were elevated in serum of patients with chronic renal failure and in haemodialysis patients (13). Karaguzel et al. showed that signal peptide, CUB domain and EGF like domain containing 1 (SCUBE-1) appears to represent a promising biomarker in the diagnosis and follow-up of cases of renal tumor (14).

FNDC5 is a type-1 membrane protein. Potential roles and applications of serum FNDC5/irisin in obesity, chronic kidney disease, Type 2 diabetes mellitus have been investigated in previous studies (3–7).

Recently, some researchers want to reveal cancer and irisin relationship. Moon et al. showed that physiological (5–10nmol/L) and physiologically/pharmacologically high concentrations (50–100nmol/L) of irisin had no in vitro effect on cell proliferation and malignancy potential of obesity-related cancer cell lines (15). Us Altay et al. study is about irisin levels in gastric cancer in mice. They revealed that irisin levels increase in the circulation with the development of gastric cancer (16). Increased irisin immunoreactivity in tissues obtained from breast, ovary, cervix carcinomas, and endometrial hyperplasia suggest critical role of this peptide during carcinogenesis (17). Provatopoulou et al. aimed to examine
the association between irisin and breast cancer and to evaluate the ability of serum irisin levels to discriminate between breast cancer patients and controls. Serum levels of irisin were significantly lower in breast cancer patients compared to controls (18). Irisin is a protein involved in heat production by converting white into brown adipose tissue, but there is no information about how its expression changes in cancerous tissues. In Aydin et al. study, they used irisin antibody immunohistochemistry to investigate changes in irisin expression in gastrointestinal cancers compared to normal tissues. Histoscores (area intensity) indicated that irisin was increased significantly in gastrointestinal cancer tissues, except liver cancers (19). Gaggini et al. showed that in human hepatocellular carcinoma FNDC5/irisin expression increased (20). Shoa et al. showed that irisin suppresses the migration, proliferation, and invasion of lung cancer cells via inhibition of epithelial-to-mesenchymal transition (21). In our research renal cancer patients FNDC5/irisin and CEA levels were significantly higher compared with the control group. Furthermore, FNDC5 is more sensitive and specific than previously investigated marker in renal tumors, CEA.

The major limitation of our study is the relatively small number of patients and controls involved. Also, no demographic values and routine laboratory findings were given to groups, because our study was for diagnostic marker research so no need to use routine laboratory findings. Only the parameters age and gender numbers were evaluated and there were nearly the same.

Our study was the first that evaluated irisin in renal cell cancer and irisin levels increased significantly. But what amount of increase irisin level in renal cell cancers yet we don’t know. Oxidative stress markers (for lipid, protein, DNA oxidations) and inflammation markers must be searched. New studies are been planned to lighten the pathways.

LIMITATIONS

The major limitation of the study is the relatively small number of patients and controls involved. However, in terms of the novel idea that FNDC5 is a diagnostic biomarker, our study can be considered pioneering research in the field and can serve as a basis for further comprehensive studies.

ETHICAL APPROVAL

Approval for the study was given by the Local Ethical Committee under reference no. 2014-16.

CONFLICT OF INTEREST

None declared.

REFERENCES


15. Moon HS, Mantzoros CS. Regulation of cell proliferation and malignant potential by irisin in endometrial, colon, thyroid and esophageal cancer cell lines. Metabolism. 2014;63:188-93.


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The preoperative stratification of patients based on renal scan data is unable to predict the functional outcome after partial nephrectomy

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ABSTRACT

Introduction: eGFR-categories are used to predict functional outcome after partial nephrectomy (PN); no study categorized patients according to preoperative renal scan (RS) data. Aim of the study was to evaluate if stratification of patients according to RS is a reliable method to predict minor/major loss of renal function after PN.

Materials and Methods: We considered patients who underwent PN and RS pre-/post-PN for T1 tumor in our Institution (2007–2017). Demographics, perioperative and specifically functional data were analysed. On the basis of the baseline Split Renal Function (SRF), patients were stratified into risk-categories: 1) baseline operated-kidney SRF range 45–55%; 2) baseline operated-kidney SRF <45%. Risk categories were analysed with postoperative functional outcome: postoperative operated-kidney SRF decrease below 90% of baseline was considered significant loss of function. Contingency tables and univariate/multivariate regression were analysed looking for independent factors of postoperative functional impairment.

Results: 224 patients were analysed, 125 (55.8%) maintained ≥90% of their baseline function. Worse probability of maintaining ≥90% baseline renal function was found in patients with Charlson’s Comorbidity Index (CCI≥3) (p=0.004) and patients with PADUA score ≥8 (p=0.023). After stratification by baseline renal function, ischemia was the only independent factor: no effect on patients with poorer baseline renal function. Patients with baseline SRF 45–55% who did not experience ischemia had the highest probability to maintain ≥90% baseline SRF (p=0.028). Ischemia >25 minutes was detrimental (p=0.017).

Conclusions: Stratification of patients by SRF before PN is not a reliable predictor of renal functional outcome. Ischemia seems to scarcely influence patients with poorer renal function.

INTRODUCTION

Preservation of the maximum amount of operated kidney renal function is the main goal of partial nephrectomy (PN) if compared to radical (1). The majority of the published studies aimed to the report of the functional outcomes after PN have used the estimated Glomerular Filtration Rate (eGFR) as a surrogate measure of the renal function (2, 3). Even if the use of eGFR is easy and
cheap, it lacks in accuracy, as it does not take in consideration the compensation by the contralateral kidney (4–6). On the other side, a limited number of studies adopted a more precise method to assess operated kidney function (7). With the aim of assessing the degree of nephron loss after PN and identifying contributing factors, some researches have studied the individual renal unit by using nuclear renal scans (8–13). Indeed, the outcomes of published studies confirmed the role of renal scanning in quantifying the functional loss. By the moment, none of them used renal scanning to classify patients into risk categories on the basis of renal scanning outcomes at preoperative assessment.

The primary aim of the study was to determine if the stratification of patients according to SRF as assessed by renal scan is a reliable method to classify risk categories for minor or major loss of renal function after PN in comparison to the standard classification according to eGFR into chronic kidney disease stages.

The secondary aim was to look for eventual risk factors for better or worse renal functional outcome on the basis of the created risk categories.

**MATERIALS AND METHODS**

**Study Population**

We retrospectively reviewed our database dedicated to minimally-invasive nephron sparing surgery and we extracted data regarding all patients who underwent PN between 2007 and 2017. The protocol for the research project was approved by the Institutional Ethics Committee, according to the Declaration of Helsinki.

**Inclusion Criteria**

Patients who underwent minimally-invasive PN for cT1 renal mass (14) who had complete data on about the following: 1) evaluation with serum creatinine (SCr), 2) eGFR, as calculated by MDRD (Modification of Diet in Renal Disease) formula (15) and 3) nuclear renal scan (performed in our Institution) both at preoperative assessment and at the third month follow-up.

**Exclusion criteria**

Missing data, including Nuclear Renal Scan performed beyond the third month follow-up. Patients who were found to have single kidney or a horseshoe-shaped kidney or renal parenchymal scars at preoperative contrast-enhanced Computed Tomography scan. Patients who experienced complications and/or management of complications potentially impacting on renal function and/or renal volume, such as severe hypotension caused by massive bleeding, embolization or kidney infections.

**Measurements**

For each patient extracted from our prospectively maintained database, the following variables were available: demographic variables (including age, gender, body mass index (BMI) and comorbidities, as classified by Charlson’s comorbidity index (CCI) (16)); preoperative variables (including the American Society of Anaesthesiologists score, the side, the location, the clinical size and the tumor PADUA score (17) at the preoperative contrast-enhanced Computed Tomography scan); peri-operative data (including the operative time, the management of the renal pedicle, the eventual warm ischemia time (WIT), the estimated blood losses and the intra-operative complications); pathological data (including the final histology, the positive surgical margins rate and the average thickness of the peri-tumoral healthy parenchyma excised); postoperative data (including the postoperative complications as classified by the modified Clavien system (18)).

**Surgical Intervention and Experience**

An experienced laparoscopic surgeon (with more than 300 procedures carried out at the beginning of the considered time span) performed the key steps of all the surgeries (tumour resection and renorrhaphy), according to a previously described technique (19). No dedicated anaesthetic procedures (such as controlled hypotension) were used. Renorrhaphy was performed in all cases dedicated running suture of the kidney medulla and cortex, secured by Absolok® (Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) and Hem-o-lok® clips (Weck Surgical Instruments, Teleflex Medical, Durham, NC, USA), respectively (20).
Functional Evaluation

Specifically for the purpose of the study, all patients had undergone evaluation of renal function with Scr, eGFR (according to the MDRD formula) and Split Renal Function (SRF) calculated as the percentage of contribution to overall renal function by the operated kidney by mean of the nuclear renal scan. All the examinations were performed preoperatively and at the third month postoperatively. Tc-99m mercapto-acetyl triglycine 3 renal scan was performed in all cases. All renal scans were performed at our Institution and read by a dedicated nuclear medicine doctor.

On the basis of the baseline assessment of SRF, patients were stratified into two risk categories. Risk category 1 included all patients with baseline operated kidney SRF ranging from 45 to 55%; risk category 2 included all patients with baseline operated kidney SRF <45%.

The criterion was arbitrary but based on institutional expert opinion (21).

Risk categories were compared on the basis of the postoperative functional outcome: risk category migration and the percentage of maintenance of operated kidney baseline renal function were both considered in the analysis. Operated kidney postoperative SRF decrease below 90% of its baseline was considered as significant loss of renal function (i.e from baseline SRF=45 to postoperative SRF=40 represented a significant decrease of operated kidney baseline SRF because equal to 11.1% decrease).

Pathology Assessment

A dedicated uro-pathologist analysed fresh-tissue specimens from the operating room and defined primary tumour extent in accordance with TNM classification (14). A mean value for peri-tumor healthy tissue thickness was obtained (22).

Statistical methods

Patient’s characteristics were tested by the Fisher’s exact test for categorical variables and by the Mann-Whitney and Wilcoxon tests for continuous ones. All results for the continuous variables were expressed as the mean and the standard deviation; all the results for the categorical variables were expressed as the median and the inter-quartile range (IQR). Different contingency tables were presented, in order to analyse the influence of unmodified patient variables either on preoperative or postoperative SRF. The univariate/multivariate binary logistic regression model was used to test age (>65 vs. ≤65 yrs), gender (male vs. female), BMI (>25 vs. ≤25), Charlson Index (≥3+ vs. <3), PADUA score (≥8 vs. <8), GFR (<60 vs. 60-90 vs. ≥90 mL/min.), blood loss (<150 vs. ≤150 mL), warm ischemia time (>25 vs. ≤25 min vs. no ischemia) and average tissue of perilesional healthy parenchyma excised (>2.65 vs. ≤2.65 mm) (independent variables) as risk factors for an SRFpostoperatory / SRFpreoperatory ratio <90% versus ≥90% (dependent variable). The median value of the distribution for every tested variable was chosen as the cut-off. All reported p-values were obtained by the two-sided exact method, at the conventional 5% significance level. Data were analysed by R 3.2.1 (https://www.r-project.org)

RESULTS

Two-hundred-twenty-four patients were considered in the analysis.

Patient’s demographics and renal nephrometric features are reported in Table-1. Eighty-eight patients (39.3%) were over 65 years old. One hundred-thirty-seven patients (61.2%) had BMI over 25. Ninety-five patients (42.4%) had Charlson Comorbidity Index ≥3. One hundred-forty-seven patients (65.6%) had PADUA score ≥8.

Patient’s baseline renal function parameters are reported in Table-2. Eighty-three (37.1%), 110 (49.1%) and 31 (13.8%) patients had baseline eGFR >90, ranging from 60 to 90 and <60 mL/min., respectively.

One hundred-sixty-six patients (74.1%) had baseline Split Renal Function as estimated by renal scan ranging from 45 to 55%. High association between SRF ranging from 45 to 55% eGFR ≥60 mL/min. was found (92.2%, respectively – Figure-1).

Patient’s perioperative data are reported in Table-3. One hundred-four (46.4%), 95 (42.4%) and 25 (11.2%) patients underwent 0, ≤25 and >25 minutes of warm ischemia, respectively.
Concerning pathological data, 188 patients (83.9%) were found to have renal cancer. Mean tumor size was 48.6±15.3 mm. Among patients with malignancies, five patients (2.6%) had positive surgical margins. Mean thickness of peritumoral healthy tissue excised was 2.8±1.7 mm.

Postoperative functional outcomes are reported in Table-2 again. As expected, the median operated kidney postoperative SRF was higher in patients classified in the risk category 1 at baseline (p=0.003).

Overall, 125 patients (55.8%) maintained ≥90% of their baseline renal function.

Concerning contingency tables, patients with PADUA score <8 were more likely to maintain their postoperative renal function ≥90% (p=0.023). Patients who underwent clampless PN were more likely to maintain their postoperative renal function ≥90% (p <0.001). Patients who underwent WIT >25 minutes were more likely to have postoperative renal function <90% of their baseline in 72.0% of cases. The worst probability of maintaining ≥90 baseline renal function was found in patients with CCI ≥3 (15.0%, p=0.004). Univariate logistic regression analysis (see Table-4) confirmed CCI, PADUA score and WIT >25 minutes as risk factors for postoperative loss of renal function (postoperative SRF <90% of the baseline value at postoperative control). At multivariate logistic regression analysis (Table-4) WIT was confirmed as independent variable.

At separate evaluation of the risk categories after stratification, 94.8% of patients classified in risk category 2 at baseline were confirmed in risk category 2 at the postoperative assessment.

Patients with baseline SRF ranging from 45 to 55% who did not experienced renal ischemia (the so called “clampless” PN) had a higher pro-

### Table 1. Patients’ demographics and lesions characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>224</td>
</tr>
<tr>
<td>Males, No. (%)</td>
<td>161 (71.8)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>60.5 (11.4)</td>
</tr>
<tr>
<td>No. Age &gt; 65 (%)</td>
<td>88 (42.4)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>24.2 (5.6)</td>
</tr>
<tr>
<td>No. BMI &gt; 25 (%)</td>
<td>137 (61.2)</td>
</tr>
<tr>
<td>CCI, median (IQR)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>CCI Age-Adjusted, median (IQR)</td>
<td>2 (2-3)</td>
</tr>
<tr>
<td>No. CCI ≥ 3 (%)</td>
<td>95 (42.4)</td>
</tr>
<tr>
<td>ECOG PS, median (IQR)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>ASA score, median (IQR)</td>
<td>1 (1-1)</td>
</tr>
<tr>
<td>Mean preop.ve Hb (SD), mg/dL</td>
<td>13.5 (2.4)</td>
</tr>
<tr>
<td>Mean CT-scan lesion size (SD), mm</td>
<td>50.8 (16.1)</td>
</tr>
<tr>
<td>No. right-sided tumors (%)</td>
<td>108 (48.2)</td>
</tr>
<tr>
<td>PADUA Score, median (IQR)</td>
<td>10 (9-11)</td>
</tr>
<tr>
<td>No. PADUA score ≥ 8 (%)</td>
<td>147 (65.6)</td>
</tr>
</tbody>
</table>

SD = Standard Deviation; BMI = Body Mass Index; CCI = Charlson’s Comorbidity Index; IQR = Inter-Quartile Range; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ASA = American Society of Anaesthesiologists; Hb = Haemoglobin; CT = Computed Tomography; PADUA = Preoperative Aspects and Dimensions Used for Anatomical.

### Table 2 - Renal function data.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative SCr (mg/dL), mean SD</td>
<td>1.04 (0.32)</td>
</tr>
<tr>
<td>Preoperative eGFR (mL/min.), mean SD – MDRD formula</td>
<td>75.7 (23.27)</td>
</tr>
<tr>
<td>No. patients with baseline eGFR (%) ≥ 90</td>
<td>67 (29.9)</td>
</tr>
<tr>
<td>≥ 60,&lt; 90</td>
<td>105 (46.9)</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>52 (23.2)</td>
</tr>
<tr>
<td>Preoperative Split Renal Function, mean SD</td>
<td>47.1 (7.6)</td>
</tr>
<tr>
<td>Split Renal Function Risk Category at baseline– No. patients (%)</td>
<td></td>
</tr>
<tr>
<td>45-55</td>
<td>166 (74.1)</td>
</tr>
<tr>
<td>&lt; 45</td>
<td>58 (25.9)</td>
</tr>
<tr>
<td>Postoperative SCr (mg/dL), mean SD</td>
<td>1.19 (0.46)</td>
</tr>
<tr>
<td>Postoperative eGFR (mL/min.), mean SD – MDRD formula</td>
<td>68.8 (26.22)</td>
</tr>
<tr>
<td>% ∆ SCr (preoperative vs postoperative)</td>
<td>+14.8 (25.97)</td>
</tr>
<tr>
<td>% ∆ eGFR (preoperative vs postoperative)</td>
<td>-12.4 (20.1)</td>
</tr>
<tr>
<td>Postoperative Split Renal Function, mean SD</td>
<td>44.5 (8.9)</td>
</tr>
<tr>
<td>% ∆ Split Renal Function (preoperative vs postoperative)</td>
<td>-10.21 (8.6)</td>
</tr>
</tbody>
</table>

SCr = Serum Creatinine; SD = Standard Deviation; eGFR = estimated Glomerular Filtration Rate; MDRD = Modification of Diet in Renal Disease.
Figure 1 - Bar chart depicting patients stratified into the risk categories based on preoperative Split Renal Function: on the right, risk category 1 (patients with baseline split renal function at renal scan ranging between 45 and 55%); on the left, risk category 2 (patients with baseline split renal function at renal scan < 45%); patients with baseline estimated Glomerular Filtration Rate > 60 mL/min. are represented in the blue bars; patients with baseline estimated Glomerular Filtration Rate ≤ 60 mL/min. are represented in the green bars, 92.2% of patients with baseline split renal function at renal scan ranging between 45 and 55% had Glomerular Filtration Rate > 60 mL/min.

Table 3 - Perioperative variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. management of renal artery (%)</td>
<td></td>
</tr>
<tr>
<td>• Clampless (0 min ischemia)</td>
<td>99 (44.2%)</td>
</tr>
<tr>
<td>• Global ischemia ≤ 25 min</td>
<td>90 (40.2%)</td>
</tr>
<tr>
<td>• Global ischemia &gt; 25 min</td>
<td>35 (15.6%)</td>
</tr>
<tr>
<td>Mean WIT (SD), min.</td>
<td>19.6 (5.7)</td>
</tr>
<tr>
<td>Mean EBL (SD), mL</td>
<td>131.5 (226.8)</td>
</tr>
<tr>
<td>Mean operative time (SD), min</td>
<td>112.1 (33.2)</td>
</tr>
<tr>
<td>No. intraoperative complications (%)</td>
<td>2 (&lt; 1.0)</td>
</tr>
<tr>
<td>No. postoperative complications (%)</td>
<td>27 (12.0)</td>
</tr>
<tr>
<td>No. Clavien grade ≥ III (%) postoperative complications</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Median hospital stay (IQR), days</td>
<td>5 (4–6)</td>
</tr>
</tbody>
</table>

\( \text{WIT} = \text{Warm Ischemia Time}; \ \text{SD} = \text{Standard Deviation}; \ \text{EBL} = \text{Estimated Blood Losses}; \ \text{IQR} = \text{Inter-Quartile Range} \)

The results of the present study showed that the classification of patients by SRF does not seem to be a reliable method to preoperative differentiate patients into risk categories influencing operated kidney functional outcome. Indeed, 55.8% of patients maintained >90% of their baseline renal function, regardless the preoperative risk category they started.

On the other side, we found that renal scan data were confirmed by the “standard” renal function parameters: indeed, more than 90% of patients with baseline operated kidney SRF ran-
ging from 45 to 55% (risk category 1) had both SCr <1.2 and eGFR >60 mL/min., confirming the normal baseline renal function.

Concerning the potential predictors of postoperative functional outcome, patients with PADUA score ≥8, or who underwent warm ischemia over 25 minutes, or who had CCI ≥3 were less likely to maintain >90% of their baseline SRF. These findings were found regardless the risk category.

Surgical ischemia was the only factor showing different effects in the two risk categories: indeed, no significant effects were found in the risk category 2 (patients with preoperative SRF <45%), whilst, in category 1 (patients with preoperative SRF ranging from 45 to 55%), patients who avoided ischemia were more likely to maintain their baseline SRF >90%; on the contrary, patients who had ischemia over 25 minutes had worsened outcome.

Some considerations about the findings of the present study are required.

The range commonly used by the nuclear medicine literature to describe a “normally” functioning kidney (21) revealed to be correct as we found in our study a more than 90% of concordance of set range for SRF with normal SCr and eGFR.

Specifically regarding the primary aim of the study, the classification of the patients by risk categories revealed to have scarce power in predicting the operated kidney functional ou-

### Table 4 - Univariate and Multivariate Logistic Regression Models.

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Outcome: &lt; 90% SRF maintained</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>&gt; 65 vs. ≤ 65</td>
<td>1.59</td>
<td>0.93–2.73</td>
<td>0.093</td>
</tr>
<tr>
<td>Gender</td>
<td>Female vs Male</td>
<td>0.85</td>
<td>0.48–1.50</td>
<td>0.569</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>&gt; 25 vs. ≤ 25</td>
<td>1.21</td>
<td>0.70–2.08</td>
<td>0.499</td>
</tr>
<tr>
<td>CCI</td>
<td>≥ 3 vs. &lt; 3</td>
<td>1.68</td>
<td>1.12–2.88</td>
<td>0.032</td>
</tr>
<tr>
<td>PADUA score</td>
<td>≥ 8 vs. &lt; 8</td>
<td>1.94</td>
<td>1.09–3.43</td>
<td>0.024</td>
</tr>
<tr>
<td>eGFR, mL/min. x 1.73 m²</td>
<td>60-90 vs. &gt; 90</td>
<td>1.14</td>
<td>0.64–2.03</td>
<td>0.649</td>
</tr>
<tr>
<td></td>
<td>&lt; 60 vs. &gt; 90</td>
<td>1.13</td>
<td>0.49–2.59</td>
<td>0.774</td>
</tr>
<tr>
<td>WIT, min</td>
<td>≤ 25 vs. 0 ischemia</td>
<td>2.40</td>
<td>1.34–4.28</td>
<td>0.003</td>
</tr>
<tr>
<td>EBL, mL</td>
<td>&gt; 150 vs. ≤ 150</td>
<td>1.10</td>
<td>0.65–1.86</td>
<td>0.733</td>
</tr>
<tr>
<td>Healthy margin excised, mm</td>
<td>&gt; 2.65 vs. ≤ 2.65</td>
<td>0.87</td>
<td>0.48–1.57</td>
<td>0.640</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate</th>
<th>Outcome: &lt; 90% SRF maintained</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCI</td>
<td>≥ 3 vs. &lt; 3</td>
<td>1.45</td>
<td>0.76–2.77</td>
<td>0.256</td>
</tr>
<tr>
<td>PADUA score</td>
<td>≥ 8 vs. &lt; 8</td>
<td>1.62</td>
<td>0.89–2.98</td>
<td>0.117</td>
</tr>
<tr>
<td>WIT, min.</td>
<td>≤ 25 vs. 0 ischemia</td>
<td>2.42</td>
<td>1.35–4.34</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>&gt; 25 vs. 0 ischemia</td>
<td>6.58</td>
<td>2.46–17.62</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SRF = Split Renal Function; OR = Odd Ratio; CI: Confidence Interval; BMI = Body Mass Index; CCI = Charlson’s Comorbidty Index; PADUA = Preoperative Aspects and Dimensions Used for Anatomical; eGFR = estimated Glomerular Filtration Rate; WIT = Warm Ischemia Time; EBL = Estimated Blood Losses.
Conclusion: The power of the risk categories in predicting the probability of experiencing a significant loss of renal function was equal to flipping a coin. Contingency tables revealed that CCI ≥3 plays a negative effect so that 15% only of patients with such feature maintained more than 90% of their baseline SRF, confirming the current knowledge about comorbidities role in influencing the postoperative functional outcomes: it is known that loss of renal function after PN is a multifactorial process related to both modifiable factors (duration of ischemia and removal of unaffected nephrons) and unmodifiable factors (age, comorbidities and preoperative renal function) (23, 24).

Again, confirming literature data, PA-DUA score ≥8 (indicating more moderate to high complexity lesions) was found to be a predictor of worse probability to maintain baseline SRF (25). Intuitively, the finding showed that more complex renal lesions could affect renal functional outcome. It could be due to the wider amount of renal parenchyma resected during PN or due to the more complex suture demanded after complex resection.

We underline that the above-mentioned findings were true regardless the risk category at baseline.

The significant finding after stratification according to the described risk group categories regarded the surgical renal ischemia. Particularly, if no effect of ischemia versus no ischemia was found in the patients with worse renal function at baseline (in risk category 2), conversely, patients starting from risk category 1 (SRF ranging from 45 to 55% at preoperative assessment) were more influenced by ischemia, both in the case of prolonged and avoided ischemia: in fact, prolonged ischemia, over the described critical threshold of 25 minutes (2, 24) was found to have detrimental effect on the
patients of the studied cohort, with only 20% of these patients maintaining >90% of their baseline renal function.

On the other side, around 75% of patients with superior operated kidney baseline function who underwent clampless PN maintained >90% of baseline renal function. In summary, it seemed that avoiding the clamping of renal artery was protective from postoperative decrease in renal function: the “unusual” was not to record this trend in patients with worse baseline function.

Indeed, previous reports were contradictory with respect to finding of the present study as stating that a trend towards a major benefit in postoperative renal function by avoided clamping of renal artery could be observed in patients with poorer baseline renal function (26-28).

In the present paper, written by analysing a larger sample size, the “novel” finding would state that a “normal” kidney with avoided ischemia represents the best condition. Maybe the healthy kidney takes more advantages by the avoided at all ischemia. It is possible that some conditions underlying in the altered renal function in case of preoperative renal disease are able to eliminate the positive effect of avoided ischemia. Moreover, we can state that the kidney with worse baseline renal function has much less to loose after the intervention, whatever the management of the renal pedicle and the ischemia.

Using total eGFR tends to overestimate the degree of renal function preservation after PN, and this is particularly relevant when studying factors affecting functional outcomes after nephron-sparing surgery like in the cases reported herein. Ipsilateral renal function is a more precise assessment method in this setting as previously described (29).

The study was not devoid of limitations, principally related to the retrospective nature and to the sample size considered. As per retrospective design studies, a selection bias could affect the results.

Notwithstanding the limitations, we underline that the rigorous selection of patients who underwent renal scan preoperatively and at the third month postoperatively in the institutional division of nuclear medicine surely increased the value of the data but it reduced the sample size at the analysis.

Further studies, ideally prospective, with a larger sample size would be needed in order to confirm our reports.

CONCLUSIONS

The stratification of patients by SRF as assessed by renal scan before PN does not seem to work as a valuable tool for predicting the postoperative renal functional outcome after the intervention. Lesion’s complexity, ischemia time and comorbidities are confirmed to play a role in determining the postoperative functional outcome, regardless the baseline renal function.

Ischemia time seems to have scarce effects on patients with poor baseline renal function maybe because they have much less to loose. No ischemia has a positive effect on patients with normal baseline renal function. The same patients were found to suffer more from a prolonged ischemia.

ACKNOWLEDGEMENTS

The Authors would like to thank Roberto Passera, PhD, for the efforts in the statistical analysis.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Ureteroscopy and stone treatment in the elderly (≥70 years): prospective outcomes over 5– years with a review of literature

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1 University Hospital Southampton, NHS Trust, United Kingdom, UK

ABSTRACT

Objective: To assess outcomes of ureteroscopy for treatment of stone disease in the elderly. Ureteroscopy (URS) is an increasingly popular treatment modality for urolithiasis and its applications are ever expanding with the development of newer technologies. Its feasibility and outcomes within the elderly population to our knowledge remain under-reported.

Materials and Methods: We examined the patient demographics and surgical outcomes from our prospective database for patients ≥70 years who underwent URS for urolithiasis, in a 5-year period between March 2012 and December 2016.

Results: A total of 110 consecutive patients underwent 121 procedures (1.1 procedure/patient) with a mean age of 77.2 years (range: 70-91 years). Stone location was in the kidney/pelviureteric junction (PUJ) in 29%, ureter in 37% and in multiple locations in 34%. The initial and final stone free rate (SFR) was 88% and 97% respectively. While 73% were done as true day case procedures, 89% patients were discharged within 24 hours. Eleven patients (9%) underwent complications of which 10 were Clavien I/II including acute urinary retention, urinary tract infection, stent symptoms and pneumonia. One patient underwent Clavien IV complication where they needed intensive care unit admission for urosepsis but fully recovered and were discharged home subsequently.

Conclusion: Ureteroscopy is a safe and effective method of managing urolithiasis in elderly patients. Although most patients are discharged within 24-hours, consideration needs to be made for patients where social circumstances can impact their discharge planning.

INTRODUCTION

The elderly population worldwide is rising. In the United Kingdom (UK) those aged over 75 are set to nearly double from 5.2 million in the year 2014 to 9.9 million by 2039 (1). There is an increasing burden of urinary tract stone disease and a rising trend towards surgical management, of which ureteroscopy (URS) is the fastest growing intervention (2). The number of ureteroscopic stone treatments has increased by 252% between 1996 and 2016 (2). With the modern evolution and technological advancement in URS, it is now recommended as a first line treatment for intra-renal stones less than 1.5cm (3).

Stone formation in the elderly (>65 years) has been reported to be between 9.6-16% of all stone patients, with a lifetime prevalence of 14% (4-6). Although a rise in the incidence of urolithiasis was seen across all ages, this was highest in...
those over 75 years where it increased by 51% in a span of 7 years (2006/2007 to 2013/2014) (4). This is thought to be due to increasing life expectancy (6). However, given the differing metabolic profile, stone composition, and co-morbidity, urolithiasis in the elderly should not be viewed merely as an extension of the population of younger stone formers, but as a disease in its own right (7, 8).

The efficacy of surgical intervention for urolithiasis in the elderly has yet to be clarified due to a paucity of evidence and contradictory results (9). We report on the outcomes for a consecutive cohort of elderly patients who underwent ureteroscopy for treatment of their stone disease with a review of literature.

**MATERIALS AND METHODS**

Prospective data collection for consecutive patients was undertaken over a 5-year period between March 2012 and December 2016, 703 patients underwent ureteroscopy for stone disease during this time. Of these patients, 110 (16%) were aged ≥70 years and underwent 121 procedures for stones in the kidney or ureter. Demographic and clinical variables were prospectively collected and are presented in Tables 1 and 2, respectively. The diagnosis of urolithiasis was confirmed by a non-contrast CT scan (CTKUB).

All patients underwent ureteroscopy (URS) and stone fragmentation/retrieval under a general anaesthesia, with stones send for analysis when retrieved. A post-operative drainage with JJ stent or ureteric catheter or stent on a string was done in majority of patients. A urethral catheter was not routinely placed unless there was a history of previous urinary retention. A repeat URS was either planned due to a large initial stone burden or if they were symptomatic with residual stones on follow-up. A post-operative follow-up was done at 3 months with a plain KUB XR for radiopaque stones or ultrasound scan (USS) for radiolucent stones. Stone free rate (SFR) was defined as endoscopically or radiologically stone free or with fragments ≤2mm.

A review of literature on all articles reporting on URS for stone disease in elderly was also carried out (10-14).

**RESULTS**

110 patients underwent 121 procedures (1.1 procedure/patient), with 11 patients undergoing repeat URS either as a planned staged procedure due to the initial stone burden or if they had symptomatic residual stones on follow-up (Table-1). The mean age of patients was 77 years (range: 70-91 years) with a male: female ratio of 3:1.

The stone location was in the kidney/pelvic ureteric junction (PUJ) in 29%, ureter in 37% and in multiple locations in 34%, with a mean stone size of 10.6mm (range 3-37mm) and the cumulative stone length was 17mm (range 3-156mm). Five patients (4%) underwent bilateral URS for stone disease. With a mean (±SD) operative time of 50±25 minutes, a ureteric access sheath (UAS) was used in 36% (43 procedures), and a post-operative drainage (JJ Stent, ureteric catheter or stent on string) was inserted in 98% (118 procedures). An elective urethral catheter was placed in 6 (5%) procedures.

The stone composition was predominantly calcium oxalate (64.1%), but also included calcium phosphate (27.2%), magnesium phosphate (4.9%) and uric acid (3.9%). A combination of stone composition was found in 34.4% of cases. Post-operatively, length of stay (LOS) was limited to day case surgery in 73% of cases (0-days), with 16% being discharged within 24 hours of the procedure (Table-2). A further 4% of patients were discharged between days 1-3, and 7% of patients required admission for >3 days, which was either due to post operative complications or social circumstances delaying discharge despite being medically fit.

The initial and final SFR was 88% (n=97) and 97% (n=107) respectively. The overall complication rate was 9% (n=11), ten patients with Clavien I/II complications and one with Clavien IV complication. Of the Clavien I/II complications, 4 developed acute urinary retention, 4 had a urinary tract infection and one patient each had stent discomfort and pneumonia. The patient with Clavien IV complication required admission to the Intensive Care Unit for management of E. coli urosepsis post operatively. He was managed appropriately with intravenous antibiotics and vasopressor support for
refractory hypotension, before being stepped down to the ward and subsequently discharged home. All patients recovered and were discharged home or to their residential/nursing home.

Ureteroscopy (URS) in the elderly (Literature review)

Our literature review shows a total of six studies (including our study) (Tables 3-5) that report on the outcomes of ureteroscopy in elderly reporting a total of 560 patients with a complication rate of 12.3% (n=69) (Table-5) (10-14). Recent advancements in URS through endoscope miniaturisation, improved deflection techniques, enhanced optical quality, have lead to an increase in popularity of URS as a first line treatment for urolithiasis (3, 15, 16). There is a significant paucity of evidence in the use of URS for the treatment of urolithiasis in elderly patients with only few previous studies reported (Tables 3-5).

**DISCUSSION**

**Meaning and strengths of the study**

With a rise in the incidence of stone disease in elderly and the use of URS for its treatment, we report on unselected consecutive elderly patients who underwent ureteroscopic management of their stone disease. Our data shows excellent SFR (97%) with low complication rates (9%, mainly Clavien I/II) for these patients where vast majority were done either as true day case

---

**Table 1 - Patient demographics and stone location (PUJ – pelvic-ureteric junction).**

<table>
<thead>
<tr>
<th>No. of patients (procedures)</th>
<th>110 (121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>77.2 years (70-91 years)</td>
</tr>
<tr>
<td>70-75</td>
<td>43</td>
</tr>
<tr>
<td>75-80</td>
<td>35</td>
</tr>
<tr>
<td>80-85</td>
<td>29</td>
</tr>
<tr>
<td>&gt;85</td>
<td>14</td>
</tr>
<tr>
<td>ASA I/II/III/IV</td>
<td>7/63/50/1</td>
</tr>
<tr>
<td>Median age, years</td>
<td>77</td>
</tr>
<tr>
<td>Pre-operative creatinine (μmol/L), mean±SD</td>
<td>104±57</td>
</tr>
<tr>
<td>Pre-operative stent n(%)</td>
<td>32 (26%)</td>
</tr>
<tr>
<td>Pre-operative positive urine culture (appropriately treated pre-operatively) n (%)</td>
<td>32 (26%)</td>
</tr>
<tr>
<td>Multiple stones n (%)</td>
<td>40 (32%)</td>
</tr>
</tbody>
</table>

**Stone position (single)**

- Upper pole, n (%) | 2 (2%)
- Middle pole, n (%) | 4 (3%)
- Lower pole, n (%) | 16 (13%)
- PUJ / Renal pelvis, n (%) | 13 (11%)
- Upper ureter, n (%) | 6 (5%)
- Middle ureter, n (%) | 15 (12%)
- Lower ureter, n (%) | 24 (20%)

**Stone position (multiple)**

- Multiple ureteric n(%) | 15 (12%)
- Multiple Renal n(%) | 16 (13%)
- Multiple ureteric and renal n(%) | 9 (7%)
- Mean largest individual stone diameter (range) | 10.6 (3-37)
- Mean cumulative stone diameter, mm (range) | 17.1 (3-156)
Table 2 - Operative details and patient outcomes.

<table>
<thead>
<tr>
<th>Operative details</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean operative time (minutes) ± SD</td>
<td>50 ± 25</td>
</tr>
<tr>
<td>Use of an access sheath (%)</td>
<td>43 (36%)</td>
</tr>
<tr>
<td>Length of stay (days), mean (range)</td>
<td>2.1 (0-90)</td>
</tr>
<tr>
<td>Day case</td>
<td>88 (73%)</td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>1-3 days</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>&gt;3 days</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Post-operative drainage (JJ stent, ureteric catheter, stent on string), n (%)</td>
<td>118 (98%)</td>
</tr>
</tbody>
</table>

**Stone Composition**

- Calcium Oxalate 66 (64.1%)
- Calcium Phosphate 28 (27.2%)
- Magnesium Phosphate 5 (4.9%)
- Uric Acid 4 (3.9%)
- Singular Stone Composition 59 (56.6%)
- Mixed Stone Composition 31 (34.4%)
- Surgical complications, n(%) 11 (9%)
- Acute urinary retention (Clavien I/II) 4 (3%)
- Urosepsis (Clavien IV) 1 (1%)
- Urinary tract infection (Clavien I/II) 4 (3%)
- Post-operative stent pain (Clavien I/II) 1 (1%)
- Pneumonia (Clavien I/II) 1 (1%)
- Overnight stay for social reasons (frail, stay alone) 12 (10%)
- Overnight stay for patients who underwent elective catheterisation 6 (5%)
- Initial stone free rate (SFR) 97 (88%)
- Final SFR 107 (97%)

Table 3 - Patient demographics across other studies reported in the literature.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Country of origin</th>
<th>Number of Patients (procedures)</th>
<th>Definition of elderly (years)</th>
<th>Mean Age, years ± SD (range)</th>
<th>Mean largest individual stone diameter, mm ± SD (range)</th>
<th>Mean cumulative stone diameter, mm ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akman et al. 2012 (11)</td>
<td>Prospective</td>
<td>Turkey</td>
<td>28</td>
<td>&gt;65</td>
<td>68.9 ± 4.1</td>
<td>15 to 30 (no mean available)</td>
<td>/</td>
</tr>
<tr>
<td>Tolga-Gulpinar et al. 2015 (10)</td>
<td>Retrospective</td>
<td>Turkey</td>
<td>170</td>
<td>&gt;60</td>
<td>66.5 (61-87)</td>
<td>/</td>
<td>17.2 (7.2)</td>
</tr>
<tr>
<td>Hu et al. 2016 (12)</td>
<td>Retrospective</td>
<td>China</td>
<td>80</td>
<td>&gt;60</td>
<td>65.1 ± 5.2</td>
<td>/</td>
<td>15.8 (3.4)</td>
</tr>
<tr>
<td>Yoshioka et al. 2016 (13)</td>
<td>Retrospective</td>
<td>Japan</td>
<td>42</td>
<td>65-74</td>
<td>69.26 ± 2.92</td>
<td>9.56 ± 3.27</td>
<td>/</td>
</tr>
<tr>
<td>Berardinelli et al. 2017 (14)</td>
<td>Prospective</td>
<td>Italy</td>
<td>91</td>
<td>&gt;65</td>
<td>72.1 ± 5.06</td>
<td>/</td>
<td>13.05 (5.79)</td>
</tr>
<tr>
<td>Current Study</td>
<td>Prospective</td>
<td>UK</td>
<td>110 (121)</td>
<td>&gt;70</td>
<td>77.2 (70-91)</td>
<td>10.6 (3-37)</td>
<td>17.1 (3-156)</td>
</tr>
</tbody>
</table>
procedures (73%) or were discharged within 24 hours (89%), without the routine use of urethral catheter post-operatively. While bilateral same session ureteroscopy was successfully done in all 5 patients, stones >1.5cm seem to need a second procedure due to a large stone burden.

Our study demonstrates comparable SFR and complication levels to those published in SWL and PCNL, and provides further evidence of the efficacy of URS in the management of elderly stone disease. We also sub-analysed the data on 43 patients (46 procedures) over the age of 80 years, and the SFR and complication rates were similar to the overall cohort.

Comparison of all studies published in the literature

Tolga-Gulpinar et al. reported a SFR of 81.1% for patients >60 years; this was comparable to the non-matched groups being <15 years (SFR 78.4%) and 16 – 60 years (SFR 77.5%) (10). Multivariate logistic regression only found that stone size and number had an impact of SFR. This is comparable to our level of SFR following single URS being 88%. A similar study from Japan stratifying by age of patients showed that URS is the preferred treatment for elderly patients even for those with multiple comorbidities (13). Complication rates for URS has been dem-
 Demonstrated to be less than that of a matched PCNL group, being 7.1% and 10.7% respectively, although not statistically significant (11). This is comparable to the intraoperative and perioperative complication rates found by Tolga-Gulpinar being 7.6% and 1.1% for the >60 year old group (10). We present a postoperative complication rate of 9% with the majority of these being either acute urinary retention or urinary tract infection. Only two patients suffered with urosepsis or pneumonia, and no mortality occurred in our series.

The attempted shift towards urolithiasis management in the outpatient setting remains achievable in the majority of geriatric patients, with a continued decrease in bed days required for management (15.8%) and rising day case procedures (9.7%) (12). Our results demonstrate that day-case URS was possible in 73% of patients, and a 24-hour discharge achievable in 89%, easing the demand for acute hospital admission and providing a cost-effective service. This is in concordance with other published LOS following URS in the elderly being 1.4 days on average for those >60 years (10).

Troubleshooting for URS in elderly
Although URS can be successfully done in elderly patients with good outcomes, there can be certain difficulties encountered during the procedure (17). Enlarged prostate can pose difficulties in access to the ureteric orifice. Similarly, care should be taken to minimise the risk of anaesthetic complications and urosepsis by pre-operative optimisation of these patients. Although a post-operative catheter is not usually necessary and most patients can be done as a day-case procedure, this might be helpful in some patients (18). As the cost of performing a URS decreases, this might prove to be a more cost efficient treatment in elderly (19). It seems like the remit of URS in elderly is increasing and the trends are similar to those seen in obesity and paediatric patients (20, 21).

Shockwave Lithotripsy (SWL) and percutaneous nephrolithotomy (PCNL) in the elderly
SWL is the least invasive method for the surgical management of urolithiasis, however it is not free of complications, normally related to the passage of stone fragments or residual stone fragments, which can cause an infection (22). There have been conflicting results on the impact age for the outcome of SWL relating to its SFR. The success of SWL has been attributed to the stone size, location, renal anatomy, stone composition and the type of lithotripter, however age, in a study by Al-Ansari, did not impact overall SFR (23). Conversely, in a study by Abdel-Khalek, which included 2954 patients with renal stones treated by SWL, demonstrated that, in multivariate analysis, age >40 years was a predictor of SWL failure (24).

SFR for the use of SWL in the elderly appears to vary widely from 37.6% - 87.1% (8, 9, 25-27). Siginholfi et al. reported on the outcomes for a cohort of 130 patients over the age of 70 who underwent shockwave lithotripsy for treatment of renal and ureteric stones. They found 52.1% of patients to be stone free after one treatment and treatment was only unsuccessful in 12.8% of patients (9). This is in comparison to Philipou et al., that also reviewed outcomes for SWL in those older than 70 years. SFR was 63.5% with 23 patients requiring URS, 14 PCNL, one patient required a laparoscopic ureterolithotomy, and 12 patients being either a poor candidate for surgical intervention or declined treatment (8).

PCNL, of all three methods of stone management in the elderly, has been the most researched, however quality evidence in this area remains lacking. Morganstern et al. demonstrated that the elderly population (>80 years) were significantly more likely to have pre operative nitrite positive urine, positive or contaminated urine cultures requiring pre-operative antibiotics, and have a history of urosepsis (28). Indeed, age has been demonstrated to be an independent risk factor for increased levels of bacteriuria when managing larger stones in SWL (29). However, there was no difference between the elderly group and the younger group (21-64 years) for post-operative complications, and length of stay was comparable (30).

Similarly, on comparison of minimally invasive PCNL (mPCNL) and URS for elderly, while mPCNL was more effective for multiple stones, URS was involved with lower complications and post-operative stay (12). Nakamon et al. demonstrated that the elderly population (>65 years) was
more likely to be of a higher ASA grade than the younger population, being ASA-1, 1.6% vs. 36.8%; ASA-2, 86.9% vs. 58.7%; and ASA-3, 11.5% vs. 4.4% respectively. However, SFR remained similar between the two groups, and only stone size and previous surgery were found to affect the success rate in a multivariate analysis (30). Indeed, SFR for the elderly population has been reported between 70.5 – 92.8% for PCNL. Resorlu et al. reviewed the impact of increasing comorbidity in the elderly on complication rate and found post operative medical complications were significantly higher in those with >2 comorbidities on the Charlson Comorbidity Index (31).

Limitations and areas of future research

A review of literature conducted showed few other studies that reported on the outcomes of URS in elderly (10-14). Although the results were similar, elderly were defined being over 60 to 75 years in these studies. The definition of elderly was variable largely (in the current literature it ranged between 60-80 years) due to the age at retirement and the life expectancy in individual countries/regions across the world. With a lack of defined cut-off for elderly, the data remains heterogeneous and reporting and comparison of results is not achievable.

Further research is also required for URS in the elderly, particularly to provide matched analysis to a younger cohort to allow univariate analysis of age on outcome following URS. There is also a lack of the definition of SFR (32). Stone disease in complex patients is rising and requires a tailored approach (20, 21, 33). With a growth in the incidence of stone disease in elderly, future URS studies should focus on outcome measures, which is standardised and these should be carried out in a multi-institutional manner especially comparing it with other treatment modalities.

CONCLUSIONS

Ureteroscopy for stone disease in elderly is a relatively safe procedure even for large and/or multiple stones with a small risk of minor complications. Cost-effectiveness is demonstrated through the overall length of stay, however prior consideration to social circumstances and pre planning for discharge may negate increased length of stay for those patients who are medically fit for discharge.

ETHICAL APPROVAL

The local ethics committee approved the study (audit number - 5400). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients had given their permission for participating in the study and informed consent was obtained.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Effect of *Phyllanthus niruri* on metabolic parameters of patients with kidney stone: a perspective for disease prevention

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ABSTRACT

*Phyllanthus niruri* (*P*. *niruri*) or stone breaker is a plant commonly used to reduce stone risk, however, clinical studies on this issue are lacking. **Objective:** To prospectively evaluate the effect of *P*. *niruri* on the urinary metabolic parameters of patients with urinary lithiasis. **Materials and Methods:** We studied 56 patients with kidney stones <10mm. Clinical, metabolic, and ultrasonography assessment was conducted before (baseline) the use of *P*. *niruri* infusion for 12-weeks (*P*. *niruri*) and after a 12-week (wash out) Statistical analysis included ANOVA for repeated measures and Tukey’s/McNemar’s test for categorical variables. Significance was set at 5%.

**Results:** Mean age was 44±9.2 and BMI was 27.2±4.4kg/m2. Thirty-six patients (64%) were women. There were no significant changes in all periods for anthropometric and several serum measurements, including total blood count, creatinine, uric acid, sodium, potassium, calcium, urine volume and pH; a significant increase in urinary potassium from 50.5±20.4 to 56.2±21.8 mg/24-hour (*p*=0.017); magnesium/creatinine ratio 58±22.5 to 69.1±28.6mg/gCr24-hour (*p*=0.013) and potassium/creatinine ratio 39.3±15.1 to 51.3±34.7mg/gCr24-hour (*p*=0.008) from baseline to wash out. The kidney stones decreased from 3.2±2 to 2.0±2per patient (*p*=0.001). In hyperoxaluria patients, urinary oxalate reduced from 59.0±11.7 to 28.8±16.0mg/24-hour (*p*=0.0002), and in hyperuricosuria there was a decrease in urinary uric acid from 0.77±0.22 to 0.54±0.07mg/24-hour (*p*=0.0057).

**Conclusions:** *P*. *niruri* intake is safe and does not cause significant adverse effects on serum metabolic parameters. It increases urinary excretion of magnesium and potassium caused a significant decrease in urinary oxalate and uric acid in patients with hyperoxaluria and hyperuricosuria. The consumption of *P*. *niruri* contributed to the elimination of urinary calculi.

INTRODUCTION

Risk factors for urolithiasis include congenital, genetic, environmental, dietary and metabolic aspects; chronic diseases including obesity, hypertension and diabetes are also associated with urinary calculus formation (1). Overall, urinary
calculi derive from a combination of some of the factors involved in its pathophysiology (1). The worldwide prevalence of urinary calculi is 8.8% and is more frequent in Caucasians, obese individuals, and those with a low income (1). The recurrence rate of urinary calculi is 50% within 10 years of the first episode (2). In addition to the conditions stated above, metabolic disorders such as hypercalciuria and hypocitraturia are typically involved in the genesis of urinary calculi (3).

Knowledge of the pathophysiological mechanisms involved and their risk factors, such as low urinary volume and high intake of calories, sodium and protein are important for modifying the natural history of the disease (2). Indeed, a reduction in the recurrence of urinary calculi of at least 50% can be achieved with dietary guidelines, lifestyle changes and the use of specific medications (4, 5).

In addition to conventional treatment for lithiasis, medicinal plants have long been used worldwide (6). Phyllanthus niruri or “stone bre-aker tea” is one such natural alternative that is inexpensive, easy to obtain and has a low incidence of adverse effects (7). To date, anti-inflammatory (8), anti-hyperuricemic (9), and diuretic properties have been described for this plant (10). Although many studies have shown the beneficial effects of P. niruri and its potential to inhibit the formation of kidney stones, clinical studies remain scarce (11, 12).

Thus, the aim of this study was to evaluate the effects of P. niruri on metabolic parameters in patients with urolithiasis.

This protocol was submitted to and approved by the Ethics Committee for Research Project Analysis of the Clinical Hospital, University of São Paulo, Medical School under number 0304/11. It was also approved and sponsored by the Foundation of Research Support of São Paulo (FAPESP) under number 12/50031-7.

**MATERIALS AND METHODS**

The study was developed at the Urologic Division of the Clinical Hospital, University of São Paulo, Medical School. All patients included presented one or multiple stones smaller than 10mm. Diagnosis was based on ultrasonography or computed tomography (CT). The age of the patients ranged between 18 and 60 years.

Exclusion criteria included patients with a serum creatinine level >2.0mg/dL, urinary tract infection, non-controlled diabetes, chronic liver disease, cancer or pregnant women.

The study was divided into three stages: baseline, P. niruri and washout. The baseline stage was that prior to intervention. The P. niruri stage consisted of 12 weeks of ingestion of an infusion tea prepared with the dry extract of P. niruri, according to literature recommendations (13), a week of rest was included without using the plant after each week of consumption (2 weeks). The final step, called washout, involved 12 weeks without ingestion of P. niruri. The patients themselves were the controls, and each patient was followed for 26 weeks. The patients were subjected to clinical, anthropometric, serum and urinary metabolic analyses at all stages of the study.

Demographic data included age, race, sex, family history and medication use. Clinical data comprised systolic and diastolic blood pressure and anthropometric evaluation (weight, height, body mass index (BMI)). Serum biochemical and urinary analyses and renal ultrasonography were performed at baseline, immediately after P. niruri use and at the end of the washout period. Image evaluation was performed for all patients by the same radiology physicians who were blinded to the group composition.

Serum biochemical analysis was performed during the baseline, P. niruri and washout periods and included a complete blood count and assessment of urea, creatinine, sodium, potassium, glucose (fasting), uric acid, total and ionized calcium, beta human chorionic gonadotropin (HCG; females only), total cholesterol and fractions, triglycerides, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, amylase and bilirubin levels. Serum samples were collected from all participants after fasting for 12 hours.

Twenty-four-hour urinary measurements included calcium, oxalate, citrate, uric acid, magnesium, sodium, potassium, creatinine, urea and phosphorus levels. Urinalysis with urinary pH
measurement and a urine culture was performed using spontaneous voided urine.

The criteria for evaluation of metabolic abnormalities in 24-hour urine samples (mg/g creatinine) were hypercalciuria (calcium >240 mg/24-hour), hyperoxaluria (oxalate >40 mg/24-hour), hypocitraturia (citrate <320 mg/24-hour), hyperuricosuria (uric acid >0.75 g/24-hour), abnormal pH (<5.8 and >6.2) and low urine volume (<2L/day) for men and women, respectively.(4).

After receiving clinical, laboratory and abdominal ultrasound evaluations, the patients included in the study received a monthly visit and 60 sachets of *P. niruri* as a dry extract containing 4.5 g of the herb. The patients were instructed to prepare an infusion containing 250 mL of boiling water for each 4.5 g herb sachet and to drink two sachets/day.

Extracts of *P. niruri* (family Euphorbiaceae) were obtained from qualified manufacturers and from medicinal plant laboratories, and we obtained physicochemical and microbiological analysis reports for all lots used in this study. The plant was produced in Brazil, subjected to a shade drying method, stored at a temperature of 15-35°C in a dry place and conserved with gamma irradiation to avoid contamination by fungi or bacteria. The minimum tannin content was 1.5%, and the moisture content was 17%. Indications for use in disorders of the urinary tract include renal lithiasis, cramps, cystitis and nephritis. The plant is known to have analgesic, anti-inflammatory and hepatoprotective properties.

The use of medications for hypertension or other diseases was not discontinued for the study or considered in the analysis. Only patients using potassium citrate were instructed to discontinue its use two months prior to initiation of the study to avoid interference with the results of 24-hour urine citrate dosing.

Statistical analysis was performed with SAS—Statistical Analysis Software Version 9. Continuous variables are presented as the mean and standard deviation, and categorical variables are presented as frequency percentages. We used analysis of variance (ANOVA) for repeated measures, which takes into account patients being evaluated at three different times (repeated measures) for comparing the results. Significant differences between periods or stages of evaluation were compared with Tukey’s test and the McNemar test. The significance level was set at 5%.

RESULTS

In total, 430 patients were enrolled and initially screened, and 75 patients were considered eligible according to the inclusion criteria. Fifty-six patients completed the study after a few dropped out due to work or personal problems, surgeries or other treatments for non-urological (breast carcinoma, biliary calculus) diseases.

Of the 56 patients who remained, 36 (64.3%) were women, and 52 (92.8%) were Caucasians. The mean age was 44±9.2 years (22-58 years), and the baseline BMI was 27.2±4.4 kg/m². Thirty patients (53.6%) had a family history of calculi, 53 (94.6%) were sedentary, 27 (48.2%) had hypertension, and 26 (46.4%) had metabolic syndrome.

Of the studied cohort, 26 patients (46.4%) were using antihypertensive drugs; one patient (1.8%) was under hypoglycaemic medication, and four patients (7.1%) were using antidepressants, among other medications. Diastolic blood pressure showed a slight increase, though not significant, during the *P. niruri* period, reaching 76.0±10.5 mmHg and then decreasing to 72.5±10.5 mmHg (p=0.02) during the washout period.

Abdominal pain was reported by 37 (66.1%) patients during the *P. niruri* period; dysuria occurred in 11 (19.6%) cases, haematuria in eight (14.3%) cases, and nausea and epigastric pain in six cases each (10.7%). However, these symptoms did not lead to discontinuation of infusion use in any case.

No significant changes in serum measurements, except for a significant decrease in alkaline phosphatase after the use of *P. niruri* when compared to the baseline period (67.7±22.2 x 63.5±20.6 mg/dL; p=0.017), were found.

The 24-hour urine analysis revealed only a significant increase in potassium levels between the basal and washout periods, from 47.3±16.7 mg/24-
-hour to 56.2±21.8mg/24-hour (p=0.017). However, a trend towards increased urinary potassium was noted during the use of the tea.

Analysis of electrolytes adjusted for 24-hour urine creatinine (Cr) revealed an increase in potassium and magnesium levels. This increase reached statistical significance in the washout period, as summarized in Table-1.

In the baseline stage, hypernatriuria was the most frequent urinary disturbance, occurring in 34 patients (60.7%). Hypocitraturia and hypercalciuria were observed in 24 (42.8%) cases, hyperuricosuria in six (10.7%), hyperoxaluria in five (8.9%), and low urine volume in 31 (55.3%). Furthermore, the pH value changed in 21 (37.5%) patients.

Evaluation of patients with urinary abnormalities at the baseline stage showed a tendency towards an increase in urinary citrate among the hypocitraturic patients (211.8±123.7 to 322.3±145.8mg/24-hour, p=0.2193). In addition, oxalate was significantly reduced, from 59.0±11.7 to 28.8±16.0mg/24-hour (p=0.0002), among those with hyperoxaluria, and uric acid was significantly decreased, from 0.77±0.22 to 0.54±0.07mg/24-hour (p=0.0057), among hyperuricosuric patients (Table-2).

Ultrasonography evaluation performed in the three periods of the study revealed that the total number of stones decreased in 38 (67.8%) patients, as summarized in Table-3 (from 3.2±2.02 to 2.0±2.07) and size. In 10 patients (17.8%), no alterations in the number of calculi were noted, and in eight patients (14.3%), an increase in the number of upper urinary stones was observed after the P. niruri period. Some patients reported spontaneous stone passage between the 21st and 70th day of the P. niruri period: four patients eliminated six stones, and another five individuals reported the presence of sandy fragments in the urine during the P. niruri period.

**DISCUSSION**

The formation of urinary calculi is associated with different risk factors. Its prevalence is

### Table 1 - Urinary parameters in patients treated with *P. niruri*.

<table>
<thead>
<tr>
<th>Measure</th>
<th>MEAN (SD)</th>
<th>ANOVA</th>
<th>TUKEY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>mg/vol.24-hour</td>
<td>Wash out</td>
</tr>
<tr>
<td></td>
<td>Calcium</td>
<td>202.7±116.1</td>
<td>211.8±96.2</td>
</tr>
<tr>
<td></td>
<td>Uric acid</td>
<td>0.5±0.2</td>
<td>0.5±0.2</td>
</tr>
<tr>
<td></td>
<td>Sodium</td>
<td>171.6±74.0</td>
<td>166.1±86.9</td>
</tr>
<tr>
<td></td>
<td>Urea</td>
<td>20.1±6.0</td>
<td>18.6±7.7</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>47.3±16.7</td>
<td>50.5±20.4</td>
<td>56.2±21.8</td>
</tr>
<tr>
<td></td>
<td>Citrate</td>
<td>379.9±191.1</td>
<td>398.1±219.0</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
<td>24.4±15.5</td>
<td>23.9±14.5</td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td>1.3±0.5</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td></td>
<td>Phosphorus</td>
<td>755.3±308.8</td>
<td>792.4±324.6</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td>73.8±35.4</td>
<td>85.6±37.6</td>
</tr>
<tr>
<td></td>
<td>&quot;Mg/&quot;Cr</td>
<td>58.0±22.5</td>
<td>66.1±23.4</td>
</tr>
<tr>
<td></td>
<td>&quot;K/&quot;Cr</td>
<td>39.3±15.1</td>
<td>42.7±19.3</td>
</tr>
<tr>
<td></td>
<td>pH</td>
<td>6.1±0.9</td>
<td>6.0±0.9</td>
</tr>
<tr>
<td></td>
<td>Volume</td>
<td>1927±614.5</td>
<td>2028.8±790.6</td>
</tr>
</tbody>
</table>

SD = standard deviation; K = potassium; Mg = magnesium; Cr = creatinine
high worldwide with an increase in morbidity and health costs in a number of countries. However, fully effective treatment and prevention have yet to be established, and the use of medicinal plants may be helpful as coadjuvants. The use of *P. niruri*, a very common plant found in different countries, has been shown to be a viable alternative, though more clinical studies are necessary.

In the present study, we sought to evaluate the use of *P. niruri* in patients with small urinary stones. When we analysed urinary variables, we found no significant changes in urinary volume for a 24-hour period with the use of an infusion of the plant. The urine volume was close to the minimum recommended in the literature, which is 2L/day (3, 4). The patients in this study exhibited average values of 1927mL, 2029mL, and 2015mL daily for the baseline, *P. niruri* and washout periods, respectively. It is possible that the patients were aware of the importance of fluid intake to prevent the formation of new calculi and were thus already consuming the quantity of liquid recommended at the beginning of the study; this would have resulted in no significant change in urine volume. The diuretic effects of *P. niruri* have been described in experimental studies (10, 15), though Nishiura et al. (11) reported different results in a clinical study.

The increase in the 24-hour urine electrolytes found in this study may be related to the decrease in the number of calculi during the imaging evaluation. Increases in urinary potassium and magnesium levels lead to alkalinisation of the urine and consequently to an increase in urinary citrate, a potent inhibitor of calcium stone formation (5).

Potassium can moderate the concentration of sodium in urine and promote the elevation of citrate, which acts to correct urinary pH and acidity, possibly contributing to an increase in calcium solubility (5). These changes may interfere with some stages of crystallization in urine, such as a reduction in the nucleation, growth and aggregation of calcium oxalate crystals (5, 14). We

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**Table 2 - Metabolic alterations in 24-hour period urine at baseline and when taking *P. niruri* and Wash out.**

<table>
<thead>
<tr>
<th>Metabolic alteration</th>
<th>Measure</th>
<th>Urine 24-hour Reference</th>
<th>Baseline</th>
<th>Mean (SD) <em>P. niruri mg/vol.24-hour</em></th>
<th>Wash out</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypercalciuria (n=24)</strong></td>
<td>Calcium</td>
<td>&lt;240/200*</td>
<td>300.3 ± 106.6</td>
<td>237.2 ± 70.7</td>
<td>227.5 ± 79.3</td>
<td>0.2619</td>
</tr>
<tr>
<td><strong>Hyperuricosuria (n=6)</strong></td>
<td>Uric acid</td>
<td>&lt;0.75/0.6*</td>
<td>0.77 ± 0.2</td>
<td>0.54 ± 0.1</td>
<td>0.56 ± 0.12</td>
<td>0.0057</td>
</tr>
<tr>
<td><strong>Hypocitraturia (n=24)</strong></td>
<td>Citrate</td>
<td>&gt;290/320*</td>
<td>211.8 ± 123.7</td>
<td>322.3 ± 147.3</td>
<td>345.3 ± 147.3</td>
<td>0.2193</td>
</tr>
<tr>
<td><strong>Hyperoxaluria (n=5)</strong></td>
<td>Oxalate</td>
<td>&lt;40</td>
<td>59.0 ± 11.7</td>
<td>28.8 ± 16.0</td>
<td>33.0 ± 4.4</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Hypernatriuria (n=34)</strong></td>
<td>Sodium</td>
<td>&lt;150</td>
<td>211.6 ± 62.8</td>
<td>183.5 ± 92.0</td>
<td>200.6 ± 59.7</td>
<td>0.1770</td>
</tr>
</tbody>
</table>

* = value reference for men/women; SD = standard deviation

**Table 3 - Number and size of upper urinary calculi in patients treated with *P. niruri*.**

<table>
<thead>
<tr>
<th>Measure</th>
<th>MEAN (SD) Baseline</th>
<th>P. niruri</th>
<th>Wash out</th>
<th>ANOVA P Baseline x P. niruri</th>
<th>Baseline x Wash out</th>
<th>P. niruri x Wash out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calculi (n)</td>
<td>3.2±2.0</td>
<td>2.0±2.1</td>
<td>2.2±2.2</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.015</td>
</tr>
<tr>
<td>Right kidney (n)</td>
<td>1.6±1.4</td>
<td>1.1±1.2</td>
<td>1.2±1.4</td>
<td>0.0176</td>
<td>0.0176</td>
<td>0.201</td>
</tr>
<tr>
<td>Left kidney (n)</td>
<td>1.6±1.4</td>
<td>0.9±1.1</td>
<td>1.0±1.1</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.003</td>
</tr>
<tr>
<td>Size (mm)</td>
<td>15.6±10.6</td>
<td>9.4±8.9</td>
<td>11.2±11.1</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.045</td>
</tr>
</tbody>
</table>

SD = standard deviation; N = 56
observed a significant increase in potassium in 24-hour period urine samples between the baseline and washout periods, which was also noted in the change in the potassium/g Cr 24-hour ratio and in the change in the magnesium/g Cr 24-hour ratio. The increased potassium and magnesium levels observed in the study patients may help to explain the normalization of metabolic changes observed following the use of *P. niruri*.

Urine pH in the sample urinalysis did not change throughout the study and remained at a mean value between 6.0 and 6.1.

Diastolic blood pressure showed a significant reduction between the *P. niruri* and washout periods (16). A report of a hypotensive effect of *P. niruri* can be found in the literature (8).

The calculus imaging evaluation performed showed a reduction in the number of calculi after the *P. niruri* stage, as shown in Table-3, considering that the number of stones shown on ultrasound was lower due to the fact the some patients probably passed some of them during the study.

Although the same method of evaluation was utilized in the study performed by Nishiura et al., those authors did not show a change in the number and size of calculi before and after the use of a *P. niruri* extract in individuals with urinary lithiasis (11). In contrast, it has been reported that *P. niruri* promoted a reduction in the number of calculi and their appearance in relation to the most fragile aspect of the calculi structure (7, 17–19).

Although ultrasonography is not considered a gold standard for the evaluation of small calculi, we performed this evaluation for the purpose of clinical monitoring of the patients because repeated CT scans in a short period of time can result in undue radioactivity exposure, which is not recommended (20).

Some patients experienced haematuria and abdominal pain. The exact cause of these events not was clear and continuous monitoring of patients at monthly visits was implemented as a precaution during the study. The haematuria and abdominal pain may be related to small calculi eliminated during that period, as patients observed the presence of sand fragments in the urine. Regardless, we cannot attribute the pain reported to the consumption of *P. niruri* because this symptom is very frequent in patients with lithiasis.

In this study, there were no changes in serum levels of liver enzymes, urea and serum creatinine. In previous experimental studies, no adverse acute or chronic toxic effects, such as kidney, heart, liver or neurological effects, were reported with the use of *P. niruri* (17, 18). In a human study, Wang et al. (21) found the normalization of liver enzymes when the plant was used in patients with chronic liver disease. However, Nishiura et al. (11) reported no change in serum and urinary parameters when analysing 69 patients and a control group with and without the use of *P. niruri* (11).

Most studies to date have focused on the hepatoprotective effects of *P. niruri*, and the genus Phyllanthus has been utilized in the treatment of various liver disorders (8). The reduction in alkaline phosphatase levels observed in this study was beneficial. In addition to showing that there was no toxicity with the use of the plant extract, this decrease may have contributed to the reduction in the number of calculi at the end of the study, because alkaline phosphatase is a biochemical marker of bone metabolism and may be involved in the mechanism of calculus formation in hypercalciuria (22).

According to our evaluation of patients with metabolic alterations at the baseline and *P. niruri* periods, a significant normalization of urinary uric acid and oxalate values occurred in those with hyperuricosuria and hyperoxaluria, respectively. Citrate levels tended to normalize in the same cohort, though without statistical significance, likely due to the small sample size. Moreover, no significant change was noted for patients with hypercalciuria or hypernatriuria at the basal stage.

Overall, clinical studies with more patients are needed to validate the use of *P. niruri* in daily practice, particularly in patients with baseline urinary metabolic disorders. *P. niruri* is an abundant natural resource available in many countries, and it can reduce the health system expenses associated with conventional drugs, which are often inaccessible to the majority of the population for long-term treatment.

**CONCLUSIONS**

*P. niruri* intake is safe and does not cause significant adverse effects or significant serum
metabolic changes. The use of the tea of this plant increases urinary excretion of magnesium and potassium. Patients with specific urinary metabolic changes such as hyperuricosuria and hyperoxaluria may benefit from ingestion of this tea.

CONFLICT OF INTEREST

None declared.

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The role of bladder diverticula in the prevalence of acute urinary retention in patients with BPH who are candidates to surgery

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ABSTRACT

Introduction: The urinary bladder diverticula (BD) secondary to benign prostatic hyperplasia (BPH) is a complication that can lead to urinary stasis, stone, urinary tract infection (UTI) and tumors. It’s role in acute urinary retention (AUR) is not totally understood.

Objectives: To determine the effect of BD size on AUR rates in patients with BPH candidates to surgery.

Subjects and Methods: We performed a retrospective cohort study of 47 patients with BPH and BD who underwent BPH surgery associated to complete bladder diverticulectomy from 2006 to 2016. We analyzed risk factors for AUR in patients with BD using univariate, multivariate and correlation analysis.

Results: There was a difference in the size of the diverticula, with 6.8 cm vs. 4.5 cm among patients with and without AUR respectively (p=0.005). The ROC curve showed a correlation between the size of BD and the risk of AUR. The value of 5.15 cm presented a sensitivity of 73% and a specificity of 72%. The area under the curve was 0.75 (p=0.01). Comparing groups with BD >5.0 cm vs. ≤5.0 cm, the AUR incidence was 74% and 27.8% respectively with an OR of 2.65 (1.20-5.85) (p=0.005). In the multivariate analysis, only the size of the diverticula reached statistical significance (p=0.012).

Conclusions: The diameter of BD is an independent risk factor for AUR in patients with BPH and BD who are candidates to surgery. A diameter greater than 5.15 cm increases the risk of AUR.

INTRODUCTION

The bladder diverticula (BD) secondary to benign prostatic hyperplasia (BPH) is more common in elderly men with an incidence range from 1 to 8% (1). Most of them are asymptomatic and discovered incidentally during investigation for other causes as BPH. The urine stasis in the diverticula can lead to complications such as stone formation, urinary tract infection (UTI) and tumors. The incidence of tumors in the diverticula range from 2 to 10% and due to the lack of the smooth muscle layer, the prognosis is usually worst (2, 3).

Publications about acquired BD are scarce in the contemporary urology literature and some authors consider it as consequence of advances in the treatment of BPH (2). In the other hand, the widespread use of medical treatment for BPH in the last 20 years may have caused an
elevated incidence of BD due to an increase of bladder damage secondary to longer periods of obstruction.

Most of the BD are treated with observation and the classical indications for surgery includes the presence of tumor, persistent infection, bladder stone, ureteral obstruction, severe reflux of the diverticulum and retention due to high residue in the diverticula. However, the role of BD in the pathogenesis of LUTS is poorly understood (4).

To our knowledge, there are no studies analyzing the relationship between the size of a diverticula and the impairment on the bladder function. This analysis could help to define a cutoff value to indicate prostate surgery and diverticulectomy. In the present study, we determined the effect of BD diameter on acute urinary retention (AUR) rates.

SUBJECTS AND METHODS

This is a retrospective cohort study of 47 patients who underwent BPH surgery and were submitted to complete bladder diverticulectomy (29 open surgeries and 18 laparoscopic surgeries) from May of 2006 to May of 2016. We used a database of surgical patients from the main Hospital of the University of Sao Paulo, a reference center in Sao Paulo – Brazil. The study was approved by the Ethical Committee under the number 5097. Patients with previous prostate or bladder surgery or suspected for congenital or iatrogenic bladder diverticula were not considered for analysis. All patients selected presented severe symptoms refractory to oral medications (alpha-blockers and 5 alpha-reductase inhibitors) and were candidates for prostate surgery.

We compared age, diabetes mellitus (DM), hypertension, prostate weight, prostate specific antigen (PSA), uroflowmetry rates between groups with and without AUR. The effect of the diameter of bladder diverticula on these clinical characteristics and on the risk of AUR were also analyzed. The size of BD was evaluated through computed tomography (CT) with the bladder full of contrast (Figure-1).

The statistical analysis was performed with the SPSS 21.0 software using Student’s t test for homogeneous variables, Mann-Whitney U test for non-homogeneous variables and Qui squared test for categorical variables. A correlation analysis with a ROC curve and a multivariated analysis for confounding variables were performed. For all statistical analysis, we considered a level of significance of 5% (P <0.05).

RESULTS

Table-1 compares patients with BD with or without AUR. Average age was similar between groups. The prostatic weight was 70.7 g (±58.2) vs. 50.1g (±30.2) (p=0.19) and the PSA was 9.6 ng/dL (±21.0) vs. 3.5 ng/dL (±5.5) (p=0.22) comparing patients with and without AUR respectively. The pre and post- maximum flow rate (Qmax) were similar between groups.

There was a difference in size of the diverticula, with 6.8 cm (±2.5) vs. 4.5 cm (±2.0) (p=0.005) in patients with and without AUR, respectively. The prevalence of hypertension was 40% in patients with AUR and 27.3% without AUR (p=0.35) and DM was 20% vs. 9.1% (p=0.29). The logistic regression with multivariate analysis for AUR as the dependent variable included age, hypertension, diabetes, prostate weight, PSA and only the size of the diverticula reached statistical significance with p=0.012.

The ROC curve showed a correlation between the size of diverticula and the risk of AUR.
The value of 5.15 cm presented the best correlation with a sensitivity of 73% and a specificity of 72%. The area under the curve (AUC) was 0.75 with p=0.01 (Figure-2).

When we compared patients with BD greater than 5.0 cm with the ones measuring 5.0 cm or less, the median age, prostate weight, PSA and uroflowmetry were similar between groups. The difference was observed in the rate of AUR, with incidence of 27.8% in the group with BD ≤5 cm and 74% in the BD >5 cm group resulting in an OR of 2.65 (1.20–5.85), p=0.005 (Table-2).

The pathologic evaluation showed that all BD were pseudodiverticula and 1 case in 47

Figure 2 - ROC curve analysis. Best correlation with 5.15 cm, sensitivity of 73% and specificity of 72%. AUC = 0.75 (p=0.01).
(2.1%) presented a low grade urothelial carcinoma restricted to the BD, excised with free margins.

DISCUSSION

The AUR is one of the worst complications of BPH with serious effects in the patient’s quality of life. The incidence is approximately 10 per cent over the 70 years and 30 per cent over the 80 years (5, 6). The Proscar Long-Term Efficacy and Safety Study (PLESS) control arm showed that 7% of the patients with BPH followed for four years had AUR (7). Large sample studies show that a prior AUR is the strongest predictor of a new AUR episode (8, 9).

Due to its low incidence, no study so far has included BD as a potential risk factor for AUR in their analysis. The Olmstead County trial found that AUR was related to age, moderate to severe symptoms, a peak flow rate of 12 mL/s and a prostate volume >30 mL (5). Meigs et al. in a study of health professionals found that age >70 years, moderate to severe LUTS and use of medications related to adrenergic or anticholinergic effects were related to an increase risk of AUR (10). Roehrborn et al. correlated the PSA value above 2.5 ng/dL, prostate volume >30 mL and severe LUTS with an increase of AUR (7, 11). None of these studies included the presence of BD in their analysis.

To date, there is no consensus in the literature regarding the role of BD in the prevalence of AUR or even when they should be treated. In the present work, we added some practical information that might help urologist’s decisions in the clinical setting. We found that a BD greater than 5.0 cm presents an OR of 2.65 for the occurrence of AUR when compared to patients with BD smaller than 5.0 cm. In the multivariate analysis, only the size of the diverticula reached statistical significance for the development of AUR. The main relevant aspect of this finding is that BD larger than 5.0 cm may have a greater influence in the bladder functioning.

BD may be congenital or acquired. A congenital diverticula involves all layers of the bladder wall, whereas acquired diverticula is always a consequence of obstruction, and is characterized by the herniation of mucosa through the muscle layer of the bladder forming a pseudodiverticula (12). An animal study with an induced rabbit model of diverticula showed that the diverticula reduces the cystometric bladder capacity and compliance besides increasing the residual urine (PVR). There is an increase in the filling detrusor pressures and detrusor thickness (13). There are no studies analyzing the impact of diverticula in bladder function or AUR in men with BPH. Additionally, there is no consensus in literature regarding the size of BD that should be an indication for surgery.

The classic indications for surgery of BD includes presence of tumor, persistent urinary tract infections, bladder stone, hydronephrosis caused by the diverticula, urinary retention with poorly draining diverticula and severe LUTS with paradoxal incontinence (1, 2, 14). A large size with small drainage orifice and diverticula in young man also can be strong indications for surgery. With the development of the minimally invasive techniques, as laparoscopy and robotic, the excision
of the BD becomes less morbid with fast recovery and excellent results (15-17).

For the laparoscopic cases of this analysis, we carried out through the extravesical access. In small BD cases, the Collins knife can be used to incise the neck of the diverticula and we prefer this technique for those smaller than 3 cm.

The traditional open method (intra or extravesical) is still very useful mainly with associated procedures as adenomectomies or cystolithotomies and ureteral reimplantation (14, 18). We have been using the intravesical approach for all open cases, because it is easier than the extravesical route and allow us to do associated surgeries with less dissections and complications (19).

To our knowledge, this is the first study analyzing the role of the size of the diverticula as a risk factor for AUR in the context of BPH patients who are candidates to surgery. The clinical aspects and the impact of BD were evaluated in order to establish a diverticula size cut-off that increase the risk of complications. The clinical setting was AUR, a dramatic complication of BPH.

Limitations of this study are the lack of information regarding preoperative international prostate symptom score (IPSS) and urodynamic data. However, all the patients included in this series were candidates to surgery and were classified into the severe symptoms group. We also did not analyze the occurrence of other complications related to bladder diverticula such as urinary tract infections.

Additionally, we did not analyze patients with BD who were not candidates to surgery. This fact precludes any conclusions regarding the actual role of the BD in the general population with BPH. Further prospective series are needed to accurately analyze the role of BD on the natural history of men with LUTS due to BPH. Finally, we didn’t include in this study a control group of patients who were candidates to prostate surgery without BD.

CONCLUSIONS

The diameter of BD is an independent risk factor for AUR in patients with BPH and BD who are candidates to surgery. A diameter greater than 5.15 cm was related to an increased risk of AUR. This information must be discussed with the patient when considering the risk and benefits of diverticula excision in the context of BPH.

ABBREVIATIONS

AUR = acute urinary retention
BD = bladder diverticula
BPH = benign prostatic hyperplasia
DM = diabetes mellitus
LUTS = lower urinary tract symptoms
Qmax = maximum flow rate
Qmax pre = preoperative maximum flow rate
Qmax pos = postoperative maximum flow rate
IPSS = international prostate symptom score
PVR = residual urine
PSA = prostate specific antigen
TURP = transurethral resection of prostate
UTI = urinary tract infections

CONFLICT OF INTEREST

None declared.

REFERENCES


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Comparison of inflammatory markers between brucella and non-brucella epididymo-orchitis

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ABSTRACT

Objectives: Brucellosis is a multi-system infectious disease that is associated with inflammation, which causes an increase in acute phase reactants. Hematological inflammatory markers of brucellosis include mean platelet volume (MPV), red cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR). In this study, we aimed to evaluate the diagnostic value of hematological inflammatory markers in Brucella epididymo-orchitis (BEO), and to investigate the utility of these markers for differential diagnosis from non-Brucella epididymo-orchitis (non-BEO).

Materials and Methods: We retrospectively reviewed the records of 22 BEO and 50 non-BEO patients. Hematological parameters were recorded and compared between the two groups. The main diagnostic criteria for BEO were positive clinical findings (i.e., testicular pain, tenderness and scrotal swelling), a positive Rose Bengal test result, standard tube agglutination (STA) titer \( \geq 1/160 \), and/or a positive blood culture.

Results: The most decisive factors in discriminating between BEO and non-BEO were NLR, RDW, and MPV, in decreasing order of their strength. Regardless of other factors, NLR values < 2.3 significantly increased the odds of BEO (OR=8.080, 95% CI: 1.929-33.843, p=0.004). After adjusting for other factors, RDW values >14.45% significantly increased the odds of BEO (OR=7.020, 95% CI: 1.749-28.176, p=0.006). Independent of the other factors, patients with MPV < 7.65 fL had a 6.336 times higher risk for BEO (95% CI: 1.393 - 28.822, p=0.017).

Conclusion: Hematological inflammatory markers such as NLR, RDW, and MPV can aid in the differential diagnosis of BEO and non-BEO.

INTRODUCTION

Brucellosis is an endemic zoonotic disease caused by gram-negative coccobacilli that affects more than half a million patients every year (1). Human brucellosis can affect the genitourinary system, the central nervous system, the respiratory system, and the cardiovascular system via hematogenous spread, and symptoms include night sweating, fever, weight loss, joint pain, anorexia, and fatigue (2). Approximately 20-40% of cases have focal complications and single-organ involvement, which can occur in almost every organ system (3). Focal involvement of the urogenital system is seen in 2–10% of patients. Of males affected by brucellosis, 2–20% have epididymo-orchitis, which is the most commonly involved site in the genitourinary system (4). Thus, Brucella
epididymo-orchitis (BEO) must be considered in the differential diagnosis of epididymo-orchitis (5). When treated in a timely manner, BEO has a good prognosis, but any delay in its diagnosis and treatment can lead to serious complications that may require orchiectomy, such as testicular abscess (6).

Brucellosis is characterized by an inflammatory state that results in increased acute phase reactants. Hematological inflammatory markers include white blood cell (WBC) count, platelet (PLT) count, mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) (7).

MPV represents the mean platelet size in the blood. It can be altered in various diseases such as cancer, thrombosis, sepsis, respiratory distress syndrome, and acute appendicitis (8, 9). PDW represents the variation in platelet diameter, while RDW is a measure of the differences in the sizes or the volumes of red cells. WBC count, eosinophil count, and leukocyte ratios (e.g., NLR) can be altered in carcinomas and inflammatory processes, and can be used to monitor inflammatory processes (10, 11).

Globally, there has been an increasing number of studies demonstrating that several hematological inflammatory markers, including MPV, RDW, PDW, and NLR, can reflect the degree of inflammation in some acute and chronic diseases (8, 11, 12). To our knowledge, only one study used these parameters for the differential diagnosis of BEO and non-BEO (13). In the present study, we aimed to compare the levels of hematological inflammatory markers, including WBC, PLT, RDW, MPV, NLR, and PLR, between BEO and non-BEO. Additionally, we aimed to evaluate the utility of these parameters in the differential diagnosis of these two conditions.

**MATERIALS AND METHODS**

We retrospectively reviewed 110 cases diagnosed with epididymo-orchitis who were followed up in our clinic between January 2012 and January 2017. Of these 110 patients, 38 were excluded due to malignancy, hematological problems, immunosuppressed state, cerebrovascular or coronary artery disease, or history of blood transfusion within the last month. Of the remaining 72 patients, 22 had BEO and 50 had non-BEO.

The diagnosis of epididymo-orchitis was based on a combination of symptoms (i.e., testicular pain, swelling, tenderness, and scrotal redness with no other identified cause) and laboratory results (i.e., complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)).

Diagnoses of BEO were made using positive clinical findings such as testicular pain, tenderness, and scrotal swelling, positive Rose Bengal test results, ≥ 1/160 standard tube agglutination (STA) titer values, and/or positive blood culture.

Blood samples were drawn via vacuum collection into tubes containing standard EDTA. All blood samples were analyzed within one hour after collection using a regularly calibrated analyzer (Abbott CELL-DYN Ruby Hematology System). Complete blood count parameters were recorded (i.e., WBC, neutrophil, monocyte, and PLT counts as well as RDW, PDW, PCT and MPV). NLR, PLR, and MLR were calculated as the ratio of neutrophils to lymphocytes, platelets to lymphocytes, and monocytes to lymphocytes, respectively. These parameters were compared between the BEO and non-BEO groups.

**Statistical analysis**

The Kolmogorov Smirnov test was used to determine whether the distributions of continuous variables were normal. As applicable, descriptive statistics for continuous variables were expressed as mean±SD or median (25th-75th) percentiles. Mean differences between groups of normally distributed data were compared with Student’s t test, while the Mann Whitney U test was used to compare non-normally distributed data.

Receiver operating characteristic (ROC) curves were constructed by calculating the sensitivities (true positive rate) and specificities (false positive rate) of each laboratory measurement. The diagnostic sensitivity, specificity, positive predictive value
(PPV), and negative predictive value (NPV) were calculated according to the following formulas, where TP = true positive, TN = true negative, FP = false positive, and FN = false negative: Sensitivity = TP/(TP+FN), Specificity = TN/(TN+FP), Positive predictive value = TP/(TP+FP), and Negative predictive value = TN/(TN+FN).

A Multiple Logistic Regression Analysis with a Forward LR procedure was used to determine the best predictor(s) for discriminating between non-Brucella epididymo-orchitis and Brucella epididymo-orchitis. Any variable with p < 0.25 via univariate test was accepted as a candidate for the multivariate model, which also included all variables of known clinical importance. Odds ratios, 95% confidence intervals, and Wald statistics for each independent variable were also calculated. Data analysis was performed using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). Values of p less than 0.05 were considered significant.

RESULTS

All BEO positive cases had positive Rose Bengal test results and ≥ 1/160 standard tube agglutination (STA) titer values. One of five patients (20%) with high fever and blood culture had positive blood culture for brucella species.

Table-1 compares the demographic properties and laboratory results of the BEO and non-BEO groups. The median MLR (p=0.002) and the median MPV, median WBC count, median neutrophil count, and median NLR were significantly lower in the BEO group (p < 0.001), while the median RDW and lymphocyte count were significantly higher (p < 0.001 and p=0.030, respectively). There were no significant differences between the groups regarding PLR or monocyte count (p > 0.05) (Table-1). In addition, NLR had a significant discriminative power in distinguishing between BEO and non-BEO (AUC=0.784, 95% CI: 0.670-0.897, p <0.001 (Table-2).

### Table 1 - Demographic and laboratory measurements of the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Brucella Epididymo-orchitis (n=22)</th>
<th>Non-brucella Epididymo-orchitis (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.6±17.8</td>
<td>43.1±15.3</td>
<td>0.043†</td>
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<tr>
<td>WBC</td>
<td>8.5 (7.5-10.5)</td>
<td>12.6 (8.5-17.0)</td>
<td>&lt; 0.001‡</td>
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<td>RDW</td>
<td>15.4 (13.0-17.2)</td>
<td>12.8 (11.6-14.1)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Platelet count</td>
<td>266.3±56.3</td>
<td>2643±92.1</td>
<td>0.923†</td>
</tr>
<tr>
<td>PDW</td>
<td>18.2 (17.6-19.8)</td>
<td>19.2 (18.1-20.4)</td>
<td>0.079‡</td>
</tr>
<tr>
<td>PCT</td>
<td>0.19 (0.14-0.23)</td>
<td>0.21 (0.16-0.24)</td>
<td>0.134‡</td>
</tr>
<tr>
<td>MPV</td>
<td>6.9 (6.5-7.5)</td>
<td>7.8 (7.1-9.7)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>PLR</td>
<td>108.2 (76.9-132.1)</td>
<td>113.1 (91.5-170.8)</td>
<td>0.136‡</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>5.3 (3.5-7.3)</td>
<td>8.9 (5.9-12.8)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>2.59±0.87</td>
<td>2.12±0.82</td>
<td>0.030†</td>
</tr>
<tr>
<td>NLR</td>
<td>1.8 (1.2-4.0)</td>
<td>4.6 (3.0-7.7)</td>
<td>&lt; 0.001‡</td>
</tr>
<tr>
<td>Monocyte</td>
<td>0.78 (0.45-0.91)</td>
<td>0.81 (0.70-1.16)</td>
<td>0.052‡</td>
</tr>
<tr>
<td>MLR</td>
<td>0.28 (0.19-0.42)</td>
<td>0.48 (0.29-0.65)</td>
<td>0.002‡</td>
</tr>
</tbody>
</table>

† = Student’s t test, data shown as mean ± SD, ‡ = Mann Whitney U test, data expressed as median (25th-75th) percentiles.
The best cut-off value for discriminating between the BEO and non-BEO groups using MPV was 7.65 fL. According to ROC analysis, an MPV < 7.65 fL reduced the likelihood of BEO, while an MPV > 7.65 fL increased the likelihood of BEO. At this cut-off level, MPV had a sensitivity of 86.4%, a specificity of 62.0%, a positive predictive value of 50.0%, a negative predictive value of 91.2%, and a likelihood ratio of 69.5% (Table-3).

The most decisive factors for discriminating between BEO and non-BEO were NLR, RDW, and MPV, in decreasing order of strength. Regardless of other factors, an NLR value < 2.3 significantly increased the odds of BEO (OR=8.080, 95% CI: 1.929-33.843, p=0.004). After adjusting for other factors, an RDW value >14.45% significantly increased the odds of BEO (OR=7.020, 95% CI: 1.749-28.176, p=0.006). Independent of the

<table>
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<th>Table 2 - Results of ROC curve analyses.</th>
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<tr>
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<td>Platelet count</td>
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<td>PDW</td>
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<td>MLR</td>
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AUC = Area under the curve; CI = Confidence interval

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<th>Table 3 - Best cut-off points for laboratory measurements and diagnostic performance statistics.</th>
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<td>Cut-off point</td>
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<tr>
<td>WBC</td>
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<td>RDW</td>
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<td>MPV</td>
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<td>Neutrophil</td>
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<tr>
<td>Lymphocyte</td>
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<tr>
<td>NLR</td>
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<tr>
<td>Monocyte</td>
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<td>MLR</td>
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</table>

PPV = Positive predictive value; NPV = Negative predictive value
other factors, patients with an MPV < 7.65 fL had a 6.336 times higher risk for BEO (95% CI: 1.393 - 28.822, p=0.017) (Table-4) (Figures 1-4).

**DISCUSSION**

Brucellosis is one of the greatest imitators in the realm of infectious diseases, as it can mimic other multi-system diseases. It has wide clinical polymorphism, which can frequently lead to misdiagnosis and treatment delays. Humans can be infected with brucellosis by consumption of uncooked dairy products (as are consumed in southeastern parts of Turkey) and infected meat (goat, cattle, sheep, cow, camel and pork). Humans may also be infected via close contact with the secretions and carcasses of these animals. Clinically, the disease may have a subclinical, acute, subacute, or chronic course (4).

BEO is a common clinical complication of brucellosis. Its diagnosis is made upon the results of clinical, serological, and microbiological tests. In areas where the disease is endemic, laboratory facilities may not always be appropriate or adequate for diagnosing the disease. Since secondary antibody titers may remain high after treatment, it is difficult to determine whether treatment needs to be continued (14). For this reason, it is believed that supplementary diagnostic methods are beneficial throughout the diagnosis and follow-up period.

Table 4 - Results of multiple logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>Wald</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
<td></td>
</tr>
<tr>
<td>RDW &gt; 14.45</td>
<td>7.020</td>
<td>1.749</td>
<td>28.176</td>
<td>7.554</td>
</tr>
<tr>
<td>MPV &lt; 7.65</td>
<td>6.336</td>
<td>1.393</td>
<td>28.822</td>
<td>5.706</td>
</tr>
<tr>
<td>NLR &lt; 2.3</td>
<td>8.080</td>
<td>1.929</td>
<td>33.843</td>
<td>8.175</td>
</tr>
</tbody>
</table>

Figure 1 - ROC curve for RDW.

Figure 2 - ROC curve for MPV.
Non-specific laboratory findings have been reported for the diagnosis and differential diagnosis of BEO; these include leukocytosis, anemia, thrombocytopenia, elevated AST and ALT levels, and increased CRP and ESR (15–18). Although some studies report a high incidence of leukocytosis (19, 20), this is not a typical feature of brucellosis (20, 21). Mild pancytopenia has also been reported in cases with BEO (21, 22). In our current study, we found that the BEO group had a significantly lower median WBC count than the non-BEO group. We did not detect pancytopenia in either of the groups. In addition, Aydın et al. reported that there was no significant difference between the mean WBC levels of BEO and non-BEO patients (13).

In brucellosis, acute phase reactants are elevated as a result of the inflammatory process (23). Indirect inflammatory markers have been defined, including MPV, PDW, RDW, NLR, and PLR. MPV is a measure of platelet size, and is the most commonly used marker of platelet function. Modern blood counters calculate MPV during the routine complete blood count analysis, but this parameter is often overlooked by clinicians (24). MPV levels usually increase with mild and acute inflammation, and decrease in severe and chronic inflammation. MPV levels can reveal inflammatory burden and the presence of disease activity in many diseases (e.g., preeclampsia, acute pancreatitis, unstable angina, and myocardial infarction) and in cases of systemic inflammation (e.g., ulcerative colitis and Crohn’s disease) (25).

Brucellosis is a systemic chronic inflammatory disease. Okan et al. found that cases with brucellosis had lower MPV levels than healthy controls (26), while Küçükbayrak et al. and Bozkurt et al. showed that these levels increased following treatment (27, 28). Aydın et al. compared the complete blood count parameters (WBC, PLT, RDW, MPV, NLR, PLR, and MLR) of BEO and non-BEO patients, and found significantly lower mean MPV in patients with BEO. To our knowledge, that study was the first of its kind published in English (13). In our current study, we found significantly lower median MPV in the BEO group. The best cut-off value for discriminating between BEO and non-BEO was 7.65 fl. Using this cut-off point, MPV showed a sensitivity of 86.4%, a specificity of 62.0%, a positive predictive value of 50.0%, a negative predictive value of 91.2%, and a likelihood ratio of 69.5%.

RDW is a measure of heterogeneity in the size of circulating red blood cells, and is commonly measured during standard complete blood count analyses. Several studies have reported altered RDW in various pathologies, including inflammatory bowel disease, celiac disease, pulmonary em-
bolism, and coronary artery disease. Furthermore, its predictive value has been shown in various inflammatory and infectious pathologies, such as acute pancreatitis, bacteremia, sepsis, and septic shock (29). Elevated RDW is an expected finding in inflammatory and infectious pathologies, as reticulocytes are often released into the circulation during the early stages. In our current study, the median RDW level was significantly higher in the BEO group. After adjusting for other factors, an RDW level above 14.45% was associated with a significantly increased risk for BEO.

Neutrophils and lymphocytes play important roles in inflammatory processes. Neutrophil and lymphocyte counts show transient changes under inflammatory conditions (i.e., as neutrophil count increases, lymphocyte count decreases). NLR has been defined as a systemic inflammation index that is useful in the differential diagnosis or prognostic prediction of various diseases (30). However, changes in platelet/lymphocyte ratio (PLR) may be related to inflammation and cytokines. Similar to NLR, PLR is also used for the differential diagnosis and prognostic prediction of various diseases, including cancer and inflammatory conditions (31). Among studies investigating NLR and PLR in brucellosis, Olt et al. (32) reported that adult patients with brucellosis had significantly increased Hb and NLR, while Aktar et al. (31) reported that NLR and PLR were direct indicators of inflammation in children with Brucella-arthritis and Bozdemir et al. (34) found significantly altered Hb and NLR in children with brucellosis. Aydin et al. compared parameters including NLR, PLR, and MLR between patients with BEO and non-BEO, and found significantly higher MLR among patients with BEO; however, they found no differences between the two groups regarding NLR or PLR (13).

In our current study, patients with BEO had significantly lower median neutrophil count, median NLR, and median MLR, but higher lymphocyte count compared to the non-BEO group. However, there were no significant differences between the groups regarding PLR or monocyte count. Regardless of other factors, an NLR value lower than 2.3 was associated with a significantly increased risk for Brucella epididymo-orchitis.

There are some limitations to our study, including that it had a retrospective design and a relatively small sample size. There is a need for larger prospective studies to investigate the alterations in differential leukocyte count and platelet parameters with long-term follow-up in patients with BEO.

In conclusion, based on our current findings, we believe complementary hematological inflammatory markers (such as MPV, NLR, PLR, and RDW), which can be measured rapidly, easily, and with no additional cost, can be used in addition to the diagnostic serological tests to aid in the diagnosis, follow-up, and differential diagnosis of BEO. Further studies are needed to confirm these findings in a clinical setting, and to understand the underlying mechanisms for these findings.

CONFLICT OF INTEREST

None declared.

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Comparison of the Kelly's plication and TOT simultaneously with vaginal hysterectomy, on the incontinence, and sexual functions

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ABSTRACT

Purpose: To compare the effect of vaginal hysterectomy-anterior/posterior colporrhaphy with Kelly’s plication (VH-KP), versus vaginal hysterectomy-anterior/posterior colporrhaphy-transobturator tape (VH-TOT) surgeries on incontinence, quality of life, and sexual functions in patients with pelvic organ prolapse (POP), and concurrent obvious stress urinary incontinence (SUI).

Materials and Methods: Between 2013 and 2017, fifty patients treated with VH-KP (n = 25), and VH-TOT (n = 25) due to POP and SUI, were evaluated prospectively consecutively. Age, parity, duration of urinary incontinence, and the daily pad use were recorded. Patients were filled “Incontinence Impact Questionnaire 7 (IIQ-7)” and “Index of Female Sexual Function (IFSF)” questionnaire forms at preoperatively, and postoperative 6th month. No usage of pads was accepted as subjective cure rate. Intraoperative, and postoperative complications were noted.

Results: There was no statistically significant difference between two groups, for the mean age of the patients, parity, duration of SUI, and the daily pad use, preoperatively (p > 0.05). Decreased UDI-6 scores, IIQ-7 scores and daily pad usage, and increased IFSF scores were found statistically significant in each group, at the postoperative 6th month (p < 0.05). However, VH-TOT group had higher improvement rates, on UDI-6 scores (69.5% vs 63.0%, p = 0.04). In addition, it was notable that the the rates of the patients had IFSF scores ≥ 25 was higher in VH-KP group (p = 0.05). Four (16%) patients had recurrent SUI in the VH-KP group (p = 0.039) and vaginal extrusion occurred in 2 (8%) patients in the VH-TOT group (p = 0.153), postoperatively.

Conclusions: Although the effects of VH-TOT surgery are superior to conventional methods for incontinence and quality of life; negative effects on sexual functions are notable. In addition, although recurrence rates of TOT are low, complications such as vaginal extrusion are accompanied by drawbacks of mesh usage.

INTRODUCTION

Pelvic organ prolapse (POP) is a common problem that occurs in half of multiparous women, and surgical treatment is required in one tenth of the patients (1–4). Accompanying urinary incontinence with symptomatic POP may affect sexual functions, may cause a decrease in self-confidence, and may
lead to a poor relationship with the opposite gender (5) Some (11-45%) of the women with urinary incontinence may avoid sexual intercourse due to the fear of urinary incontinence (6-9).

Surgery of POP and stress urinary incontinence (SUI) enables the resolution of dysfunctions and helps to provide anatomic balance of organs. Although surgical success is aimed for anatomic recovery, subjective functional results, cosmetic appearance, quality of life, and sexual functions are required to be evaluated all together (6-9). SUI accompanying POP may be treated using conventional methods or other methods that require the use of mesh, such as the mid-urethral slings (MUS). Anterior / posterior colporrhaphy with Kelly’s plication (CA-KP) is one of the conventional methods performed in the treatment of SUI. Although it is an old method and the success rate is lower in the long term, it has been a popular method in some clinics among gynecologists and urologists (10). However, after the description of transoburator tape (TOT) procedure in the treatment of SUI in 2001 by Delorme, TOT has been the gold standard in many centers as a minimally invasive method (11).

The number of studies comparing the different surgical techniques in POP accompanying SUI, and simultaneously investigating the effect of these surgical procedures on sexual functions are limited in the literature. We aimed to compare the effect of vaginal hysterectomy-anterior / posterior colporrhaphy with Kelly’s plication (VH-KP), versus vaginal hysterectomy-anterior / posterior colporrhaphy-transobturator tape (VH-TOT) operations on incontinence, quality of life, and sexual functions in patients with POP and concurrent obvious SUI.

**MATERIALS AND METHODS**

**Study participants**

After obtaining local ethics committee approval, 50 patients who were treated with VH-KP or VH-TOT due to POP and concurrent obvious SUI between 2013 and 2017, were evaluated prospectively and consecutively. In the scope of the study, VH-KP was performed in the first 25 patients, and VH-TOT (Unitape T®, Promedon, Cordoba, Argentina) was performed in the second 25 patients. Age, parity, duration of SUI, and the number of pads used daily were recorded. All patients were evaluated during the preoperative period using physical and gynecologic examinations, complete urine analysis, urine culture, stress and Q-type test, and urodynamics studies. POP was evaluated using the Baden-Walker Halfway System. All patients were selected from similar diagnostic group to create a more homogeneous group. Therefore, only patients with stage 4 POP (4: the maximum possible prolapse) were included in the study.

Patients with POP and concurrent obvious SUI, aged over 18 years with symptoms lasting more than 1 year, who were not willing pregnancy, who did not prefer organ protective methods, and in whom SUI was urodynamically demonstrated after prolapse reduction, were included in the study. Patients with neurogenic bladder, urinary system infection, and history of previous surgery due to POP and urinary incontinence, pelvic radiation history, whose residual urine after prolapse reduction was over 100 mL, and who had stage 1-3 prolapse according to the Baden-Walker Halfway System were excluded. In addition, patients who preferred pubovaginal sling surgery rather than mid-urethral sling surgery were not evaluated in the study.

**Efficacy evaluation**

The efficacy of the surgical procedures was compared using the “Urinary Distress Inventory-6 (UDI-6)” and the “Incontinence Impact Questionnaire 7 (IIQ-7)”. Patients completed the UDI-6 and IIQ-7 forms preoperatively and at the postoperative 6th month. Patient’s daily pad usage was re-examined in the 6th month, and improvement rates were calculated. Non usage of pads was accepted as subjective cure rate. In addition, sexually active patients in both groups completed “Index of Female Sexual Function (IFSF)” questionnaires. If the total IFSF score was lower than 25, it was accepted as sexual dysfunction (12-14).

**SURGICAL TECHNIQUES**

Transobturator tape surgery was performed in accordance with the description of Delorme’s,
vaginal hysterectomies plus anterior / posterior colporrhaphy in accordance with the description of Heaney, and Kelly plication was performed using Howard Kelly’s method. A vaginal pack was inserted in the vagina after surgery. Vaginal pack, and urethral catheter were removed on postoperative first day. Urethral catheters remained for several days in patients who had a post-voiding residual urine volume higher than 100 mL. Intraoperative and postoperative complications were recorded.

**Statistical analysis**

The statistical package program Statistical Package for the Social Sciences (SPSS) 11 for Windows was used in statistical calculations. Data are described as arithmetic mean and standard deviation. The Chi-square distribution test was used for the calculation of categoric variables, and the Mann-Whitney U test was used for the comparison of means. "p values" lower than 0.05 were accepted as significant.

**RESULTS**

Mean age in the VH-KP group was 62.20 ± 11.23 years, and 65.12 ± 11.18 years in the VH-TOT group (p = 0.460). There was no statistically significant differences between the two groups regarding parity, duration of SUI, and the number of daily pad use (p = 0.322, p = 0.585, p = 0.301, respectively) (Table-1).

<table>
<thead>
<tr>
<th>Table 1 - Demographic data of the patients and the operations.</th>
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<tbody>
<tr>
<td><strong>VH-KP</strong></td>
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<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Parity (n)</td>
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<tr>
<td>Incontinence period (year)</td>
</tr>
<tr>
<td>Pre-operative daily pad usage (n)</td>
</tr>
<tr>
<td>Post-operative daily pad usage (n)</td>
</tr>
<tr>
<td>Sexual active patients (n, %)</td>
</tr>
</tbody>
</table>

Decreased UDI-6 scores, IIQ-7 scores and daily pad usage, and increased IFSF scores were found statistical significantly in each group, at the postoperative 6th month (Table-2). When we compared the groups for improvement rates, UDI-6 and IIQ-7 scores were observed higher in the VH-TOT group, but IIQ-7 scores were not calculated as statistical significantly (69.5% vs. 63.0%, p = 0.04, 67.3% vs. 57.8%, p = 0.182). Although subjective cure rates (68% vs. 64%, p = 0.765), and improvements on the daily pad usage (88.76% vs. 85.92%, p = 0.782) were higher in the VH-TOT group, there was no statistical difference. Eighteen (72%) patients in both groups were sexually active. It was notable that the rate of patients with IFSF scores ≥ 25 was higher in VH-KP group at the postoperative 6th month (p = 0.05) (Table-3).

No intraoperative complications were observed in either group. At the postoperative 6th month, 4 (16%) patients had recurrent SUI in the VH-KP group (p = 0.039), and vaginal extrusion occurred in 2 (8%) patients in the VH-TOT group (p = 0.153).

**DISCUSSION**

Sexual dysfunction rates increase in pelvic floor disorders such as POP and SUI, especially in older patients (15). Urinary incontinence is detected in 20–90% of women with POP, POP is found in 30–70% of women with UI, and sexual dysfunction is reported in 31–44% in women with POP and UI (16). Surgical intervention against POP and
Comparison of the Kelly’s plication and TOT

SUI provides higher rates of cure in incontinence compared with surgery for POP alone (17). In the present study, we performed VH for the treatment of POP, and KP or TOT procedures were additionally performed for SUI. Significant improvement in incontinence symptoms was observed at the postoperative 6th month, on the UDI-6 scores, IIQ-7 scores, and daily pad usage in both groups (p = 0.001, p = 0.001, p = 0.001, respectively).

In a comprehensive meta-analysis that evaluated the effect of POP and UI surgeries on sexual functions, 21 studies were analyzed. Specific sexual symptoms were examined, or questionnaires were used in the evaluation of sexual functions in patients with UI. General sexual symptoms did not change after incontinence surgery in 18 studies (n = 1578 patients), in more than half (55.5%) of the patients. Sexual symptoms improved in 31.9% of the patients, and deterioration was reported in 13.1% of the patients. An analysis of the effects of mid-urethral sling surgeries [TOT, and tension-free vaginal tape (TVT)] on sexual functions in 16 studies comprising 1252 patients revealed that sexual functions

<table>
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<th>Table 2 - Improvements on UDI-6, IIQ-7, IFSF scores, and daily pad use, at the postoperative 6th month.</th>
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<tr>
<td><strong>UDI-6 scores</strong></td>
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<tr>
<td>VH-KP</td>
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<tr>
<td>VH-TOT</td>
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<tr>
<td><strong>IIQ-7 scores</strong></td>
</tr>
<tr>
<td>VH-KP</td>
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<td>VH-TOT</td>
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<tr>
<td><strong>Daily pad usage</strong></td>
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<tr>
<td>VH-KP</td>
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<tr>
<td>VH-TOT</td>
</tr>
<tr>
<td><strong>IFSF scores</strong></td>
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<tr>
<td>VH-KP</td>
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<tr>
<td>VH-TOT</td>
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</tbody>
</table>

UDI-6 = Urinary Distress Inventory-6; IIQ-7 = Incontinence Impact Questionnaire-7; IFSF = Index of Female Sexual Function; VH-KP = vaginal hysterectomy – anterior/posterior colporrhaphy with Kelly’s plication; VH-TOT = vaginal hysterectomy – anterior/posterior colporrhaphy - transobturator tape

*p values lower than 0.05 were accepted as significant.

<table>
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<tr>
<th>Table 3 - Improvements on UDI-6, IIQ-7, IFSF scores, and daily pad use, at the postoperative 6th month.</th>
</tr>
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<tbody>
<tr>
<td><strong>UDI-6 scores (%)</strong></td>
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<tr>
<td>VIH-H-KP</td>
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<td><strong>IIQ-7 scores (%)</strong></td>
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<tr>
<td>daily pad usage (%)</td>
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<tr>
<td>subjective cure rates (%)</td>
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<td>IFSF scores (%)</td>
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<tr>
<td>IFSF scores ≥ 25, n (%)</td>
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<tr>
<td>IFSF scores ≥ 25, n (%)</td>
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</tbody>
</table>

UDI-6 = Urinary Distress Inventory-6; IIQ-7 = Incontinence Impact Questionnaire-7; IFSF = Index of Female Sexual Function

*p values lower than 0.05 were accepted as significant.
did not change in 56.7%, improved in 33.9%, and worsened in 9.4%. The meta-analysis emphasized that improvement of sexual functions was 3-fold higher than the worsening of sexual functions with SUI surgery (18). However, in the present study, we observed that sexual function improved in both groups (p = 0.001, p = 0.001, respectively). Although it was not statistically significant, improvement in sexual function rates on IFSF questionnaires were found higher in the VH-KP group (91.1% vs. 78.7%, p = 0.226). In addition, the patients with IFSF scores ≥ 25 was higher in VH-KP group at the postoperative 6th month (p = 0.05).

In a recent randomized study, Sohbeti S et al. randomized 60 patients into two groups (TOT vs. anterior colporrhaphy and Kelly’s plication) who underwent SUI surgery. The cure rates in the first, 6th, and 12th months in the TOT group were 86.7%, 80%, and 80%, respectively, and the cure rates in the anterior colporrhaphy with Kelly’s plication group were 80%, 70%, and 66.7% (p = 0.68, p = 0.54, and p = 0.22, respectively). The authors reported that although there was no significant differences between the two surgical methods for the improvement of UI at the short-term follow-up, these outcomes might change in the long term (19). In the present study, decreased UDI-6 scores, IIQ-7 scores and daily pad usage, and increased IFSF scores were found statistical significantly in each group, at the postoperative 6th month. But, VH-TOT group had higher improvement rates, on UDI-6 scores (69.5% vs. 63.0%, p = 0.04). According to current guidelines and recent studies, it is a reality that long-term recurrence of SUI will be lower in patients underwent TOT owing to the mesh usage (17).

However, improvements on sexual functions do not show concordance with improvements on SUI after surgical corrections of POP and / or SUI. It was remarkable to observe more recovery in UI symptoms in the VH-TOT group, and greater recovery in sexual functions in the VK-KP group. The finding of no change or deterioration in the sexual function could be due to changes in vaginal anatomy (mucosal damage, vaginal wall elevation, and narrowing), decreased sensation, libido loss, dyspareunia, anorgasmia, presence of high levels of residual urine, and de novo urgency after surgery (18, 20, 21). These results demonstrate the drawbacks of the mesh use. A recent meta-analysis by Jha et al. revealed that a significant increase in sexual function and decrease in dyspareunia was reported after POP surgery with conventional tissue repair (22). Mesh erosion / extrusions, which may be detected in 1% of patients after sling surgery, have a negative effect on sexual functions (18). In a study investigated the female sexual function after TOT, vaginal erosion was reported as 4.9%, de novo urgency as 4.9%, vesico-vaginal fistula as 1.2%, and urinary retention as 3.7% (23). In our study, vaginal extrusion was detected in 2 (8%) patients who underwent TOT, and mesh excision was performed. Although there was a significant improvement in sexual functions in the VH-KP group, recurrent SUI developed in 4 (16%) patients at the 6th postoperative month.

There are limited studies comparing effects of surgeries on incontinence, quality of life, and sexual function in patients with POP, and concurrent obvious SUI. Therefore, we believe that the present study will contribute to the current literature. But, our study has certain limitations. The small sample size and short-term post-operative follow-up are the primary limitations. The current findings should be supported by prospective, randomized studies including wider patient series and long-term results.

CONCLUSIONS

Although the improvement rates of VH-TOT surgeries are superior to conventional methods for SUI, and quality of life, the negative effects on sexual function are notable. Even though the SUI recurrence rates of TOT surgeries are lower, complications such as vaginal extrusion are known drawbacks associated with mesh usage. Therefore, in addition to treatment success, patients treated with mesh should be informed about its effects on sexual functions and potential complications. In addition, although it is an outdated method, conventional surgical methods such as Kelly’s plication may be offered as an option for patients who request native tissue repair.
CONFLICT OF INTEREST

None declared.

REFERENCES


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Clinical features of carriers of reciprocal chromosomal translocations involving chromosome 2: report of nine cases and review of the literature

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1 Center for Reproductive Medicine and Center for Prenatal Diagnosis, First Hospital, Jilin University, Changchun, China

ABSTRACT

Objective: To explore the clinical features of carriers of chromosome 2 translocations, enabling informed genetic counseling of these patients.

Materials and Methods: Eighty-two male carriers of a translocation who were infertile or receiving fertility counseling were recruited. Cytogenetic analyses were performed using G-banding. A search of PubMed was performed to determine whether the identified translocations on chromosome 2 are involved in male infertility. The relationships of translocation breakpoints with male infertility and recurrent pregnancy loss were analyzed.

Results: Of the 82 translocation carriers, 9 (11%) were carriers of a chromosome 2 translocation. Four cases had oligozoospermia or infertility, while five had normal semen. In an analysis of the literature, 55 patients who were carriers of chromosome 2 translocations were also reviewed. Breakpoints at 2p13 and 2q31 were observed in six patients each, and were the most common. Breakpoints at 2p23, 2p13, 2p11.2, 2q31, and 2q37 were associated to both pre-gestational and gestational infertility, while other breakpoints were associated with gestational infertility.

Conclusions: All breakpoints at chromosome 2 were correlated with gestational infertility. Carriers of chromosome 2 translocations should therefore receive counseling to continue with natural conception and use of different technologies available via assisted reproductive technology, such as preimplantation genetic diagnosis.

INTRODUCTION

Infertility affects approximately 15%-20% of couples who attempt to have children. Reciprocal translocations are present in 0.9/1000 newborns, and the incidence in the infertile male population is 7-10 times higher than in fertile men (1, 2). Balanced translocation is the most common structural rearrangement in humans (3). Chromosomal translocations may cause the loss of genetic material at the breakpoints and could result in testicular failure (4). Individuals affected by such translocations are associated with reproductive problems such as infertility, recurrent pregnancy loss, and malformed offspring (5). These effects are related to the specific chromosomes and breakpoints involved in the translocation (6, 7). Some translocation break-
points can disrupt the structure of an important gene, leading to male infertility (8).

The genetic counseling of male carriers of translocations remains challenging. Preimplantation genetic diagnosis (PGD) is a recommended part of such counseling for those with balanced translocation with normal or abnormal semen. In vitro fertilization accompanied by PGD increases the chance of their fathering a healthy child (9). In azoospermia patients, pregnancy success and fertility may be achieved via intracytoplasmic sperm injection, using spermatozoa obtained from testis by microdissection testicular sperm extraction (10, 11).

However, De Krom et al. (12) reported that clinical characteristics including spontaneous abortion do not differ between those couples who accept and those who decline PGD. A systematic review also showed a lack of sufficient evidence that PGD improves the live birth rate in couples with repeated miscarriage carrying a structural chromosome abnormality (13). In addition, the natural pregnancy success rates for couples in which the male carries a translocation ranges from 30% to 70% (14). This suggests that continuing attempts to conceive naturally are a viable option for successful pregnancy. Hence, the relationship between chromosome structure abnormality and clinical features warrants further studies.

There may be important genes associated with spermatogenesis on chromosome 2. For example, follicle-stimulating hormone receptor (FSHR) is located on chromosome 2p16.3, and is expressed in testicular tissue of idiopathic azoospermic patients with severe spermatogenic defects. Its differential expression may be associated with the degree of spermatogenesis (15). A study has also shown that genetic polymorphisms in the FSHR gene might increase the susceptibility to azoospermia in Iranian men (16). However, the FSHR polymorphisms at the studied sites were shown not to be associated with idiopathic male infertility or to influence FSH levels in both normal and infertile males in the Han-Chinese population (17). In addition, the SPAG16 gene (sperm-associated antigen 16), mapped on chromosome 2 at 2q34, has been reported to be associated with impaired sperm motility (18). The breakpoints of 2q25.1, q11.2, and q31 have also been shown to be related to impaired spermatogenesis (19).

The present study was established to explore the clinical features and translocation breakpoints in carriers of reciprocal chromosomal translocations involving chromosome 2. This study also highlights the importance of genetic counseling for infertile patients.

MATERIALS AND METHODS

Study subjects

Between July 2010 and December 2015, we recruited 82 male carriers of translocations experiencing infertility, or receiving counseling, from the outpatient’s department at the Centre for Reproductive Medicine, the First Hospital of Jilin University, Changchun, China. All patients underwent a thorough physical examination and semen analysis, and were required to complete a detailed questionnaire pertaining to their smoking habits, marital status, medical history, and working conditions. The study protocol was approved by the Ethics Committee of the First Hospital of Jilin University, and written informed consent was obtained from all participants.

Semen analysis

Semen analysis was performed according to the procedures recommended by the World Health Organization guideline. If no sperm was found, sperm was analyzed by sedimentation of semen samples through centrifugation. Patients with oligozoospermia were diagnosed as a sperm cell count <15×10^6/mL in their last 3 semen samples (taken at intervals of 1-3 weeks). Azoospermia and oligozoospermia were defined as previously described (8). All analyzes were performed at the same laboratory, and all data were accessed from medical records.

Cytogenetic analysis

Cytogenetic analysis was carried out on all patients. Peripheral blood (0.5mL) was collected in sterile tubes containing 30U/mL heparin. Lymphocytes were then cultured in appropriate culture medium (Yishengjun; Guangzhou Baidi Biotech, Guangzhou, China) for 72h, and subsequently treated with colcemid for 1h. G-banding of metaphase chromosomes and karyotype analysis were
performed using previously described methods (20). Twenty metaphases were counted and 6 karyotypes were analyzed for per patient. The karyotype nomenclature was described in accordance of ISCN 2009. The resolution level of the chromosome analysis was 400-550 band levels.

Analysis of the identified translocation breakpoints

A search for the translocations identified in chromosome 2 from infertile males was performed using PubMed. The keywords were “chromosome/translocation/abortion” and “chromosome/translocation/sperm” for Pubmed search. The criteria were that the patients included reciprocal chromosomal translocations involving chromosome 2 in reported papers. The relationships of translocation breakpoints with male infertility and recurrent pregnancy loss were analyzed. Such searches were performed for a total of 46 carriers of chromosomal 2 translocations. This study included the cases of reciprocal chromosomal translocations involving chromosome 2 in reported papers and excluded the cases without breakpoints involving chromosome 2.

RESULTS

A total of 82 translocation carriers were detected in this study. Of these, nine (11%) were carriers of a chromosome 2 translocation. Karyotype results from these nine patients are summarized in Table-1. Four cases had oligozoospermia or infertility (pre-gestational infertility), while five cases had normal semen. Of these latter five cases, it was evident that their partners were able to conceive, but had a tendency to miscarry (gestational infertility); one case had experienced recurrent spontaneous abortions, one case had experienced two stillbirths, and one case had experienced biochemical pregnancy on three occasions, while two cases produced a phenotypically normal child.

An analysis of the literature was also performed, from which karyotype results, clinical manifestations, and the breakpoints on chromosome 2 were collected, as shown in Table-2. Breakpoints at 2p13 and 2q31 were observed in six patients each, and were the most common. Breakpoints at q10 and q11.2 were related to pre-gestational infertility, while breakpoints at 2p23, 2p13, 2p11.2, 2q31, and 2q37 were connected to both pre-gestational and gestational infertility. Other breakpoints were associated with gestational infertility. It is noteworthy that two carriers of a translocation at 2q33 produced normal children, as did one carrier of a translocation at 2q35 (Table-3).

DISCUSSION

Karyotype analysis is able to detect chromosomal translocations or deletions, which sometimes have very detrimental effects on gene structure, and remains a powerful and cheap method to use (21). This technology thus provides valuable information for the genetic counseling of infertile males (22). Previous studies have reported that infertile men have an 8-10-fold higher prevalence of

<table>
<thead>
<tr>
<th>Infertility causes</th>
<th>Clinical findings</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gestational infertility</td>
<td>Oligozoospermia or infertility</td>
<td>46,XY,t(1;2)(q21;p23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,XY,(1;2)(q21;q37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,XY,t(2;13)(q10;q10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,XY,t(2;15)(p11.2;q15)</td>
</tr>
<tr>
<td>Gestational infertility</td>
<td>Normal sperm density; a history of miscarriage, stillbirth, or normal fertility</td>
<td>46,XY,t(2;6)(q21;p21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,XY,t(2;11)(q33;q23)</td>
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<td></td>
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<td>46,XY,t(2;11)(q35;q13)</td>
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<tr>
<td></td>
<td></td>
<td>46,XY,t(2;14)(q31;q24)</td>
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<tr>
<td></td>
<td></td>
<td>46,XY,t(2;16)(p23;q13)</td>
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</tbody>
</table>
Table 2 - Breakpoints in chromosome 2 translocation carriers and clinical features.

<table>
<thead>
<tr>
<th>Case</th>
<th>Karyotype</th>
<th>Breakpoints</th>
<th>Clinical findings</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>t(1;2)</td>
<td>1p22;2q31</td>
<td>2 miscarriages</td>
<td>Dong et al., 2014 (31)</td>
</tr>
<tr>
<td>2</td>
<td>t(1;2)</td>
<td>1q21;2p23</td>
<td>Oligozoospermia</td>
<td>The present study</td>
</tr>
<tr>
<td>3</td>
<td>t(1;2)</td>
<td>1q21;2q37</td>
<td>Oligozoospermia</td>
<td>The present study</td>
</tr>
<tr>
<td>4</td>
<td>t(1;2)</td>
<td>1q21;2q37</td>
<td>Oligozoospermia</td>
<td>Li et al., 2012 (23)</td>
</tr>
<tr>
<td>5</td>
<td>t(1;2)</td>
<td>1q32;2q36</td>
<td>Abortion</td>
<td>Templado et al., 1990 (32)</td>
</tr>
<tr>
<td>6</td>
<td>t(1;2)</td>
<td>1q32.1;2q11.2</td>
<td>Oligozoospermia</td>
<td>Vozdova et al., 2013 (9)</td>
</tr>
<tr>
<td>7</td>
<td>t(1;2)</td>
<td>2q42;2q37</td>
<td>2 fetal malformations</td>
<td>Zhang et al., 2006 (33)</td>
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<tr>
<td>8</td>
<td>t(1;2)</td>
<td>1q42;2q33</td>
<td>Miscarriage</td>
<td>Stasiewicz-Jarocka et al., 2000 (34)</td>
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<td>9</td>
<td>t(2;3)</td>
<td>2p13;3q27</td>
<td>Recurrent pregnancy loss</td>
<td>Ocan et al., 2013 (35)</td>
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<td>10</td>
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<td>2q21;3p21</td>
<td>Recurrent spontaneous abortion</td>
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<td>11</td>
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<td>2q24;3p26</td>
<td>Normal semen</td>
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<td>12</td>
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<td>Recurrent abortion</td>
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<tr>
<td>13</td>
<td>t(2;4)</td>
<td>2q31;4q31</td>
<td>Stillbirth</td>
<td>Li et al., 2012 (23)</td>
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<tr>
<td>14</td>
<td>t(2;4)</td>
<td>2q31.4q31</td>
<td>2 stillbirths</td>
<td>Dong et al., 2014 (31)</td>
</tr>
<tr>
<td>15</td>
<td>t(2;5)</td>
<td>2p21;5p15</td>
<td>Recurrent spontaneous abortion</td>
<td>Gada Saxena et al., 2012 (25)</td>
</tr>
<tr>
<td>16</td>
<td>t(2;5)</td>
<td>2p11;5q15</td>
<td>Abortion</td>
<td>Templado et al., 1988 (39)</td>
</tr>
<tr>
<td>17</td>
<td>t(2;5)</td>
<td>2p11.5q31</td>
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<td>Portnoi et al., 1988 (37)</td>
</tr>
<tr>
<td>18</td>
<td>t(2;5)</td>
<td>2q12;5q35.3</td>
<td>Spontaneous miscarriage</td>
<td>Kochhar et al., 2013 (40)</td>
</tr>
<tr>
<td>19</td>
<td>t(2;6)</td>
<td>2p13;6p21.3</td>
<td>Recurrent abortion</td>
<td>Al-Hussain et al., 2000 (41)</td>
</tr>
<tr>
<td>20</td>
<td>t(2;6)</td>
<td>2p12.6p24</td>
<td>Two earlier miscarriages</td>
<td>Lim et al., 2003 (42)</td>
</tr>
<tr>
<td>21</td>
<td>t(2;6)</td>
<td>2p21;6p21</td>
<td>3 first-trimester abortions</td>
<td>The present study</td>
</tr>
<tr>
<td>22</td>
<td>t(2;6)</td>
<td>2q34;6p24</td>
<td>Recurrent spontaneous abortion</td>
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<tr>
<td>23</td>
<td>t(2;7)</td>
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<td>Frys et al., 1998 (38)</td>
</tr>
<tr>
<td>24</td>
<td>t(2;7)</td>
<td>2p13;7q34</td>
<td>Normal semen, IVF/PGD ET, twins 46,XX</td>
<td>Vozdova et al., 2013 (9)</td>
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<tr>
<td>25</td>
<td>t(2;7)</td>
<td>2q31;7q34</td>
<td>Abnormal semen</td>
<td>Vozdova et al., 2013 (9)</td>
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<tr>
<td>26</td>
<td>t(2;7)</td>
<td>2q12.1;7q22.1</td>
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<td>Wiland et al., 2008 (3)</td>
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<tr>
<td>27</td>
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<td>2q37.3q34</td>
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<td>Ahn et al., 2003 (43)</td>
</tr>
<tr>
<td>28</td>
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<td>2p13.8q13</td>
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<tr>
<td>29</td>
<td>t(2;8)</td>
<td>2p22;8p23.1</td>
<td>Spontaneous abortions</td>
<td>Kyu Lim et al., 2004 (45)</td>
</tr>
</tbody>
</table>
Chromosomal abnormalities than fertile men (23). Chromosomal translocation alters the complex and vital process of spermatogenesis, and leads to recurrent pregnancy loss (24). In particular, chromosome 2 translocation has often been associated with male infertility and recurrent miscarriage (9, 25, 26). In the present study, nine of our cases were identified as carriers of chromosome 2 translocations, and 55 cases of chromosome 2 translocation from the literature were also reviewed.

Generally, male infertility can be broadly divided into two types of reproductive failure: pre-gestational and gestational infertility (23). In this study, the breakpoints that we identified on chromosome 2 were found to be associated with pre-gestational or gestational infertility. Four cases were associated with pre-gestational infertility and five cases were related to gestational infertility. Kim et al. (19) reported that the breakpoints at 2p25.1, 2q11.2, and 2q31 could interfere with spermatogenesis, and that the breakpoint at 2p13 was related to recurrent abortion. In addition, Manvelyan et al. (27) reported that the breakpoint at 2q12 in male carriers was associated with repeated abortion. To study the relationship of these breakpoints on chromosome 2 with male infertility, we analyzed recent

<table>
<thead>
<tr>
<th>Case</th>
<th>Breakpoint</th>
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<tbody>
<tr>
<td>32</td>
<td>t(2;8)</td>
<td>2q35;8q11.2</td>
<td>Spontaneous abortions</td>
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<tr>
<td>33</td>
<td>t(2;8)</td>
<td>2q37;8q22</td>
<td>3 abortions</td>
</tr>
<tr>
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<td>2q21;9p22</td>
<td>Abortion</td>
</tr>
<tr>
<td>35</td>
<td>t(2;9)</td>
<td>2q37.3;9q12</td>
<td>Normal semen, increased risk of miscarriage</td>
</tr>
<tr>
<td>36</td>
<td>t(2;10)</td>
<td>2q33.10q24</td>
<td>Produced a child, 46,XX</td>
</tr>
<tr>
<td>37</td>
<td>t(2;11)</td>
<td>2p14;11q21</td>
<td>Repeated abortion</td>
</tr>
<tr>
<td>38</td>
<td>t(2;11)</td>
<td>2q24;11q32</td>
<td>Recurrent abortion</td>
</tr>
<tr>
<td>39</td>
<td>t(2;11)</td>
<td>2q33;11q23</td>
<td>Produced a child, 46,XX</td>
</tr>
<tr>
<td>40</td>
<td>t(2;11)</td>
<td>2q35;11q13</td>
<td>Produced a child, 46,XX, t(2;11)</td>
</tr>
<tr>
<td>41</td>
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<td>2q31;12q24</td>
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<tr>
<td>42</td>
<td>t(2;13)</td>
<td>2q35;13q32</td>
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<tr>
<td>43</td>
<td>t(2;13)</td>
<td>2q10;13q10</td>
<td>Oligozoospermia</td>
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<td>46</td>
<td>t(2;14)</td>
<td>2q31;14q24</td>
<td>2 stillbirths</td>
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<td>47</td>
<td>t(2;14)</td>
<td>2q37.1;14q31.2</td>
<td>Fetal malformations</td>
</tr>
<tr>
<td>48</td>
<td>t(2;15)</td>
<td>2p11.2;15q15</td>
<td>Infertility</td>
</tr>
<tr>
<td>49</td>
<td>t(2;15)</td>
<td>2q21;15p12</td>
<td>Recurrent fetal wastage</td>
</tr>
<tr>
<td>50</td>
<td>t(2;16)</td>
<td>2p23;16q13</td>
<td>Recurrent spontaneous abortion</td>
</tr>
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<td>52</td>
<td>t(2;17)</td>
<td>2q37.2;17q25</td>
<td>Recurrent spontaneous abortion</td>
</tr>
<tr>
<td>53</td>
<td>t(2;18)</td>
<td>2p21;18q11.2</td>
<td>5 miscarriages</td>
</tr>
<tr>
<td>54</td>
<td>t(2;20)</td>
<td>2p16;20p12</td>
<td>Recurrent abortion</td>
</tr>
<tr>
<td>55</td>
<td>t(2;20)</td>
<td>2p24.1;20q13.1</td>
<td>Recurrent abortion</td>
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</table>
published literature and revealed clinical features in carriers of chromosome 2 translocations. The karyotype results and clinical findings at chromosome 2 are summarized in Table-2. Clinical features associated with the breakpoints at 2p13, 2q11.2, and 2q12 were consistent with the above two reports (19, 27).

Table-3 also shows that 2p23, 2p13, 2p11.2, 2q31, and 2q37 were connected to both pre-gestational and gestational infertility. These cases indicated that these breakpoints are not responsible for pre-gestational infertility, so another breakpoint of translocation must be the cause in these individuals. Similarly, the APOB gene is located on chromosome 2p24.1, and the APOB gene signal peptide deletion polymorphism was reported not to be associated with infertility in Indian men (28). Furthermore, FSHR, mapped on chromosome 2 at 2p16, was shown not to be correlated with sperm count in infertile males (29).
Besides the breakpoints at q10 and q11.2, other breakpoints were identified as being associated with gestational infertility. For those affected by these breakpoints, natural conception is possible and they have the potential to bear normal children. For example, Ikuma et al. (30) reported that the live birth rate with natural conception for translocation carriers was 37%-63% in the first trial and 65%-83% cumulatively. However, natural conception is still a greater risk, since the number of chromosomal unbalanced gametes is large, leading to repetitive pregnancy loss, which may have repercussions on the fertility of the translocation carrier. For these carriers, informed choice should be performed. In addition, the breakpoints at 2p13 and 2q31 were found to be the most common, and were associated with gestational infertility.

CONCLUSIONS

In the present study, 55 carriers of chromosome 2 translocations were reviewed. The breakpoints at 2p13 and 2q31 were the most common, and were associated with gestational infertility. All breakpoints at chromosome 2 were correlated with gestational infertility. Carriers of chromosome 2 translocations should therefore be counselled to attempt natural conception and to use the different technologies available via assisted reproductive technology, such as PGD.

ABBREVIATIONS

PGD = Preimplantation genetic diagnosis
FSH = Follicle-stimulating hormone
FSHR = Follicle-stimulating hormone receptor
SPAG16 gene = Sperm-associated antigen 16 gene
APOB gene = Apolipoprotein B gene

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.

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Low serum melatonin levels are associated with erectile dysfunction

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ABSTRACT

Objective: Melatonin is a hormone secreted from the pineal gland and has anti-oxidative and anti-inflammatory effects. Oxidative stress is considered as an important factor in the etiology of erectile dysfunction (ED), and in many experimental models, positive results have been obtained with melatonin treatment. This study aimed to measure serum melatonin levels in ED patients and to investigate the possible relationship between ED and melatonin levels.

Materials and Methods: Sixty-two patients diagnosed with mild, moderate or severe ED according to the five-item International Erectile Function Index (IIEF-5) and 22 healthy individuals were included in the study. The serum melatonin levels, anthropometric data, and other biochemical and hormonal parameters of all the subjects were recorded. Detailed anamnesis was also obtained in terms of diabetes, hypertension, cardiovascular diseases, smoking status, and alcohol use.

Results: The serum melatonin level was found 34.2±13.3 ng/dL in the mild ED group, 33.3±14.7 ng/dL in the moderate ED group, 34.8±17.2 ng/dL in the severe ED group, and 44.6±16.5 ng/dL in the control group. The serum melatonin levels were significantly lower in all ED groups compared to the control group (p=0.019). There was no significant difference in the serum melatonin levels between the three ED groups. Diabetes, hypertension, cardiovascular diseases, smoking and alcohol use were not significantly different between the ED groups (p>0.05).

Conclusion: We consider that if our findings are supported by further studies with larger populations, the measurement of the serum melatonin level may have a future role in the diagnosis and treatment of ED.

INTRODUCTION

Erectile dysfunction (ED) is defined as an inadequate or unsustainable penile erection for satisfactory sexual performance (1). The incidence of ED has been reported to increase with age, reaching 20-40% in males in the age range of 60-69 years and 50-100% in those aged 70 to 80 (2). In ED etiology, among the major causes are chronic diseases, such as hypertension, diabetes mellitus, and coronary artery diseases (CAD), as well as the negative effects of the drugs used for these conditions (3). The mechanism underlying these etiologic diseases is the development of degenerative
changes leading to endothelial dysfunction (4). The pathophysiological mechanism of endothelial dysfunction is multifactorial and often characterized by degraded nitric oxide bioavailability, decreased vasodilatation, and worsening inflammation, preceded by atherosclerotic lesions (5). Nitric oxide (NO) production plays a central physiological role in the erection process. Neurogenic nitric oxide (NO) is considered as the most important factor for the relaxation of corpora cavernosa (CC) and the penile vessels necessary for erectile response (5).

Melatonin is a hormone secreted from the pineal gland and has anti-oxidative and anti-inflammatory effects (6). Studies have shown that melatonin detoxifies highly reactive hydroxyls (OH) in vitro and sweeps free radicals (7). Although melatonin has been reported to increase all aspects of sexual activity in rats (8), it has also been stated that chronic administration of this hormone may lead to the inhibition of sexual activity of male rats (9). Previous research suggests that melatonin may have positive effects on erectile function. It was also demonstrated that acute administration of melatonin restored complete sexual activity in selected impotent male rats (10). Furthermore, melatonin treatment reduced oxidative stress and improved the contractility of CC in diabetic Wistar rats (11). Melatonin treatment has also been reported to result in reduced / prevent the functional and morphological changes induced by chronic ischemia in penile structure and function (12).

Erection is essentially a neurovascular event that requires intact and functional endothelium and smooth muscle in the corpus cavernosum (CC) (13). It is known that atherosclerosis is an inflammatory process involving a number of proinflammatory cytokines, representing an increased state of oxidative stress (14). Melatonin protects tissues from oxidative damage induced by the various processes that produce free radicals (15). In addition, melatonin acts an indirect anti-oxidant by activating major anti-oxidant enzymes, such as superoxide dismutase (16). Evidence in the literature suggests that melatonin has a role in reducing oxidative stress induced in many organs by diabetes (17, 18).

However, to our knowledge, no studies have explored the relationship between serum melatonin levels and ED; therefore, we decided to investigate the possibility of melatonin deficiency in ED patients to serve as a potential simple to use diagnostic marker.

**MATERIAL AND METHODS**

Prior to the commencement of the study, approval from the local ethics committee and the informed consent of all the participants were obtained. A total of 62 ED patients and 22 healthy volunteers (control) were included in the study. The patients referred to the urology clinic were divided into three groups as having mild, moderate and severe ED.

All the patients had ED complaints about their sexual activities for at least six months. The erectile function of all the patients was determined according to the five-item version of the International Index of Erectile Function (IIEF-5) (19). Based on their IIEF-5 scores, participants were divided into three ED groups as follows: severe (score: 1-7), moderate (8-16), and mild (17-21). All the participants had been sexually active for the previous six months and responded to the IIEF-5 items concerning sexual activities.

The exclusion criteria were: the presence of neurological disorders, history of pelvic trauma, anemia, major psychiatric diseases, psychogenic erectile dysfunction, thyroid disease, acute or chronic urinary tract disease and end stage renal disease; having used medication that would affect their sex hormones or vitamin metabolism within the last three months; and being under treatment for ED. The informed consent of the participants was taken prior to the collection of blood samples.

**Medical History and Physical Examination**

Demographic and medical information was obtained from all the participants, including age, medical history, presence of hypertension, smoking status, duration of sexual dysfunction. Physical examination comprised the digital rectal examination (DRE), genital examination and measurement of height and weight and calculation of body mass index (BMI) by dividing wei-
ght in kilograms by height in meters squared. The patients suspected having prostate cancer in DRE or symptoms of hypogonadism, were excluded from the study.

**Laboratory tests**

For the laboratory tests, blood samples were taken from all the participants at 8 a.m. after fasting for 12 hours and stored at -20°C until assayed. Fasting blood glucose (FBG), total testosterone, triglyceride, low-density and high-density lipoprotein cholesterol (LDL-C and HDL-C), and serum melatonin levels were recorded. Serum melatonin level was measured using an enzyme-linked immunosorbent assay (SunRedbio ELISA Kit) and an Epoch microplate spectrophotometer (BioTek Instruments, Inc., Winooski, VT, USA). Serum testosterone level was measured using an enzyme-linked immunosorbent assay (Siemens Centaur XP Kit, Germany).

**Statistical analysis**

For discrete and continuous variables, descriptive statistics (mean, standard deviation, n and percentile) were given. To compare the differences between three and more groups, one-way analysis of variance was used when the parametric test prerequisites were fulfilled, and the Kruskal Wallis test was used when such prerequisites were not fulfilled. The relationship between two continuous variables was assessed by the Pearson Correlation Coefficient, and by the Spearman Correlation Coefficient when the parametric test prerequisites were not met. Data (SPSS, Chicago IL, Version 17) was assessed in the SPSS package program (Chicago IL, Version 17). p<0.05 was taken as significance levels.

**RESULTS**

The mean ages of the participants were 54.7±7.6, 54.8±9.5 and 57.0±7.1 in the mild, moderate and severe ED groups, respectively, and 51.9±7.6 in the control group. There was no statistically significant difference between the four groups in terms of the mean age, BMI, HT, smoking, alcohol use, diabetes mellitus, total testosterone, LDL-C, HDL-C, triglyceride and cholesterol (p>0.05). However, statistically significant differences were obtained between the groups concerning melatonin and FBG (p<0.05). The mean serum FBG level in severe ED group was significantly highest in all groups, (P<0.05). and FBG level were 103 mg/dL, 115.6 mg/dL and 127 mg/dL in the mild, moderate and severe ED groups, respectively, and 100 mg/dL in the control group. The mean IIEF-5 scores were 5.85±0.93, 10.22±0.8, 15.26±3.2 and 24±1.38 in the severe, moderate, mild ED and control groups, respectively. Furthermore, all patients in the ED groups had a lower IIEF-5 score than the control group (p<0.05). This shows that the highest total testosterone level was observed in the control group, but the difference between the other groups wasn’t statistically significant.

Table-1 presents clinical information and the fasting endocrine values of all participants. The serum melatonin levels were significantly lower in all ED groups compared to the control group (p=0.019): 34.2±13.3 ng/dL in the mild ED group, 33.3±14.7 ng/dL in the moderate ED group, 34.8±17.2 ng/dL in the severe ED group, and 44.6±16.5 ng/dL in the control group. There was no significant difference among the ED groups in terms of melatonin levels (p>0.05). In all ED groups, there was a statistically significant association (r=0.586, p=0.047) between IIEF-5 and melatonin levels with the increase being parallel in both parameters.

**DISCUSSION**

We found that in the present study, serum melatonin levels in ED patients were found to be significantly lower than controls. In their study, Qiu et al. detected increases in both erectile function and the endothelial density of the CC in diabetic rats after melatonin treatment (20). In another study conducted on diabetic rats, melatonin was reported as contributing to many histological and functional changes through its local anti-oxidative effect on CC and having a relaxing effect on smooth muscles in CC (11). Drago et al. (10) demonstrated that selected impotent male rats regained full sexual activity following a low dose
of melatonin treatment (10-100 mg/kg). Similarly, Paskaloglu et al. (11) reported reduced oxidative stress and improved CC contraction in diabetic Wistar rats following melatonin treatment (6 mg/kg per day for six weeks). In a recent animal study, Sawada et al. (12) reported that after melatonin treatment (20 mg/kg per day for 8 weeks), erectile responses were regained, collagen deposition in CC was reduced, contractile and relaxant responses were protected in isolated CC strips, and there was increased neuronal and endothelial NO synthase (NOS) and decreased inducible NOS expression in CC. It is considered that ischemic erectile tissue dysfunction may involve multiple mechanisms, such as chronic nutrient deficiency, hypoxia and metabolic wastes, and may affect NO production or function due to cytotoxicity (21). Sawada et al. (12) also showed that the down-regulation of eNOS and nNOS proteins might lead to a further deterioration of corporal tissue and eventual ED.

In addition to that, eNOS and nNOS proteins were found to be reduced tissues of chronic ischemic CC, and both of which were significantly improved by melatonin treatment. As a result of chronic use, melatonin exhibits protective effects on chronic ischemic CC by scavenging free radicals and through anti-oxidative properties.

Endothelial dysfunction leading to atherosclerosis and/or smooth muscle dysfunction plays a major role in the pathogenesis of both ED and CAD.

The results of the study by Tavukcu et al. (22) indicated the critical pathogenic contribution of increased oxidative stress to ED caused by spinal cord injury and they finally suggested that melatonin and tadalafil combination led to similar beneficial effects through different mechanisms of action.

The circadian organisation of melatonin on human physiological functions such as immu-

### Table 1 - Participant clinical data and fasting endocrine values.

<table>
<thead>
<tr>
<th></th>
<th>Severe ED (n:20)</th>
<th>Moderate ED (n:23)</th>
<th>Mild ED (n:19)</th>
<th>Control (n:22)</th>
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<tr>
<td>Clinical values</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>57.05±7.1</td>
<td>54.8±9.5</td>
<td>54.7±7.6</td>
<td>51.9±7.6</td>
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<tr>
<td>IIEF-5 score</td>
<td>5.85±0.93</td>
<td>10.22±0.80</td>
<td>15.26±3.21</td>
<td>24±1.38</td>
<td>0.001**</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.2±3.0</td>
<td>28.8±4.2</td>
<td>29.6±3.8</td>
<td>27.5±2.9</td>
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<tr>
<td>Hypertension (%)</td>
<td>20.0</td>
<td>8.7</td>
<td>10.5</td>
<td>9.1</td>
<td>0.704</td>
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<td>Smoking (%)</td>
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<td>47.8</td>
<td>30.0</td>
<td>26.3</td>
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<tr>
<td>Diabetes (%)</td>
<td>15.0</td>
<td>8.7</td>
<td>5.3</td>
<td>9.1</td>
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<tr>
<td>CAD (%)</td>
<td>15.0</td>
<td>8.7</td>
<td>10</td>
<td>5.5</td>
<td>0.109</td>
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<td>Haematoclinical values</td>
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<tr>
<td>FBG (mg/dL)</td>
<td>127 (73-277)</td>
<td>115.65 (72-209)</td>
<td>103 (81-160)</td>
<td>100 (86-162)</td>
<td>0.036*</td>
</tr>
<tr>
<td>TT (ng dL⁻¹)</td>
<td>380.7±53.5</td>
<td>306.17±83.8</td>
<td>404.6±143.4</td>
<td>341.0±106.7</td>
<td>0.46</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>127.1±37.0</td>
<td>109.5±30.1</td>
<td>107.5±33.4</td>
<td>110.6±40.8</td>
<td>0.264</td>
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<tr>
<td>HDL (mg/dL)</td>
<td>41.80±9.2</td>
<td>42.2±8.3</td>
<td>42.1±10.4</td>
<td>44.3±7.12</td>
<td>0.196</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>209.5±100.6</td>
<td>187.8±97.0</td>
<td>150.6±61.6</td>
<td>176.5±83.2</td>
<td>0.231</td>
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<tr>
<td>Total cholesterol, (mg/dL)</td>
<td>195.6±48.9</td>
<td>172.7±28.1</td>
<td>205.8±33.3</td>
<td>182.0±36.8</td>
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<tr>
<td>Melatonin(ng/dL)</td>
<td>34.8±17.2</td>
<td>33.3±14.7</td>
<td>34.2±13.3</td>
<td>44.6±16.5</td>
<td>0.019*</td>
</tr>
</tbody>
</table>

IIEF-5 score = International Index of Erectile Function 5; BMI = body mass index; CAD = Coronary artery disease; FBG = Fasting blood glucose; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TG = Triglyceride; TT = Total Testosterone.

*p<0.05; **p<0.01
ne system, antioxidant defences, haemostasis and glucose regulation was demonstrated (23). Javanmard et al. (24) reported that even in patients with severe and advanced atherosclerotic plaques, melatonin may have beneficial effects on endothelial dysfunction. In that study, the authors found a significant reduction in the mean levels of intercellular adhesion molecule, vascular cell adhesion molecule and C-Reactive Protein following one month of melatonin treatment. Furthermore, they noted higher serum NO levels in the study group compared with the controls. The authors concluded that melatonin might reduce the markers of endothelial cell damage and increase vasodilator cytokines. These positive results obtained with the replacement of melatonin deficiency made us think that melatonin deficiency may be of importance in ED etiology. And we think that melatonin treatment may be useful for both atherosclerosis and ED.

In human studies, reduced levels of melatonin were reported to exist in patients with type 2 diabetes (25) and hypertension (26). It has also been shown that blood melatonin levels were correlated with the severity of disease in patients with cardiovascular disease (27). These studies show that melatonin deficiency might compromise many systems and it could play a causative role for many disease. In the present study, serum melatonin levels in ED patients were found to be significantly lower than controls. However, no significant difference was detected among the ED groups in melatonin levels. There was not any proportional relationship between melatonin deficiency and ED severity in our small sample. This result made us think that the level of melatonin deficiency may not reflect the ED severity.

As far as we know, this is the first study evaluating serum melatonin level as a causative factor in this patient group. A low serum melatonin level may result in an inadequate erection by preventing sufficient antioxidant capacity. There is a need for additional studies to determine the exact role of melatonin deficiency in ED patients. The limitations of our study were the absence of Doppler ultrasound findings, the lack of a treatment group and follow-up data on melatonin levels and the small sample size. Future studies may assess the association or a possible correlation between serum melatonin levels and Doppler ultrasound parameters of erectile function. Furthermore, serum inflammatory markers may also be measured for investigating the relationship between melatonin and inflammation level.

CONCLUSIONS

In the present study, we found a significant relationship between ED presence and low serum melatonin levels. This relationship suggests that melatonin deficiency may be of importance in ED etiology. If larger clinical trials confirm our findings, measurement of serum melatonin level may have an additive future role in ED diagnosis and melatonin replacement would find an indication for ED treatment.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Penile refracture: a preliminary report

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ABSTRACT

Objective: To report our institutional experience with penile refracture, including demographic data, recurrence time, etiology and operative findings in the first and second episodes.

Materials and methods: Between January 1982 and September 2017, 281 patients underwent surgical treatment for penile fracture (PF) at our institution. Demographic data, clinical presentation, besides operative findings and follow-up of patients with relapsed PF were retrospectively assessed by reviewing medical records.

Results: Of a total of 281 cases of PF operated at our institution, 3 (1.06%) patients experienced two episodes of trauma. Age ranged from 38 - 40 years (mean: 39.3). The recurrence time varied from 45 to 1560 days (mean: 705). Two patients presented the new fracture episode at the same site of the previous lesion, while in the other case the lesion was observed at another site.

Conclusion: Recurrent FP is an extremely rare entity. The risk factors for its occurrence are still unknown. Although the lesion of the corpus cavernosum ipsilateral to the scar tissue of the prior FP is more common, contralateral rupture may be present. Nevertheless, prospective studies with larger samples should be conducted.

INTRODUCTION

Penile fracture (PF) represents a rare urologic emergency situation, corresponding to 1 in every 175,000 emergency hospital visits (1). A recent literature review evaluating data from different regions of Iran has estimated that the incidence of PF in the Middle Eastern country can be estimated to be between 1.1 and 9.9 per 100,000 male inhabitants, being that urologists encounter, on average, 1 patient with FP in every 3.5 months (2). However, this is probably an underreported entity, due to the possible shame of patients seeking medical attention. The actual incidence of PF is possibly much higher than that reported in the literature (3).

The occurrence of a second episode of PF consists of an even rare situation, with only 10 cases described in the world literature (4-13). The aim of this study is to evaluate the demographic data, recurrence time, etiology and operative findings in the first and second episodes.

MATERIALS AND METHODS

Between January 1982 and November 2017, 281 patients underwent surgical treatment for PF at our institution. Demographic data, etiology, clinical presentation and operative findings of patients with penile refracture, besides recurrence time between first and second episodes were
retrospectively assessed by reviewing medical records. The injury mechanism and the sexual position were assessed.

All patients underwent the standardized surgical technique in our institution, as previously described (4), which consists of penile degloving through subcoronal incision. In this access, lesions of the corpora cavernosa are identified and the tunica albuginea is sutured with separate stitches of 3 - 0 Polyglactin. Associated partial urethral lesions are treated primarily through simple suturing with 5 - 0 Polyglactin. Postectomy is routinely performed in all uncircumcised patients. Bilateral rupture of the CC, with or without associated urethral transection were classified as severe. The patients were evaluated after six months follow-up.

The experimental protocol described below was approved by the ethical committee for human experimentation of our university, and the study was carried out in accordance with the ethical standards of the hospital’s institutional committee on human experimentation.

RESULTS

Of a total of 281 cases of PF operated at our institution, 3 (1.06%) patients experienced a second episode of PF. The age, etiology of the first and second episode, the recurrence time and the type of the two fractures of the 3 patients with penile refracture can be observed in Table-1.

Case 1: 38-year-old, white, heterosexual patient entered our emergency room in June 2016 with pain and penile hematoma 19 hours after trauma during anal intercourse with his wife, who was in the “doggy style” position. Surgical exploration revealed injury to the distal portion of the right corpus cavernosum (Figure-1). The patient underwent surgical reconstruction with satisfactory evolution. This same patient underwent surgical treatment for a second FP in our department 52 months ago. The chart review disclosed that he was operated 33 hours after trauma during anal intercourse with his wife in “doggy style” position. During surgery, an injury was observed in the distal portion of the right corpus cavernosum, as well as in the first episode. After 6 months of the refracture, the patient progressed satisfactorily, without any sexual complaints.

Case 2: A 40-year-old black heterosexual patient was admitted to our hospital in June 2013 with penile pain, immediate detumescence and eggplant deformity 3 hours after trauma during sexual intercourse with vaginal intercourse, and the wife in “doggy style” position. Surgical exploration demonstrated bilateral lesion of the corpora cavernosa in its medial shaft. Approximately 45 days earlier, this patient had undergone surgery for PF in our facility 14 hours after trauma during anal intercourse with “man - on - top” position. On that occasion,

Table 1 - The table shows the demographic data and operative findings of the 3 cases of penile refracture in our sample.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Etiology (First episode)</th>
<th>Etiology (Second episode)</th>
<th>Recurrence time</th>
<th>Type of lesion (First episode)</th>
<th>Type of lesion (Second episode)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>Anal intercourse/ “doggy style” position</td>
<td>Anal intercourse / “doggy style” position</td>
<td>52 months</td>
<td>Right CC (distal portion)</td>
<td>Right CC (distal portion)</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>Anal intercourse / “man-on-top” position</td>
<td>Vaginal intercourse / “doggy style” position</td>
<td>45 days</td>
<td>Right CC (proximal portion)</td>
<td>Bilateral CC (medial shaft)</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>Refused</td>
<td>Refused</td>
<td>17 months</td>
<td>Left CC (distal portion)</td>
<td>Left CC (distal portion)</td>
</tr>
</tbody>
</table>

CC = corpus cavernosum
lesion was observed in the proximal segment of the right corpus cavernosum (Figure-2). This patient evolved with premature ejaculation, controlled after treatment with paroxetine.

Case 3: A 40-year-old black patient sought care in our hospital in December 2014 with pain, cracking and penile hematoma suggestive of PF, with 3 hours of evolution. He refused to provide data on the etiology of the trauma, but revealed that he had been operated on by us for the same reason 17 months ago. He was submitted to immediate surgical exploration, in which an injury was observed in the distal portion of the left corpus cavernosum. The patient’s chart review disclosed that he had been operated on for FP 9 hours after trauma, not providing details, with injury finding at the same site of the second fracture episode. This patient did not follow-up in our postoperative clinic.

**DISCUSSION**

PF consists of a rare urologic emergency. It is believed that its incidence is much higher than that reported in the literature, since a large number of patients does not seek emergency medical care in virtue of embarrassment (14). This was demonstrated in our sample, where one of our patients, despite seeking medical attention, refused to provide personal information and details of the etiology of the trauma. Recurrent FP is an even rarer entity and no case has been documented in the main publications with
higher casuistic (15). To date, only 10 cases have been reported in the world literature (4-11). In our knowledge, although small, this is the largest series of recurrent PF described in the literature to date.

The risk factors for recurrent fracture are difficult to verify due to their extreme rarity. However, some associations have been postulated. De Rose et al. (16) revealed histological evidence of an underlying chronic inflammatory process in the tunica albuginea of patients with PF. The fibrous and inelastic scar tissue of the anterior lesion seems to weaken the corpora cavernosa, making it weaker and vulnerable to a new fracture episode. This theory is supported by the predominance of PF cases that recur in the ipsilateral cavernous body (5, 10). In contrast, according to Sharma et al. (12), the scar tissue can lead to an unequal distribution of tension in the tunica albuginea, causing rupture of the contralateral side.

Although there is no standardized period of sexual abstinence to be recommended for patients operated on as a result of PF, most authors advice at least six weeks, which corresponds to the time at which collagen deposition is completed. El-Assmy et al. (17), as well as Kozacioglu et al. (18) instructed their patients to maintain abstinence for 6 weeks after PF surgery. In the study by Özorak et al. (19), it is evidenced that patients were instructed to abstain from sexual activity during the first 8 weeks after the surgical intervention. However, according to Prasanna et al. (20), ipsilateral recurrence is more likely to occur within two years after repair of the primary fracture. We routinely advise patients operated on the possibility of a refracture and all patients in our study were instructed to avoid intercourse for at least 8 weeks. However, one of our cases presented the second episode after only 45 days. Interestingly, in addition to injury at the same point of the primary repair, contralateral involvement was observed. This can be explained, in addition to the histological changes, by the fact that the “doggy - style” position is generally associated with more severe lesions, with bilateral involvement of the corpora cavernosa and urethra (21).

Some authors recommend the use of non-absorbable suture material in PF repair to minimize the risk of recurrence. Nonetheless, there is no evidence to suggest that nonabsorbable material would result in less fracture recurrence. In addition, knots can be felt under the thin skin of the penis, which can cause discomfort during sexual intercourse (5).

Ridyard et al. (11) reported a case of relapsed PF in which the patient was under the influence of alcohol at the time of both episodes of trauma and raised the hypothesis that drug or alcohol abuse may predispose to this type of injury. However, we did not observe this association in any of our cases.

Traumatic experience with PF may raise fears about upcoming sexual intercourse, leading to performance anxiety and the development of ejaculatory dysfunctions (22). One of the patients in our study developed secondary premature ejaculation after recurrence of PF.

CONCLUSIONS

Recurrent PF is an extremely rare entity. However, patients should be advised of this possibility after the first episode of PF. The risk factors for its occurrence are still unknown. Although the lesion of the corpus cavernosum ipsilateral to the scar tissue of the prior FP is more common, contralateral rupture may be present. Nevertheless, prospective studies with larger samples should be conducted.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Are uroflowmetry and post-void residual urine tests necessary in children with primary nocturnal enuresis?

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ABSTRACT

Objectives: To examine the benefits of repetitive uroflowmetry and post-void residual urine (PVR) tests in children with primary nocturnal enuresis (PNE).

Material and methods: Children aged ≥ 6 years with PNE who visited our clinics for management of enuresis were included for study. Patients were requested to complete a questionnaire including baseline characteristics and Dysfunctional Voiding Symptom Score (DVSS), 2-day bladder diary, and Rome III criteria for constipation. Two uroflowmetry and PVR tests were requested. Children with congenital or neurogenic genitourinary tract disorders were excluded. All children underwent urotherapy and desmopressin combined with anticholinergics or laxatives if indicated. The definition of abnormal flow patterns (≥1 abnormal), elevated PVR (≥1 abnormal), small maximal voided volume (MVV), nocturnal polyuria (NP) and response to treatment complied with the ICCS standardization document. Kaplan-Meier survival analysis and Cox proportional-hazards regression tests were used to evaluate the predictors of response.

Results: In total, 100 children aged 8.5±2.3 years were enrolled for study (M: F=66:34) with 7.3±7.4 months of follow-up. Poor correlation was observed between DVSS/small MVV and PVR (p>0.05). Univariate analysis revealed that elevated PVR is associated with significantly less hazard of complete response to medical treatment (HR: 0.52, p=0.03), while not significantly associated with abnormal flow patterns, NP, constipation or small MVV. Multivariate analysis revealed that only elevated PVR (HR 0.30, 95% CI 0.12-0.80) and NP (HR 2.8, 95% CI 1.10-7.28) were significant predictors for complete response.

Conclusions: In managing pediatric enuresis, elevated PVR is a significant predictor for lower chance of complete response to treatment whether they had high DVSS or not.

INTRODUCTION

Nocturnal enuresis is defined as intermittent incontinence of urine during sleeping, with prevalence of 16.1% and 10.1% at age of 5 and 7 years, respectively, and decreasing as age increases (1, 2). The etiology could be attributed to nocturnal polyuria, small functional bladder capacity, arousal problem, or a mixture of the etiologies (3). Enuretic children can be classified as non-monosymptomatic (NMNE) or monosymptomatic nocturnal enuresis (MNE), depending on whether the child has daytime lower urinary tract symptoms or not (4). The first-line management of NMNE is to manage constipation, lower urinary tract symptoms and comorbid behavioral...
disorders. For enuresis symptoms in NMNE and MNE, the management included enuresis alarm as behavioral therapy and desmopressin. The predictive factors for response to medical treatment include age, disease severity, nocturnal diuresis and functional bladder capacity (3). Elevated post-void residual (PVR) was regarded as an important poor prognostic factor in NMNE while the prevalence rate of elevated PVR is assumed to be low in children with MNE (5); the International Children’s Continence Society (ICCS), therefore, does not suggest bladder ultrasound as a preliminary screening diagnostic tool (5, 6). In our clinics, we routinely screen all enuretic children with two sets of uroflowmetry and post-void residual urine tests (PVR). Recent studies have stated that PVR was the only non-invasive diagnostic test to predict the treatment outcome in children with non-neurogenic lower urinary tract dysfunction (7). Elevated PVR may be associated with lower urinary tract dysfunction that cannot be identified by other noninvasive tests. Recently, the ICCS has adopted new criteria for defining elevated PVR in children (8, 9). Therefore, we retrospectively review the charts of children visiting our clinics for primary nocturnal enuresis to evaluate whether abnormal uroflowmetry and elevated PVR results are predictive of treatment response to urotherapy and medical treatment.

MATERIALS AND METHODS

The study was approved by the institutional review board of our hospital and was designed as a retrospective review of the treatment response of primary nocturnal enuresis in toilet-trained children aged 6 years or older presenting to our pediatric urologic clinic. The parameters used for analysis included age, gender, and questionnaires. One parent who primarily cares for the child was asked to fill out the questionnaire, which included a 7-day enuresis diary before medical treatment, 48 hour bladder diary, Rome III questionnaire for functional constipation (10), and dysfunctional voiding symptom score (DVSS, 10 items, each scored 0-3) (11, 12). Children with neurological anomalies, neurogenic bladder or congenital genitourinary anomalies were excluded. Each child was asked to undergo a non-invasive diagnostic workup for lower urinary tract function with two sets of uroflowmetry and PVR tests on the same day. Only uroflowmetry curves with a voided volume of >50 mL were considered to be relevant for interpretation (13). PVR was calculated using the equation of height × width × depth × 0.52 (14). Maximal voided volume (MVV), daily voiding frequency, and nighttime diuresis volume were determined based on the 2-day bladder diary. MVV included the first void in the morning. Daily voiding frequency was determined as the average voiding frequency of the two days of records. Expected bladder capacity (EBC) was defined as (age in years x 30+30) mL (4). Nocturnal polyuria was defined as nighttime urine output >130% EBC (4). For children aged 6 and ≥7 years, elevated PVR in milliliters was defined as >20 and >10 mL, respectively (15). All enuretic children underwent urotherapy after the evaluations and were asked to have fluid restriction 1 to 2 hours before going to bed. Children with daytime urgency and small MVV were given oxybutynin and constipation was managed with magnesium oxide. As the alarm therapy was not covered by our insurance system and there existed no approved alarm system by Ministry of Health and Welfare in Taiwan, all children underwent desmopressin therapy with dosages of 0.1 to 0.4mg, and a structured withdrawal strategy was used. Follow-up data included the types of medication taken, enuretic episodes per week after treatment, and dryness status. Complete response to treatment was defined as a reduction of enuresis episodes by more than 90% in the past month during the follow-up, without recurrence (4).

Statistics analysis

Data was expressed as mean±standard deviation and analyzed with MedCalc Statistical Software version 16.8 (MedCalc Software®, Ostend, Belgium; https://www.medcalc.org; 2016). Demographic and voiding parameters were compared via an independent sample t test (continuous demographic variables), a χ² test (nominal data), and a Mann-Whitney U test (ordinal data). The log-rank test was used to compare the complete response between each parameter. The multivariate Cox proportional hazards regression with stepwise
selection (enter and remove variable if p>0.05 and >0.1, respectively) was used to evaluate the predictive factors, including age [years], gender [boys vs. girls], constipation defined by Rome III [yes vs. no], DVSS (>6 vs. ≤6 [12]), nocturnal polyuria (nighttime urine amount >130% or ≤130% EBC), small functional bladder capacity (MVV≥65% vs. <65% EBC [4]), abnormal flow patterns (both bell vs. ≥1 non-bell), elevated PVR (≥1 abnormal vs. no abnormal) for complete response of enuresis. A Kolmogorov-type supremum test was used to assess the proportional hazards assumption. Correlation between DVSS and PVR were evaluated with Spearman’s correlation. A p value of <0.05 was considered to be statistically significant.

RESULTS

Between 2005 and 2013, 100 children with a mean age of 8.5±2.3 years that visited our clinics for management of primary enuresis were enrolled for study (M: F=66:34). Table-1 summarizes the demographic data and results of the medical tests for these children. There were no significant differences in age, follow-up period, maximal voided volume or daily voiding frequency between genders, except that girls had higher peak flow rate. There was no difference between the results of the first and second uroflowmetry and PVR tests in terms of voided volume (139.0±93.9 vs. 146.9±82.6 p=0.32), peak flow rate (17.9±7.1 vs. 18.9±8.3; p=0.11) or PVR (14.7±19.2 vs. 12.6±11.2; p=0.28). Among these children, the prevalence of constipation defined with Rome III, high DVSS (>6 on total score [12]), nocturnal polyuria (>130% EBC), small functional bladder capacity (MVV<65% EBC), ≥1 abnormal flow patterns, and ≥1 elevated PVR, were 20%, 38%, 19%, 18%, 42%, and 54% respectively.

Correlation of DVSS and small functional bladder capacity with PVR

The comparison of first and second PVRs in children with and without high DVSS was 13.4±18.3 vs. 14.5±18.7 (p=0.33) and 12.0±10.5 vs. 12.1±11.1 (p=0.94), respectively. Poorly correlation between PVR and DVSS (correlation coefficient: -0.01, p=0.94) was observed among these enuretic children. The comparison of first and second PVRs in children with and without small functional bladder capacity was 13.1±19.2 vs. 14.6±16.5 (p=0.18) and 12.5±11.8 vs. 12.8±10.7 (p=0.97), respectively.

Predictive factors for complete response of enuresis

Univariate analysis showed that older age (HR: 0.88, 95CI: 0.75-1.02), boy gender (HR: 1.34, 95CI: 0.72-2.51), constipation (HR: 0.54, 95CI: 0.26-1.09, Figure-1A), high DVSS (HR:

Table 1 - Baseline characteristics of the enrolled patients.

<table>
<thead>
<tr>
<th></th>
<th>Girls (n=34)</th>
<th>Boys (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.1±2.6</td>
<td>8.2±2.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>135.9±15.8</td>
<td>132.1±15.7</td>
<td>0.37</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>30.8±10.1</td>
<td>29.1±11.3</td>
<td>0.54</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.0±3.2</td>
<td>16.7±3.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Enuresis episode/week</td>
<td>5.7±1.7</td>
<td>5.9±1.8</td>
<td>0.56</td>
</tr>
<tr>
<td>MVV (mL)</td>
<td>91.7±65.6</td>
<td>108.3±85.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Urine frequency 1st/2nd (times/day)</td>
<td>7.8±3.2 / 6.8±3.9</td>
<td>8.4±2.8 / 8.1±2.8</td>
<td>0.37/0.10</td>
</tr>
<tr>
<td>Daily urine amount 1st/2nd (mL)</td>
<td>753.8±333.0 / 904.4 ± 342.3</td>
<td>932.3±497.1 / 925.7±413.6</td>
<td>0.13/0.84</td>
</tr>
<tr>
<td>DVSS (score)</td>
<td>4.7±4.1</td>
<td>4.7±3.9</td>
<td>0.96</td>
</tr>
<tr>
<td>Peak flow rate 1st/2nd (mL/sec)</td>
<td>21.2±7.8 / 19.4±7.6</td>
<td>17.5±6.7 / 18.8±8.5</td>
<td>0.02/0.81</td>
</tr>
<tr>
<td>PVR1st/2nd (mL)</td>
<td>11.8±9.6 / 10.3±5.7</td>
<td>14.8±20.4 / 13.3±12.3</td>
<td>0.46/0.33</td>
</tr>
</tbody>
</table>
1.08, 95CI:0.54-2.15), nocturnal polyuria (HR: 1.71, 95CI: 0.71-4.14, Figure-1B), small functional bladder capacity (HR: 0.92, 95CI: 0.40-2.15, Figure-1C), ≥1 abnormal flow patterns (HR: 0.87, 95CI: 0.44-1.73) were not associated with complete response, while ≥1 elevated PVR (HR: 0.52 95CI:0.27-0.98, p=0.03, Figure-1D) was statistically associated with complete response.

Multivariate cox proportional hazards regression revealed that only ≥1 elevated PVR (HR 0.30, 95% CI0.12-0.80) and nocturnal polyuria (HR 2.8, 95% CI 1.10-7.28) were significant predictors for response of enuresis to treatment, while older age, boy gender, high DVSS, small functional bladder capacity, constipation and ≥1 abnormal flow patterns did not have a significant impact on response of enuresis to treatment.

DISCUSSION

This is the first study that confirms the diagnostic role of PVR tests in predicting the response of primary enuretic children to treatment. Enuretic children with at least one elevated PVR are at significantly less risk (HR 0.30, 95% CI0.12-0.80) of having complete response to urotherapy and medical treatment. Previous studies evaluating predictive factors for response focused on small bladder capacity (16), nocturnal polyuria (17, 18) and arousal problems (19). Few studies have addressed issues of
lower urinary tract dysfunction, and the studies have mainly investigated the role of bladder wall thickness. In children with LUT dysfunction, PVR was one of the most important factors for diagnosing LUT dysfunction and monitoring treatment response (7). Elevated PVR may suggest some type of lower urinary tract dysfunction that cannot be identified by uroflowmetry and other noninvasive urodynamics studies. The ICCS does not recommend that children with enuresis receive routine evaluation of uroflowmetry or PVR tests (20, 21). Our study revealed poor correlation between DVSS/small MVV and PVR. Based on the significant predictive ability and on the fact that about half of enuretic children studied (54%) had at least one elevated PVR on current ICCS standards, we suggest that all children visiting clinics for primary nocturnal enuresis be evaluated with PVR tests whether they had high DVSS or not.

Cayan et al. (5) evaluated children with and without monosymptomatic enuresis, using uroflowmetry and PVR tests, and the authors concluded that monosymptomatic enuretic children did not have significantly higher PVRs compared with the control (5). The PVRs were 14.5±20.5 (n=48), 31.6±36.8 (n=40) and 19.8±26.4 (n=18) mL in enuretic children of variable age groups, respectively, compared to 6.4±9.9 (n=21, p=0.09), 23.7±30.4 (n=26, p=0.364), and 7.3±10.1 (n=10, p=0.08) mL in non-enuretic controls. There was a clear trend towards higher PVR in enuretic children; however, the difference was not statistically significant due to small sample size. In 2014, the ICCS adopted a new nomogram for defining elevated PVR (8). The PVR nomogram was established from data of normal healthy children (15). The results of the present study now confirm that the standard can be used to identify enuretic children who are less likely to respond to medical treatment. The new standards for the PVR nomogram were also used to predict the probability of recurrent urinary tract infection in children (22) and resolution of lower urinary tract dysfunction (7). Bladder wall thickness is the parameter of bladder dysfunction most commonly investigated to evaluate pediatric lower urinary tract dysfunction (23). However, the main drawback of bladder wall thickness lies in that wide inter-observer variability has been observed, and bladder volume greatly affects bladder wall thickness, which would compromise predictive ability.

Therefore, only some specific centers routinely measure bladder wall thickness. Unlike bladder wall thickness, the PVR test is widely adopted in physician’s daily clinical practice for screening of lower urinary tract dysfunction and monitor treatment response. In enuretic children with elevated PVR, combined treatment with biofeedback and alpha blockers may help improve the treatment outcome (20).

The results of the current study show that 19% of children had nocturnal polyuria, and multivariate analysis revealed that children with nocturnal polyuria had a significantly higher chance for complete response. The results were in line with previous studies that showed that children with NP benefit more through desmopressin therapy, because the effect of the desmopressin is to suppress nighttime diuresis (17).

Practical consensus guidelines for the management of enuresis suggest that small for age bladder volume is associated with a lower rate of response to desmopressin and a higher response to enuresis alarm (3). Our study did not find a significant association of low functional bladder capacity (MVV<65%) with response to medical treatment in univariate (HR: 0.92, 95% CI: 0.40–2.15) and multivariate analysis. The possible explanations are incompleteness of 48 hour bladder diary, only a small proportion of children (18%) having small functional bladder capacity, and the combination therapy with oxybutynin.

DVSS is a validated symptom score used for screening children suspected of having lower urinary tract dysfunction (11). In our previous study, we found that children with a DVSS of >6 points were at higher risk of having dysfunctional voiding without gender difference (12). However, children with high DVSS were not significantly at greater risk of having poor response, which may be explained by these children presented with enuresis, while not daytime lower urinary tract symptoms, and small number of participants enrolled.

The pathophysiology for the impact of constipation on lower urinary tract dysfunction could be explained in that urinary bladder and rectum share common nerve innervations (24). Second, chronic constipation and rectal distention with stool may lead to external anal sphincter and pelvic floor muscle overactivity that lead to bladder dysfunction (24).
Constipation diagnosed via the Rome III criteria was not significantly associated with the poor response in our study either (HR: 0.54, 95CI: 0.26-1.09). The small sample size and regular management of constipation at our clinics may attribute to the non-significance.

The major limitations of the study lie in that it is a retrospective review with a small sample size of patients enrolled from one institution. Larger-scale observations with this new PVR nomogram are required to further consolidate the role of PVR in predicting response to urotherapy and medical treatment. However, the PVR test is a significantly independent predictor for response, in addition to nocturnal polyuria. Despite the small sample size, elevated PVR clearly played a significantly diagnostic role. Second, as these children were referred from pediatric clinics for further management, most children had higher number of wet nights compared with other studies, and therefore the prevalence rate of PVR may be higher among them, though these children had not received medical treatment before. The major strength of our study is that each enrolled child had two sets of uroflowmetry and PVR tests. As such, we were able to identify the difference between repetitive elevated PVR and one elevated PVR on the response of enuresis to urotherapy and medical treatment.

CONCLUSIONS

In summary, our retrospective review confirmed that elevated PVR in the newly published PVR nomograms predicted poor response of enuretic children with or without high DVSS to treatment.

CONFLICT OF INTEREST

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Isolated low grade prenatally detected unilateral hydronephrosis: do we need long term follow-up?

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ABSTRACT

Purpose: To assess the need for postnatal evaluation and the medium term outcome in patients with isolated unilateral low grade prenatally detected hydronephrosis. Materials and Methods: We prospectively selected 424 patients (690 kidney units) with a prenatal diagnosis of urinary tract dilatation between 2010 and 2013. We included only those patients with isolated unilateral low-grade hydronephrosis who underwent at least 2 postnatal ultrasound examinations. The Society for Fetal Urology (SFU) grading system was utilized for assessment of the hydronephrosis. We excluded patients with bilateral dilation or other urological abnormalities. The fate of hydronephrosis including resolution, stability or worsening was documented. Results: A total of 66 infants (44 boys and 22 girls) with antenatally diagnosed unilateral urinary tract dilatation (23 right and 43 left) were identified. Ultrasounds showed SFU grade 1 hydronephrosis in 32 patients (48%) and SFU grade 2 hydronephrosis in 34 (52%). After a mean follow-up period of 32 months (range 12 to 60), 37 patients (56%) had complete resolution of hydronephrosis while the remaining 29 were stable (44%). None of our patients developed UTIs during follow-up and none required surgical intervention. Conclusions: Prenatally detected, isolated unilateral low-grade hydronephrosis usually have a favorable prognosis. All cases in our cohort showed either stability or resolution of hydronephrosis without any harmful consequences. Based on our findings on medium-term in this category of patients, long-term follow-up is not warranted.

INTRODUCTION

Before the era of antenatal screening and the use of prenatal ultrasound, most of the urogenital anomalies were diagnosed only when they were symptomatic or complicated. Even to the extent that some patients might incidentally present with symptoms of end stage renal disease as their initial presentation (1). With the advancement of antenatal care, prenatal ultrasonography started to detect significant fetal anomalies during pregnancies. Out of these, 20-30% were attributed to urogenital anomalies and 50% were due to hydronephrosis (HN) (1, 2).

Hydronephrosis occurs in 1-5% of all pregnancies (3). Once diagnosed, the debate will arise whether it is obstructive or non-obstructive in nature, harmful to the kidney and whether any prenatal or postnatal surgical intervention will be required. Different etiologies have been attributed to the diagnosis of antenatal hydronephrosis (ANH) which might include, transient phenomena, pelvic ureteric junction obstruction, vesicoureteral reflux (VUR), posterior urethral valves or other anomalies (4).
The exact definition of significant ANH is evolving. Multiple grading systems and parameters were used to define this entity. However, the society for fetal urology (SFU) grading system and the measurement of the antero-posterior diameter (APD) of the renal pelvis were among the commonest utilized (5). Isolated unilateral low-grade HN is usually benign in nature and about 50% of fetuses and infants diagnosed with this entity might show complete resolution on follow-up (6). On the contrary, high-grade HN will usually require more extensive evaluation and strict follow-up (7). This might require the use of continuous antibiotic prophylaxis (CAP), further evaluation, longer follow-up period and they might require surgical intervention, depending on the underlying etiology (6-8).

In our study, we prospectively followed up infants diagnosed with ANH and confirmed postnatally to have isolated unilateral, low-grade (SFU grade 1 or 2) HN, in order to determine the necessity for further evaluation, follow-up and outcome.

MATERIALS AND METHODS

After obtaining the approval of institutional review board at Prince Sultan Military Medical City, a prospective study design was constructed. Signed parental consent for participation was obtained before the start of the study. Study inclusion period started from January 2010 to December 2013.

A total of 522 fetuses diagnosed with antenatal AHN were selected for postnatal screening. Infants were referred prospectively after routine detection in the maternity unit with a mean gestational age at diagnosis of 33 weeks (range 28 to 36 weeks). All of these infants had complete physical examination (to exclude any other significant congenital abnormalities) in addition to a postnatal ultrasound (US) performed after the first week and within the first month of life. This first performed postnatal US was used as a baseline for assessing the presence of HN and only including those with unilateral low-grade HN and excluding any patient with other suspected anomalies, namely: duplication anomaly, multicystic dysplastic kidney, dilated ureter, ureteroceles, ectopic ureter, urinary bladder diverticulum, thickened bladder wall or posterior urethral valves. The SFU grading system was used to classify all patients independently by at least two physicians, a pediatric radiologist, and a pediatric urologist, to minimize inter-reviewer variability. If physicians disagreed, the higher grade was taken.

Of the 522 patients (788 renal units) with prenatal HN, 98 patients were excluded due to two consecutive normal postnatal renal US (absent HN). Additional 275 patients (550 renal units) were excluded due to bilaterality. Of the 149 patients with unilateral HN, 83 cases were excluded, 44 with high-grade HN and 39 were found to be associated with other urological anomalies postnatally. Our study included 66 patients, with isolated unilateral low-grade HN (SFU grade 1 and SFU grade 2) who met our study criteria.

Further follow-up plan for our cohort of patients incorporated performance of US at 6, 12 months and annually thereafter. Patients were kept off any CAP and were monitored for growth parameters and occurrence of any signs and symptoms of febrile urinary tract infections (UTI’s) by their care givers and pediatricians. Urine cultures were performed if there were any suspected symptoms of UTI’s. If any febrile urinary tract infection was documented, it was recorded and additional screening for vesicoureteral reflux by voiding cystourethrogram (VCUG) was planned. Further follow-up US were utilized to identify patients who had a complete resolution, remained stable or had progression of their HN. We identified resolution as complete regression of HN, stability as same or downgraded HN, progression as upgraded HN. Figure 1 and 2 showed both initial and last follow-up renal US in two children with grade 1 and 2, respectively.

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). We used binary and logistic regression analysis. Values are shown as mean±SD unless otherwise reported. Kaplan-Meier estimates were used to show the effect of HN grade, side, and gender on the resolution rate of HN and compared with the use of the log-rank test. All tests were 2-sided. A p value of less than 0.05 was considered statistically significant.

RESULTS

All of our 66 patients with isolated unilateral low-grade HN completed the study. The
mean follow-up period was 32 months (range, 12-60). Patient’s demographics are shown in Table-1.

Resolution rate was 56% with a mean time for resolution was 13.5 months (range, 6-36). Using Kaplan-Meier estimates, the side of HN had a statistically significant effect on the resolution rate of HN \( p=0.008 \), while the grade of HN and patients gender did not have any statistically significant impact on the resolution rate \( p=0.785 \) and \( 0.107 \), respectively) as shown in Figures 3-5.

During the course of follow-up, none of our patients had relapse/progression of their HN, developed UTI’s (either febrile or afebrile), or required another mode of investigation. Additionally, none required any form of surgical intervention.

**DISCUSSION**

With the improvement in health care facilities and ultrasound technology, fetal HN could be detected between 12th to 14th weeks of gestation and now readily diagnosed by maternal antenatal screening. The rationale for following patients with antenatal AHN is to avoid hazardous drawbacks on the patient’s kidneys. Many controversies coexist on how best to manage antenatal HN, which arise from the incomplete understanding of the natural history of this anomaly (5). In the past, evaluation included postnatal US, VCUG and often renal scans, so that there was an increase in the yield of abnormalities that is deemed to be clinically insignificant (8). Other controversies were the debate on the usage of CAP with the lack of evidence on benefits over a prolonged follow-up interval (9).

**Table 1 - Patients’ Demographics.**

<table>
<thead>
<tr>
<th>Unilateral isolated low grade HN</th>
<th>Number No. = 66</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>33</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Left</td>
<td>43</td>
<td>65</td>
</tr>
<tr>
<td>SFU grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>32</td>
<td>48</td>
</tr>
<tr>
<td>Grade 2</td>
<td>34</td>
<td>52</td>
</tr>
</tbody>
</table>

HN = Hydronephrosis, SFU = Society for Fetal Urology
In our study, we aimed to identify all patients with a history of antenatal AHN, evaluate them postnatally, and then prospectively follow those with isolated unilateral low-grade HN to determine the fate and proposed follow-up plan for them. We used the first postnatal US as the base line for categorization of these patients since we believe, as many others do, that in experienced hands, the first detailed postnatal US is the cornerstone imaging to establish the grade of HN and to decide on further investigation (10). Other studies used the prenatal APD of the renal pelvis as the base for categorization of patients postnatally and determining further work-up and follow-up plans (11).

Of the 522 fetuses diagnosed with antenatal AHN in our study, 98 (18.7%) were found to have a normal first postnatal renal US as well as a second confirmatory scan within the first year of life and hence were excluded from our study. This group of infants has a very low incidence of complications as reported by many studies (12, 13).

In a study on 143 infants with antenatal AHN, 50 of them had normal postnatal sonograms without HN. Only three were later diagnosed with VUR (all were low grade) (12). Similarly, in another study including 103 infants with ANH, 53 infants had a normal postnatal renal US and only 3 had VUR (grade-I). The conclusion of both studies indicated that VUR was infrequent in this subset of infants and carries a good prognosis (13).

The need for starting CAP and performing VCUG in patients with isolated unilateral low-grade HN is a debatable issue. Some authors recommend starting CAP and performing VCUG in all neonates with antenatal ANH (14–16), while others do not recommend this approach (17, 18). The American Academy of Pediatrics (AAP) and the National Institute for Health and Care Excellence (NICE) guidelines as well as the Italian so-
ciety of pediatric nephrology excluded the routine use of antimicrobial prophylaxis for low-grade VUR, concluding that in mild and moderate isolated hydronephrosis the search for VUR becomes clinically irrelevant \(19, 20\). Based on these data, we did not start any of our patients with CAP nor did we perform routine VCUG.

Out of the 66 patients in our study, resolution of HN was noticed in 37 patients (56%) with a mean time to resolution of 13.5 months and this rate of resolution coincided with those reported in several recent studies \(6, 21, 22\). In addition, there was no significant difference between the grades of HN and the gender of patients regarding the rate of resolution. However, resolution rate in relation to the side was statistically significant, which might be attributed to a statistical error related to proportionally small sample size.

Gökaslan et al. \(2012\), in their prospective study which included 49 patients with (SFU grade 1 and 2), with a follow-up period of 18 months, 64% showed spontaneous resolution. They strongly suggested that low-grade HN is a relatively self-limited condition and needs minimal investigations \(21\). Furthermore, Madden-Fuentes and associates \(2014\) published in their retrospective review of 623 kidney units, with a mean follow-up 14.6 months, an overall resolution rate (SFU grade 1 and 2) of 60% with no significant difference between grade 1 and 2 \(6\). They concluded that low-grade HN diagnosed within the first year of life remained stable or improved in 97.4% of renal units. They recommended observation for 12 months after diagnosis unless HN completely resolves \(6\).

In another prospective study performed by Coelho and colleagues in 2007, 192 patients were included, 89 with low-grade HN and were followed for a median period of 24 months. They found that cumulative rate of resolution of mild HN was 60% after 5 years follow-up \(7\). Similarly, Tombesi and Alconcher \(2012\), reported their results on 227 renal units with mild prenatally diagnosed HN. They found that 73% of their cohort showed complete resolution, 26% continued to be stable and only 1% deteriorated \(22\). Also, Barbosa and colleagues reported on 144 patients with mild HN and found 46.5% of them had a complete resolution in comparison to 47.2% who remained stable \(23\). In another meta-analysis by Sidhu et al., they reported that 98% of all mild hydronephrosis resolved, stabilized, or improved on follow-up, emphasizing favorable outcome of this patient category \(24\).

In a study with long-term follow-up \(142\) months) carried on isolated antenatal HN by Yang et al. \(2010\), with a median follow-up 142 months, results showed stabilization in all children with grade 1 HN and in 87% of children with grade 2 HN. The mean interval to spontaneous resolution was 13.4 months. They suggested that there is no need for invasive procedures and recommended observing patients closely during the first 2 years of life \(25\). On the other hand; none of our patients had relapse/progression of their HN or developed UTI’s during the follow-up period. In contrast to our study, several investigators reported progression rate between 1-13% and that may be due to longer follow-up period and different inclusion criteria in their studies \(6, 7, 20-25\).

Though we have chosen not to start any patients on continuous antibiotic prophylaxis (CAP) based on the low rate of UTI in cases with low-grade HN, none of our patients developed UTI’s \(26\). Madden-Fuentes et al., reported a UTI rate of 8.9% with isolated unilateral low-grade HN \(6\). Coelho et al. reported a UTI rate of 7.8% despite CAP \(7\). Others reported an incidence of 1.3 to 12% \(27, 28\). Given the low rate of UTI in their subset of patients, they concluded that antibiotic prophylaxis has a limited role in low-grade HN management \(6\). Moreover, all boys included in our study had ritual circumcision early in their life that might have an impact on the risk of UTI incidence in our cohort.

We had some limitations in our study including a relatively small number of patients with highly selective inclusion criteria. Selections were based on a subjective SFU grading system (as a single parameter) in addition to the inherent limitations of a non-randomized, non-blinded study without a control group. Measurements of biomarkers for obstruction were not used. UTI may be underestimated as it was evaluated by primary health care provider based on clinical symptomatology only.
CONCLUSIONS

Isolated unilateral low-grade HN is a benign entity with no risk of significant morbidity. Patients of this category usually will not require invasive investigations or CAP. We recommend performing at least 2 postnatal US within the first year of life and no further evaluation if they showed resolution or stability of HN. Long-term follow-up is not warranted in the majority of cases and family reassurance will be sufficient.

ABBREVIATIONS

ANH = Antenatal Hydronephrosis
CAP = Continuous Antibiotic Prophylaxis
HN = Hydronephrosis
SFU = Society for Fetal Urology
US = Ultrasound
UTI’s = Urinary Tract Infections
VCUG = Voiding Cystourethrogram
VUR = Vesicoureteral Reflux

CONFICT OF INTEREST

None declared.

REFERENCES


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Pro-inflammatory cytokines and metalloproteinase activation in polypropylene mesh implant in rat subcutaneous tissue

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ABSTRACT

Aims and Objectives: Polypropylene meshes have been increasingly adopted for correction of pelvic organ prolapse due to its lower recurrence rate when compared to surgeries without meshes. The study of the interaction of these materials with the host tissue may contribute to the development of materials with best biocompatibility and, consequently, less complication rates.

Materials and Methods: The present study compares the inflammatory reaction of standard-weight (SW) and lightweight (LW) meshes (72 g/m² 16g/m² respectively), implanted in the abdomen of 20 adult rats, which were euthanized in four or 30 days. Quantification of pro-inflammatory markers, IL-1 and TNF-α, and of metalloproteinases, MMP2 and MMP3, were carried out through immunohistochemistry with AxioVision® software.

Results: There were no significant differences in the quantification of IL-1 and TNF-α in LW versus SW meshes. However, IL-1 quantification increased along time (30 days > 4 days, p=0.0269). Also, MMP-2 quantification was similar to SW and LW and both presented a significant increase along time (30 days > 4 days, p <0.0001). MMP-3 quantification also showed no difference between the SW and LW groups, but increased along time (30 days > 4 days, p=0.02).

Conclusions: Mesh’s density did not influence the quantification of pro-inflammatory cytokines IL-1 and TNF-α and metalloproteinases 2 and 3. The increased expression of IL-1, MMP-2 and MMP-3 over time could represent a longstanding inflammatory response after PP mesh implantation. Possibly, the occurrence of adverse events following PP prosthetic implants can be influenced by other factors, not solely related to the amount of implanted material.

INTRODUCTION

The use of meshes for pelvic organ prolapse (POP) correction and urinary incontinence has been widely adopted due to its efficacy, especially regarding recurrences, which are significantly lower than conventional techniques which are based on use of structurally compromised tissue. (1-5). In fact, POP recurrence after the advent of mesh implants have dropped from 30-50% to 10-30% (5).

However, complications related to compatibility flaws on tissue integration of the implanted material are still challenging despite the evolution of biomaterials. These complications, such as mesh
erosion, infection and local pain directly affect quality of life, which has led the FDA (Food and Drug Administration) to recently publish warnings about the lack of class I proof of efficacy and safety on the use of meshes to correct POP (6). Thus, complications related to mesh tissue integration justify studies aiming at better understanding the inflammatory reactions that may compromise the healing process (7).

The weight of the mesh may influence the intensity of the inflammatory reaction and consequently the result of the surgery. There is no consensus in the literature on the classification of mesh weight, but using the classification of Coda et al., it is considered lightweight <70 g/m², standard-weight ≥70<140 g/m² and heavy weight >140 g/m² (8).

Surgery, as well as a mesh implantation, generates a local wound, which triggers the release of cytokines and growth factors such as interleukin-1 (IL-1), transforming growth factor beta (TGF-β) and tumor necrosis factor alpha (TNF-α). In the presence of such substances, neutrophils, macrophages, monocytes, fibroblasts and keratinocytes release the matrix metalloproteinases (MMP) from specific storage granules into extracellular matrix (9).

Metalloproteinases play a fundamental role in all stages of healing, acting in tissue remodeling for degrading components of the extracellular matrix (ECM) and are able to act on the synthesis of collagen and other components. The imbalance between MMP and their inhibition propagates an inflammatory reaction, which slows healing and, thus, generates complications (10).

There are more than 25 metalloproteinases that can be grouped according to their substrate and structure: collagenases (MMP-1, 8 and 13), stromelysins (MMP-3, 7 and 10), gelatinases (MMP-2 and 9), matrilysins (MMP-7 and 26), membrane type MMPs (MMP-14, 15, 16, 17, 24) and other MMPs (Table-1) (10-12).

Table 1 - Main matrix metalloproteinases, their enzymes and their substrates.

<table>
<thead>
<tr>
<th>Metalloproteinase</th>
<th>Enzyme</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-1</td>
<td>Collagenase 1</td>
<td>Collagen type 1, pro MMP-2</td>
</tr>
<tr>
<td>MMP-8</td>
<td>Collagenase 2</td>
<td>Proteoglycans</td>
</tr>
<tr>
<td>MMP-13</td>
<td>Collagenase 3</td>
<td>Collagen type 1</td>
</tr>
<tr>
<td>MMP-2</td>
<td>Gelatinase A</td>
<td>pro MMP-9, fibronectin, Collagen IV, V, VII and X; proteoglycans</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Gelatinase B</td>
<td>Gelatin, fibronectin, elastin, collagen IV, V, VII, X denaturated Type I collagen</td>
</tr>
<tr>
<td>MMP-3</td>
<td>Stromelysin-1</td>
<td>Fibronectin, laminin, elastin, proteoglycan, collagen VI, V, IX, X, proMMPs -1,7,8,9,13</td>
</tr>
<tr>
<td>MMP-10</td>
<td>Stromelysin-2</td>
<td>Fibronectin, laminin, elastin, proteoglycan, collagen IV, V, IX, X</td>
</tr>
<tr>
<td>MMP-14</td>
<td>MT1-MMP</td>
<td>proMMP-2, -13, helical collagen</td>
</tr>
<tr>
<td>MMP-15</td>
<td>MT2-MMP</td>
<td>Surface transglutaminase</td>
</tr>
<tr>
<td>MMP-16</td>
<td>MT3-MMP</td>
<td>proMMP-2</td>
</tr>
<tr>
<td>MMP-17</td>
<td>MT4-MMP</td>
<td>Fibrin</td>
</tr>
<tr>
<td>MMP-7</td>
<td>Matrilysin</td>
<td>Fibronectin, elastin, collagen IV</td>
</tr>
<tr>
<td>MMP-12</td>
<td>Metalloelastase</td>
<td>Elastin</td>
</tr>
<tr>
<td>MMP-20</td>
<td>Enamelysin</td>
<td>Dental enamel matrix</td>
</tr>
</tbody>
</table>
The metalloproteinases analyzed in this study were MMP-2 and MMP-3, which have greater expression in the proliferation and maturation phases of healing, respectively. MMP-2 and MMP-9 are fundamental during angiogenesis, and they degrade collagen IV and other components of the extracellular matrix. MMP-3 is related to the maturation phase of wound healing (9).

OBJECTIVE

To study the immunohistochemical quantification of IL-1 and TNF-α cytokines and MMP-2 and MMP-3 metalloproteinases in standard-weight (SW) versus lightweight (LW) meshes implanted in abdominal subcutaneous tissue of adult rats.

MATERIALS AND METHODS

The study used high-weight polypropylene mesh, referred to as standard-weight and low weight, respectively 72 g/m² and 16 g/m² (Figure-1).

Twenty female rats were submitted to the surgical procedure consisting of midline incision in the lower abdomen and subcutaneous dissection, where it was performed mesh implants, setting them side by side with polypropylene sutures 4.0 to a standardized procedure (SW on the right and LW on the left). Surgical scheme is presented at Figure-2.

They were then sorted into two groups regarding their time of euthanasia, 4 or 30 days.

The inflammatory reaction induced by the polypropylene mesh was then studied through immunohistochemical analysis quantifying the expressions of interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α) and matrix metalloproteinases 2 and 3 (MMP-2 and MMP-3).

The slides were analyzed by quantification of the inflammatory reaction surrounding the mesh, measuring the percentage of the area where there was expression of immunohistochemical reagents for IL-1 and TNF-α and metalloproteinases MMP-2 and MMP-3.

Slide images were processed and stored with AxioVision® software (Carl Zeiss Solutions). In Figure-3 it is shown an example of the software output image showing the immunoreactivity density and extension in slides marked for MMP3.

Statistical analysis was carried out from ANOVA for comparison between groups SW and LW, considering the euthanasia time of four or 30 days as well (13, 14).

RESULTS

There were no deaths or complications during the post-implant period. No dehiscence or mesh exposure was observed either.

There was no statistically significant difference in the expression of inflammatory mediators IL-1 and TNF-α between the different types of mesh (lightweight or standard-weight). Nevertheless, there was an increase of IL-1 in the animals euthanized at the 30th day (30 days >4 days) (p =0.0269).

No significant difference was also found regarding metalloproteinases MMP-2, between SW and LW meshes. However, there was an increase in the MMP-2 expression in the LW group compared to the group euthanized at the 30th day. (LW: 30days >4 days) (p <0.001).

MMP-3 presented similar expression in SW and LW meshes. In both groups its expression increased along time (30days >4 days) (p =0.02). Figure-4 exemplifies standard-weight mesh, in which MMP3 immunoreactivity was quantified. The brown area represents the MMP3 immunore-
activity after 4 days (A) and 30 days (B) - (200x). Note the higher brown intensity and extension in B (30 days > 4 days) (Table-2).

**DISCUSSION**

The surgery, as well as the mesh implant, generates an inflammatory reaction with release of cytokines and other inflammatory factors for tissue healing. The inflammatory reaction to biomaterial implant has been studied in order to better understand its integration to the host tissue and, consequently, to develop biocompatible materials that may cause fewer complications. Thus, some studies describe the histological and molecular alterations after biomaterial implants.

The absence of significant difference in the quantification of these inflammatory markers, when comparing standard-weight and lightweight meshes, corroborate the findings from the literature, which do not relate the weight of the meshes with complications.

Utiyama et al. (15) concluded, in their study comparing heavyweight and lightweight meshes implanted in the abdomen of 30 rats who were euthanized after 21 days, that there was no difference in the inflammatory response (fibrosis, or infiltration of foreign body giant cells, macrophages, neutrophils or lymphocytes), mesh shrinkage, adherences or other complications.

Studies have pointed out that lightweight meshes are more malleable, tending to cause less
Figure 3 - A) The brown color characterizes areas that are reactive to MMP3, B) Representation of Software AxioVision® application that selects the reactive area in green and generates tables of the percentage area. *The gaps correspond to area occupied by mesh filaments.

Figure 4 - Example of MMP3 immunoreactivity (brown area) after 4 days (A) and 30 days (B) - (200x). Note a higher brown intensity and extension in B (30 days > 4 days).

Table 2 - Immunohistochemistry analysis (mean percent area/SD) Immunohistochemical analysis of IL-1, TNF, MMP2 and MMP3 on euthanasia time and implant type, standard or low weight.

<table>
<thead>
<tr>
<th></th>
<th>IL-1*</th>
<th>TNF*</th>
<th>MMP2*</th>
<th>MMP3*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SW (SD)</td>
<td>LW (SD)</td>
<td>SW (SD)</td>
<td>LW (SD)</td>
</tr>
<tr>
<td>4 Days</td>
<td>10.28</td>
<td>11.92</td>
<td>12.22</td>
<td>11.22</td>
</tr>
<tr>
<td></td>
<td>3.04</td>
<td>4.73</td>
<td>4.06</td>
<td>4.74</td>
</tr>
<tr>
<td>30 Days</td>
<td>14.83</td>
<td>14.15</td>
<td>13.31</td>
<td>11.64</td>
</tr>
<tr>
<td></td>
<td>3.64</td>
<td>5.54</td>
<td>2.27</td>
<td>3.43</td>
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</tbody>
</table>

p1 0.0269  0.5509  0.2278  0.02  
p2 0.8347  0.2461  0.1115  0.8844 
p3 0.4157  0.7543  0.1854  0.8223

*Mean percentage of the area marked by the immunohistochemistry reaction.

p1 = euthanasia time; p2 = type of implant; p3 = interaction euthanasia and type of implant; SD = Standard deviation; SW = standard-weight; LW = lightweight; IL-1 = interleukin 1; TNF = tumor necrosis factor alpha; MMP2 = matrix metalloproteinases 2; MMP3 = matrix metalloproteinases 3.
chronic pain rates after abdominal hernia surgeries; nevertheless, they also show that there are no significant differences regarding complications or recurrences (16, 17).

Deffieux et al. have carried out a comparative study with 138 women who underwent repair of cystocele, and have not found any significant differences between lightweight and heavyweight meshes. Multifactorial analyses have evidenced age as a factor associated to erosion (18).

The present study has not found differences between standard-weight and lightweight meshes in the quantitative analysis of the interleukine-1 and tumor necrosis factor alpha. The difference in mesh’s density did not influence the foreign body reaction, which lead us to assume that the occurrence of adverse events after implantation of PP prostheses could be influenced by other factors not exclusively related to the amount of implanted material.

In the initial phase of the inflammation, fibroblasts increase the production of extracellular metalloproteinases (MMP) which have an important role in tissue remodeling. Several studies have highlighted the role of MMP-2 in wound healing, from natural wounds to chronic wounds generated by biomaterial implants. The more intense the reaction to foreign body, the higher the MMP-2 gene expression, and with the stability of this reaction over time, there would be a reduction of MMP-2 surrounding the mesh (19).

The fact that in the present study there was not a significant expression of metalloproteinases MMP-2 in the groups where the rats were euthanized four days after the implant meets the findings of Iba et al. who have observed that, in rodents, the levels of MMP-2 and MMP-9 are increased 10 to 15 days after the wound, coinciding with angiogenesis activation (20).

MMP-3 is an enzyme related to the remodeling phase, thus, the increase of its expression in later phases was confirmed in the study (30 days >4days). However, there was no significant difference between groups SW and LW.

Another study in 49 Rhesus monkeys found that in the heavyweight less porous and less malleable mesh implants, the degradation of vaginal collagen and elastin has exceeded synthesis, probably as a result of the increased activity of the MMPs, resulting in structurally compromised tissue (21).

Jansen et al. implanted monofilament heavyweight polypropylene meshes, lightweight multifilament and absorbable meshes in 72 mice, and did not find differences in the number of macrophages, fibroblasts and MMP-2, concluding that these parameters depend on the location and on the types of cells rather than on mesh structure (22).

Histological and molecular studies on inflammatory reactions to biomaterials can lead to the better understanding of the interaction of these biomaterials with the host tissue, helping to clarify which parameters would improve tissue integration, and thus reduce complication rates. However, conclusions on which cells and markers must be assessed are not yet conclusive.

This study has limitations, such as not using vaginal site, no counting of differential inflammatory cells, absence of supply division of collagen type I and III, no quantification of immunostaining of anti-inflammatory cytokines such as TGF-β and quantification of TIMP (metalloproteinase inhibitors) and no quantification of the vessels (angiogenesis).

CONCLUSIONS

Standard-weight and lightweight mesh implants in subcutaneous abdominal tissue of female adult rats induced similar histochemical reactivity of the pro-inflammatory cytokines IL-1 and TNF-α and metalloproteinases MMP-2 and MMP-3. We infer that other pathways should be studied to justify the differences between standard-weight and lightweight mesh implants in clinical setting.

ABBREVIATIONS

POP = pelvic organ prolapse
FDA = Food and Drug Administration
IL-1 = Interleukin-1
TGF-β = Growth factor beta
TNF-α = tumor necrosis factor alpha
MMP = matrix metalloproteinases
PP = polypropilene
TIMP = metalloproteinase inhibitors
CONFLICT OF INTEREST

None declared.

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Accidental cystectomy during laparoscopic excision of prostatic utricle cyst - a rare complication

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ABSTRACT

Prostatic utricle cyst is a rare congenital anomaly. Symptomatic cysts require treatment. Surgical excision is the treatment of choice, but is challenging due to close proximity to vas deferens, ejaculatory ducts, bladder, prostate, rectum and pelvic nerves. Complications include rectal injury, ureteral injury, impotence, infertility and faecal incontinence. We here report a rare complication in which bladder was accidentally removed during laparoscopic excision of prostatic utricle cyst. To best of our knowledge such a complication has never been reported previously. We also describe the possible cause of this accident and suggest ways to prevent this disastrous complication.

INTRODUCTION

Prostatic utricle cyst is a rare congenital anomaly. Cysts vary in size and presentations differ. Symptomatic cysts require treatment (1). Surgical excision is treatment of choice. Surgery can have its own complications. We report a rare case of accidental urinary bladder cystectomy during laparoscopic excision of prostatic utricle cyst.

CASE REPORT

A 24 year old male presented to us with urinary diversion by bilateral percutaneous nephrostomies (PCN), performed six months ago. He had undergone laparoscopic surgery for removal of prostatic utricle cyst elsewhere. Postoperatively he developed anuria. A sonogram revealed bilateral hydro-ureteronephrosis. Bladder was not commented upon. This acute crisis was treated by bilateral PCN. Nephrostomogram revealed complete cut-off of both lower ureters (Figure-1).

He had history of lower abdominal pain with burning micturition on and off since two years. Investigations had revealed a prostatic utricle cyst with infection. Following conservative management, he was asymptomatic for about 18 months. Recurrence of symptoms was associated with increase in cyst size (Figure-2). Surgical treatment was advised at this time. Laparoscopic cyst exci-
Accidental cystectomy during laparoscopic surgery

Systemic examination was normal. Abdominal examination revealed port site scars, bilateral nephrostomies and coronal hypospadias. Investigations revealed normal hemogram and creatinine. Bilateral lower ureteric injury was the suspected diagnosis initially. Ascending and micturating cysto-urethrogram (MCU) showed smooth walled bladder with mildly reduced capacity and normal urethra (Figure-3).

With evidence of bilateral ureteric cut-off and normal lower urinary tract, bilateral ureteric re-implantation was planned. Urethrocystoscopy showed normal anterior urethra. There was an opening on verumontanum, which accommodated 17 French cystoscope sheath easily. This lead to a smooth walled cavity containing about 200 mL of turbid fluid. The epithelium was not like normal urothelium. Ureteric orifices were not seen. Then we realized that this cavity was indeed the cyst which was falsely mistaken as bladder on MCU. The proximal urethra was completely cut off below the level of bladder neck, ending blindly. A situation of accidental urinary bladder cystectomy and not prostatic utricular cystectomy was realized. Further surgery was abandoned.

Patient was explained about absence of urinary bladder. MRI pelvis confirmed the same (Figure-4). Surgical options were discussed and he opted for orthotopic neo-bladder. Ureters were dissected, prostatic utricle cyst was marsupialized, it’s opening into urethra closed and Studer’s orthotopic ileal neobladder was constructed.

Postoperative MCU showed good capacity neobladder and no extravasation (Figure-5). Nephrostomies were clamped and removed.
At follow-up, he was voiding well with minimal residue and no incontinence. His outcomes in terms of ejaculation are yet not known.

**DISCUSSION**

Prostatic utricles are remnants of Mullerian ducts. Normally Mullerian ducts regress under influence of mullerian regression factor and is represented by appendix testis (cephalad part) and utricle (caudal part). Utricular anomalies result from incomplete regression of Mullerian ducts or incomplete androgen mediated closure of the urogenital sinus in form of prostatic utricular cyst (2).

Mullerian duct remnants are uncommon. Incidence of enlarged prostatic utricle is 11-14% in association with hypospadias or intersex anomalies, more so with perineal hypospadias (>50%). About 10-25% show an association with renal agenesis / dysgenesis and 25% cases with hypospadias (1).

Cysts are quite often asymptomatic. They may present with lower urinary tract symptoms, urinary retention, stone formation, epididymitis, obstructive azoospermia, rectal mass, and rarely malignant growth. Symptoms are determined by degree of obstruction of bladder neck or seminal vesicles and ejaculatory ducts, and infection (2).
The relation of cyst size and symptoms is debated (1, 2).

Symptomatic cysts require intervention. Modalities include endoscopic deroofing, transrectal ultrasound guided or transperineal cyst aspiration and sclerotherapy, endoscopic fulguration of cyst lining (1, 2), marsupialisation of cyst into bladder (3), open / laparoscopic (4) excision of cyst, and recently robot assisted surgical excision (5).

Surgical excision is the treatment of choice, but is challenging due to close proximity to vas deferens, ejaculatory ducts, bladder, prostate, rectum and pelvic nerves. Approaches described include abdominal extravesical, transvesical (transtrigonal), perineal and anterior or posterior transrectal sagittal approaches. Complications include rectal injury, ureteral injury, impotence, infertility and faecal incontinence (2).

In our patient there was accidental re- moval of urinary bladder. To best of our knowledge, such complication has never been reported. Possibly Foley catheter was lodged into utricular cyst, misleading the surgeon to excise urinary bladder.

Preoperative cystourethroscopy could have shown that opening of utricle cyst was directly in line with urethra, bladder neck was high at an angle, and would have more clearly shown anatomical relationship of cyst with bladder.

Preoperative cannulation of cyst has been described to facilitate laparoscopic identification and mobilization of cyst (4).

Intraoperative flexible cystoscopy helps in identifying the bladder from cyst, by seeing light of cystoscope during laparoscopy. By chance, if bladder gets injured, it could be identified immediately.

Preoperative cannulation of ureters with ureteral catheters helps in identifying them intraoperatively. By seeing the structure into which ureters enter, bladder could have been differentiated from cyst. Ureteral injury could be identified intraoperatively.

Adopting above mentioned measures could potentially avoid such disastrous complication.

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Idiosyncratic reaction after injection of polyacrylate – polyalcohol copolymer

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ABSTRACT

Context: Polyacrylate-polyalcohol copolymer is a synthetic product, non-biodegradable, with low rate of therapeutic failure and lower incidence of reactions at the site of injection, when compared to biodegradable agents. We report an unprecedented, exuberant and persistent inflammatory reaction following injection of that substance.

Patient: A 17 years-old patient with vesico-ureteral reflux and complete pyelocaliceal right duplication was submitted to treatment with polyacrylate-polyalcohol copolymer (STING technique). In the seventh day of post-operative, she presented intense dysuria and hypogastric pain, without laboratory exams alterations; a symptomatic treatment was started. After two months, the symptoms persisted and an ultrasound detected thickening of bladder wall close to the uretero-vesical junction. After that exam, a cystoscopic biopsy showed epithelial hyperplasia with increased edema of lamina propria, suggesting an adverse reaction to the polymer. After four months, there was complete remission, but the reflux persisted with the same grade.

Hypothesis: This is an unprecedented reaction following injection of this copolymer. The presence of characteristics such as absence of infection, temporal relation between treatment and beginning of symptoms, and detection of epithelial hyperplasia at the local of injection reinforce the hypothesis of association of the substance and adverse reaction. In that patient, important complains motivated early investigation of urinary tract, that confirmed those aspects. Maybe if that reaction had occurred in patients with lower capacity of expression (such as in infants) it would be unnoticed.

SCENARIO

A female 17 years-old patient presented for urologic consultation with history of repeated cystitis and acute pyelonephritis (in the last episode it was necessary intensive care). She denied micturition and intestinal complaints as well as comorbidities. She referred that acute cystitis emerged after the beginning of sexual activity. Urethrocystogram showed the presence of vesico-ureteral reflux grade II associated to complete right pyelocaliceureteral duplication (both ureters at that side showed reflux). DMSA-scintigraphy and blood and urinary exams were normal. After discussion of possible therapeutic interventions with the patient, it was opted for endoscopic treatment
of reflux. During cystoscopy, it was identified two parallel ureteral meatus on the right side. Next, two wire-guides were introduced (one at each right ureteral meatus) in order to characterize the lower and superior units of the kidney. Then, using the STING technique (sub-ureteral injection), 1.5mL of polyacrylate-polyalcohol copolymer was injected at the lower meatus (single puncture obtaining correct volumetric effect). The detected increase following injection involved also the correspondent meatus of the superior unit. The procedure was carried out without any problems. However, after seven days of surgery, the patient presented with intense dysuria and hypogastric pain. In that moment, blood and urine exams were normal and it was started a symptomatic treatment. After two months, the complains persisted and an ultrasound showed focal thickening of 3.0x3.0cm at the bladder wall close to the right uretero-vesical junction (Figure-1). Due to this atypical and refractory presentation, it was performed a diagnostic cystoscopy, that showed an elevated lesion, hyperemic, of bullous aspect, with size and location similar to those described at ultrasound (Figure-2). The lesion was biopsied, and the pathologic exam showed epithelial hyperplasia with marked edema of lamina propria (Figures 3 and 4), suggesting a possible adverse reaction to polymer. For that reason, it was introduced betamethasone and anti-inflammatory drugs. After four months of the beginning of the symptoms, the patient completely improved. However, a new urethrocytogram showed persistence of same grade reflux.

HYPOTHESIS

This is an unprecedent reaction of polyacrylate-polyalcohol copolymer injection. The intense inflammatory reaction at the site of injection could have been caused by any hypersensitivity to the substance. The factors that suggested that hypothesis include: absence of infection (several negative urine cultures), temporal relationship between treatment and beginning of symptoms, detection of epithelial hyperplasia coincident to the site of injection and significant improvement with the use of corticosteroid. Also, the thickening observed at ultrasound was much more intense than
that usually observed at post-operatory. The significant complaints of the patients motivated early investigation of urinary tract, that detected those findings. Therefore, if the reaction was lighter or in patients with lower capacity of expression (such as in infants, for example), it could be unnoticed. Until the present, the patient does not present any other alterations aside from persistence of reflux during a six months follow-up.

DISCUSSION

Polyacrylate-polyalcohol copolymer is a synthetic product of the acrylic family, non-biodegradable, with high molecular weight, that, when injected, forms a fibrotic capsule due to its stability and durability. These proprieties associated to its biocompatibility are the main advantages of that substance in relation to biodegradable agents. These last present a high rate of reabsorption, associated to higher rate of failure of treatment and allergic reactions (1).

Several studies evaluated the efficacy of polyacrylate-polyalcohol copolymer and showed high rates of reflux resolution, including more severe cases (2-4). After literature review, we did not identify any relationship between polyacrylate-polyalcohol copolymer and foreign body reaction or hypersensitivity. Inflammatory reaction observed in that patient could have been similar to rheumatologic diseases that affect the ureter (such as eosinophilic ureteritis), that could lead to ureteral obstruction, explaining some patients with late obstruction described with the use of that agent (5). Among known complications of the injection of that copolymer, it is observed ureteral obstruction (early or late), contralateral reflux and local calcification (6).

There are some evidences of granulomatous inflammatory reaction (typical of foreign body reaction) after injection of biodegradable agents. For example, in one study, some patients with persistence of reflux after injection of dextranomer/hyaluronic acid were submitted to ureteral reimplantation. During those procedures, it was collected samples of tissue of the region of the implant for histologic analysis, that showed high rate of eosinophilic infiltrate in 7 patients. These findings suggest the occurrence of hypersensitivity against some component of the used copolymer (7).

In relation to polyacrylate-polyalcohol copolymer, literature shows one 9 years-old patient with ureteral obstruction at post-operatory. In that case, during ureteral reimplantation, it was observed a lush inflammatory reaction (similar to a “tumor”), and the histologic exam described it as a pseudotumor inflammatory reaction with the presence of giant cells. It was suspected that the injection technique (HIT) and the high dose of polyacrylate (1.2mL) could have been the causes of that reaction (8).

Foreign body reaction, previously described after injection of dextranomer (7), is typically observed as a granulomatous inflammation with multinucleated giant cells and other inflammatory cells such as lymphocytes, mastocytes and some eosinophils. The reaction in this patient seems more lenient and there were not the alterations above.

Due to the presence of ureteral duplication and age of our patient, it was necessary to use a high volume of copolymer (1.5mL) to obtain a volumetric effect at the site of injection. That fact, along with the possible unprecedent reaction, could explain the adverse event. However, other authors have already used the same dose without this reaction (8, 9). Also, it was
reported some complications such as obstruction, for example, with usual doses of polyacrylate-polyalcohol copolymer (0.5-1.0mL) and dextranomer/hyaluronic acid (0.7-1.2mL) (9, 10). In relation to the patient’s age, although higher than most studied patients, there is no evidence that that fact may have collaborated for the event - in literature, there is one 32 years old patient that was injected, for example (9). Also, there is no reason to relate the reaction to therapeutic failure.

Complication in that patient was not accompanied of any sign of urinary obstruction, loss of renal function, or infection, and also, the patient responded well to conservative treatment without the need of other interventions. However, the important presented symptoms and the lack of data on the theme, diffcultened the treatment. It is possible that such complication was an idiosyncratic reaction related to a specific susceptibility of that patient, instead of, for example, hypersensitivity. Anyway, this is an unprecedented case related to copolymer injection. At last, we highlight the importance of strict follow-up of those patients, in view of the great variety of early and late complications that not always present symptoms.

ABBREVIATIONS

STING = Subureteral transurethral injection
HIT = Hydrodistension implantation technique

CONFLICT OF INTEREST

None declared.

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BCG instillations can mimic prostate cancer on multiparametric MRI

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CASE DESCRIPTION

A 63-year-old man presented with rising PSA that was 6.13ng/mL on last visit. He had a negative prostate biopsy 1 year ago, and is currently being treated with intravesical Bacillus Calmette-Guérin (BCG) instillations for pT1G3 bladder carcinoma. Multiparametric magnetic resonance (mpMRI) was carried out using a 1.5T system (Signa Excite, GE Healthcare) with a PI-RADS v2 score of 4 for diffusion-weighted imaging (DWI) in the right posteromedial peripheral zone at the midgland level (Figure-1). Thus, a

Figure 1 - A) Axial T2-weighted image with a round hypointense focal lesion (6mm) in the right posteromedial peripheral zone at the midgland level (arrow). B) On diffusion-weighted imaging with high b value (1000), a focal markedly hyperintense lesion (arrow), with markedly hypointense (arrow) value on ADC map (0.8x10-3mm2/s), consistent with a PI-RADS 4 lesion. C) is described. On Dynamic Contrast Enhanced image an enhancement (arrow) of nodular lesion is showed (D).
systematic 42-core, sector-guided transperineal prostate biopsy, with additional cognitive targeted biopsy of the suspicious lesion was performed (Figure-2). Histological findings showed typical features of granulomatous prostatitis (GP) with epithelioid cells, multinucleated giant cells and infiltration lymphocytes (Figure-3).

Patients with mycobacterial GP are mostly asymptomatic, with elevated PSA levels and indurated prostate at digital rectal examination, but because of its relative rarity, the MRI characteristics of infective GP caused by Mycobacterium tuberculosis or after intravesical BCG instillations have not been described extensively and only a few cases have been reported (1, 2). GP is found in approximately 75% of patients after intravesical administration of BCG for superficial bladder cancer (3). Despite the consistent ability of mpMRI to identify lesions suspicious for prostate cancer (PCa), there are other entities which can cause a false-positive result as GP, bacterial prostatitis or malacoplakia. GP chronic pattern is common, with low mean ADC value <1000, decreased signal on the ADC map images and isointense or decreased signal on high-b-value imaging (b>1200) (4) that could be differentiated by the intralesional ADC values, significantly lower in PCa, as suggested by Rais-Bahrami (5). Recent studies also demonstrated an acute pattern (less than six months prior to the mpMRI) of GP lesions, with lower signal intensity on T2-weighted imaging (T2WI) (1), decreased signal on the ADC map images (3) and increased signal on high-b-value imaging (5), that is indistinguishable from aggressive prostate cancer.

CONFLICT OF INTEREST

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REFERENCES


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Double inlay plus ventral onlay buccal mucosa graft for simultaneous penile and bulbar urethral stricture

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ABSTRACT

Objectives: Buccal mucosa grafts and fascio-cutaneous flaps are frequently used in long anterior urethral strictures. The inlay and onlay buccal mucosa grafts are easier to perform, do not need urethral mobilization and generally have good long-term results. In the present video, we present a case where we used a double buccal mucosa graft technique in a simultaneous penile and bulbar urethral stricture.

Materials and Methods: A 54 year-old male patient was submitted to appendectomy where a urethral catheter was used for two days in May 2015. Three months after surgery, the patient complained of acute urinary retention and a suprapubic tube was indicated. Urethrocytography was performed two weeks later and showed strictures in penile and bulbar urethra with 3.5 cm and 3 cm in length respectively. Urethroplasty was proposed for the surgical treatment in this case. We used a perineal approach with a ventral sagittal urethrotomy in both strictures. Penile urethra stricture measuring 3.5 cm in length was observed and a free graft from the buccal mucosa was harvested and placed into the longitudinal incision in the dorsal urethra and fixed with interrupted suture as dorsal inlay. Bulbar urethra stricture measuring 3 cm was observed and a free graft from the buccal mucosa was harvested and placed into the longitudinal incision in the ventral urethra and fixed with interrupted suture as ventral onlay. The ventral urethrotomy was closed over a 16Fr Foley catheter and the skin incision was then closed in layers.

Results: No intraoperative or postoperative complications occurred. The patient could achieve satisfactory voiding and no complication was seen during the six-month follow-up. Postoperative imaging demonstrated a widely patent urethra, and the mean peak flow was 12 mL/s.

Conclusion: The BMG placement can be ventral, dorsal, lateral or combined dorsal and ventral BMG in the meeting of stricture but the first two are most common. Ventral location provides the advantages of ease of exposure and good vascular supply by avoiding circumferential rotation of the urethra. Early success rates of dorsal and ventral onlay with BMG were 96 and 85%, respectively. However, long-term follow-up revealed essentially no difference in success rates. Anterior urethral stricture treatments are various, and comprehensive consideration should be given in selecting individualized treatment programs, which must be combined with the patient’s stricture, length, complexity, and other factors. Traditionally, anastomotic procedures with transection and urethral excision are suggested for short bulbar strictures, while longer strictures are treated by patch graft urethroplasty preferably using the buccal mucosa as gold-standard material due to its histological characteristics. The current management for complex urethral strictures commonly uses open reconstruction with buccal mucosa urethroplasty. However, there are multiple situations whereby buccal mucosa is inadequate (pan-urethral stricture or prior buccal harvest) or inappropriate for utilization (heavy tobacco use or oral radiation). Multiple options exist for use as alternatives or adjuncts to buccal mucosa in complex urethral strictures (injectable antifibrotic agents, augmentation urethroplasty with skin flaps, lingual mucosa, colonic mucosa, and new developments in tissue engineering for urethral graft material). In the present case, our patient had two strictures and we chose to correct the first stricture with a dorsal graft and the bulbar stricture with a ventral graft because of our personal expertise. We can conclude that the double buccal mucosa graft is easier to perform and can be an option to repair multiple urethral strictures.
CONFLICT OF INTEREST

None declared.

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Dusting utilizing suction technique (DUST) for percutaneous nephrolithotomy: use of a dedicated laser handpiece to treat a staghorn stone

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ABSTRACT

Introduction: Dusting, use of high frequency and low pulse energy is commonly performed during ureteroscopic holmium laser lithotripsy but reports on the ability of this method to treat large stones via percutaneous nephrolithotomy (PCNL) are limited. We report on the first clinical feasibility of a dusting technique during PCNL using a specially designed laser suction handpiece (LSHP).

Materials and Methods: We performed PCNL on a patient with spinal cord injury, and recurrent urinary tract infection. Computed tomography demonstrated a left complete staghorn stone, 1000 Hounsfield units. Standard (30F) prone PCNL was performed via lower pole access and balloon dilatation. A 120-Watt holmium (P120H, Lumenis) was used to perform Dusting Utilizing a Suction Technique (D.U.S.T.) for PCNL with a 550um fiber in the LSHP which was connected to a suction pump in the P120H. The LSHP has a stainless steel cannula with inner lumen diameter of 3.25mm, with fiber positioned in a separate working channel on top of the cannula. Suction is activated via the LSHP, and fragments are sucked into a collection container. We used it in “automatic” mode where suction occurred only during laser activation.

Results: We successfully performed DUST-PCNL to treat the staghorn stone using settings of 0.6Jx70Hz, and 1.0Jx60Hz, (long pulse width). Total operative time was 110 minutes; laser time 21.29 minutes, laser energy 47.68kJ. We did not encounter any difficulty with fragment aspiration or clogging of the cannula or suction tubing. Ancillary devices used included a basket to retrieve large fragments, and flexible nephroscopy to dust an upper pole branch of the staghorn stone. A nephrostogram on post-operative day POD 1 demonstrated a 4mm residual fragment. Patient was discharged on POD 2. There were no complications; stone analysis demonstrated a struvite stone.

Conclusions: We confirmed initial clinical feasibility and safety of DUST-PCNL to perform simultaneous lithotripsy and aspiration for effective stone clearance. An advantage of this method is versatility in treating a stone with both rigid and flexible endoscopy using a single energy source. Further evaluation is needed to better understand the efficacy of this technique.
CONFLICT OF INTEREST

None declared.

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Retzius-sparing robot-assisted radical prostatectomy is safe for patients with prior transurethral prostate surgery

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INTRODUCTION

Several studies have shown that patients with prior transurethral prostate surgery are associated with greater perioperative complications, as well as inferior oncological and functional outcomes when they undergo robot-assisted radical prostatectomy (RARP).

Objectives: To the best of our knowledge, there is no study thus far evaluating the association between prior transurethral prostate surgery and the above outcomes following Retzius-sparing robot-assisted radical prostatectomy (RS-RARP).

MATERIALS AND METHODS

A retrospective review of 413 patients who underwent RS-RARP by a single surgeon from November 2012 to December 2015 was analyzed. There are no certain selection criterions to perform or not Retzius-sparing approach. Patients were divided into two groups based on the history of prior transurethral surgery. Patient clinicopathological characteristics, perioperative outcomes as well as short term oncological outcome and continence rates up to one year post RS-RARP were compared between the two groups.

RESULTS

Seventeen patients (4.1%) underwent prior transurethral prostate surgery. There was no difference in the baseline patient clinicopathological characteristics apart from older age in the TURP group. Perioperative, and oncological outcomes were comparable between the groups. Continence rates at one month, three months, six months and one year post RS-RARP were also similar between the two groups.

CONCLUSION

Equivalent perioperative, oncological and functional outcomes were achieved between the two groups. RS RARP is a safe and feasible option following previous transurethral prostate surgery.
Video abbreviations:
B = Bladder
P = Prostate
U = Urethra
BN = Bladder neck
DF = Denoviller’s fascia
PF = Pelvic Floor
NVB = Neurovascular bundle
DA = detrusor apron

CONFLICT OF INTEREST

None declared.

ARTICLE INFO

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The pubovesical complex-sparing technique on laparoscopic radical prostatectomy

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Introduction: Preservation of urinary continence is a great challenge in Radical Prostatectomy. In order to improve functional results, Asimakopoulos et al. (2010) described a robot-assisted surgical technique with preservation of the pubovesical complex (PVC). We present a pure laparoscopic execution.

Presentation: A 61-year-old male patient with a diagnosis of prostate cancer, with PSA 6.54ng/ml, DRE: T1C and Gleason 6 (3+3) 1/12 fragments. All therapeutic possibilities were discussed, including active surveillance. The patient opted for surgical treatment.

A transperitoneal technique was used. We started the dissection on the left side, in the limit between the detrusor and the base of the prostate. The left seminal vesicle was dissected and left neurovascular bundle released by a high anterior dissection. We repeated the same procedure on the right side. The urethra was then divided, prostatic apex was laterally drawn and PVC was released. The bladder neck was divided and an urethrovesical anastomosis was achieved. A pelvic drain was placed.

Results: The total operative time was 150 minutes. The estimated blood loss was 300mL. The drain was removed on the 1st postoperative day and the patient was discharged. The Foley catheter was removed after 7 days and the patient remained completely dry. Hystopathology revealed adenocarcinoma Gleason 6, negative margins. PSA after 30 days was <0.04ng/mL, and the patient reported partial penile erection.

Conclusion: The Pubovesical Complex-Sparing Technique on Laparoscopic Radical Prostatectomy was feasible and safe. Further adequately designed studies are needed to confirm whether this technique enhances early functional outcomes.

CONFLICT OF INTEREST

None declared.
ARTICLE INFO

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Letter to the editor

We read with interest the recent paper by Zhong et al. examining the variety of endourological strategies available for the management of urinary tract stone disease in patients following urinary diversion (1).

The authors report a retrospective study involving 26 patients who underwent urinary diversion and who subsequently presented with stone related problems and allude to the variety of techniques available (1).

Specific to the lower tract it is stated that 3 patients underwent orthotopic neobladder surgery and were subsequently treated for vesical calculi with neobladder lithotripsy and in select cases a second look procedure was performed 3-5 days later (1).

The authors list the treatment modalities mentioned: PCNL, SWL, Percutaneous antegrade and retrograde ureteroscopy and open removal (1) but should acknowledge that in the diverted patient a variety of hybrid techniques have evolved to permit safe lower tract stone removal. Specific to the neuropathic patient with an ablated urethra and Mitrofanoff bladder laser cystolithotripsy with a flexible cystoscope (Leighton Technique) allowing complete stone removal in one sitting has been described (2). In the paediatric patient with an augmented bladder a separate hybrid technique involving endoscopic and laparoscopic approaches with preoperative lithotripsy has also been described (3). In patients with stone disease in a continent diversion another hybrid technique involving laparoscopic entrapment and fragmentation with conventional lithotripsy has been documented (4). The Mini PCNL technique has also been adapted for use in a spinal patient with an ablated urethra to achieve stone removal via a Mitrofanoff tract (5).

CONFlict OF INTEREST

None declared.
REFERENCES


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REPLY TO THE AUTHORS: Re: Endourologic strategies for a minimally invasive management of urinary tract stones in patients with urinary diversion

FangLing Zhong ¹, Gurioli Alberto ², GuangMing Chen ¹, Wei Zhu ¹, FuCai Tang ¹, Guohua Zeng ¹, Ming Lei ¹

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To the editor,

We appreciated the valuable comments on our recent published article in the International Braz J Urol (1, 2). We agree with the commentary, to our knowledge, these studies have shown that the complicated patients with lower tract stone were treated by endoscopic management.

In patients with reservoir stone after urinary diversion, stone management present unique challenges. In our research, 3 patients with reservoir stones following urinary diversion were treated by tranurethral neo-bladder lithotripsy, and one patient had 6 mm residual stone postoperatively and received subsequently conservative watching treatment (2). Recently, percutaneous pouch access and laparoscopic techniques to facilitate the treatment of lower tract stones has become popular (3,4).

With the advancement of equipments and increasing experience, the surgical management of urolithiasis in patients with urinary diversion are varied, individualized consideration and comprehensive evaluation must be taken into account, which depending upon diversion type, patient fitness, stone size, stone location, available resource and surgeon experience (5,6).

CONFLICT OF INTEREST

None declared.
REFERENCES


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ARTICLE INFO
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Re: Transition to adulthood with a bladder augmentation: histopathologic concerns

Ines Mendes Pina 1, Ahmed M. Omar 1, Rauf N. Khadr 2, Michael S. Floyd Jr. 1, 2

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To the editor,

We read with interest the recent paper by Mammadov et al. examining the concerns regarding histological changes in adult neurogenic patients who have undergone bladder augmentation with bowel interposition as an adolescent or in childhood (1).

The authors report a small study involving 20 patients who underwent selective anatomic bladder biopsies following augmentation for either neurogenic bladder, extrophy or bladder neck trauma.

Two patients underwent open bladder biopsy as a simultaneous stone extraction procedure was planned. Neuropathic patients with a reconstructed or ablated urethra pose a challenge for the Urologist as they do not have dependant bladder drainage (2). Specific to the neurogenic patient with bladder calculi the authors should acknowledge that mitrofanoff cystolitholapaxy and concomitant bladder biopsy has been reported using a minimally invasive, hybrid technique thus avoiding the morbidity of open surgery (3).

Mammadov et al. reported no malignant histology in the study but did detect 2 cases of squamous metaplasia and 1 case of intestinal metaplasia (1). One case of squamous metaplasia had a history of bladder stones similar to the case reported by Floyd Jr et al. (3).

In 2011, Higuchi et al examined 250 surveillance cystoscopies and although 4 lesions were identified, none were malignant leading the authors to conclude that annual surveillance cystoscopy was not cost effective (4). A separate publication by Higuchi et al also commented on immunosuppression as an independent risk factor for neoplastic development in bladder augmentation patients (5) and this has not been addressed by Mammadov et al.

The authors conclude by stating that surveillance cystoscopy in augmented patients less than 5 years post operatively is now limited to those with symptoms. This is a very pertinent clinical point. Hamid et al. detected no malignancy in a series of 92 augmented and substituted patients undergoing surveillance cystoscopy but detected higher rates of chronic inflammation in the augmented group (6). Furthermore, they concluded by stating that surveillance cystoscopy was not merited in patients less than 15 years post operatively but advised that investigations should be prompted by development of appropriate symptoms in these patients (6).
REFERENCES


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