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DOES THE TESTOSTERONE LEVEL AFFECT THE SEVERITY OF URETHRAL STRICTURE OR THE OUTCOME OF URETHROPLASTY?

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Objectives: Testosterone has an important role in the development of the urethra and the smooth muscle integrity of the corpora cavernosa. The present study aimed to evaluate the impact of testosterone levels on the surgical outcome of excision and primary anastomosis (EPA) urethroplasty for the treatment of urethral stricture disease (USD).

Methods: This is a prospective clinical observational study that included adult patients with primary USD who were scheduled for urethroplasty. The serum testosterone (free and total) levels were assessed on the morning of the operation day (8–10 a.m.). At 1 month postoperatively we assessed the International Prostatic Symptoms Score (IPSS), maximum flow rate (Q-max) and post-voiding residual volume (PVR).

Results: This study included 70 patients. Preoperative total testosterone levels ranged from 212 to 1093.7 ng/dL, with a mean of 684.16 ± 339.99, and the serum free testosterone ranged from 3.54 to 12.9 ng/dL, with a mean of 8.34 ± 2.4. Based on the total testosterone levels, 19 patients (27.1%) had low testosterone. The serum testosterone levels showed a statistically significant negative correlation with the patient's age, BMI, and preoperative post-voiding residual volume (PVR) and a significant positive correlation with Q-max levels. The overall surgery success rate was 90%. The predictors for procedure failure were the presence of DM (p=0.039; OR: 0.179, 95% CI: 0.035-0.92), the levels of PVR (p=0.002; OR: 1.013, 95% CI: 1.005-1.021), and serum total testosterone levels (p=0.026; OR: 0.996, 95% CI: 0.993-1). However; serum testosterone levels failed to show significant association with the surgery outcome or the postoperative complications in the multivariate regression analysis.

Conclusion: The present study supports the impact of low testosterone levels on the severity of USD. However, its impact on the surgery outcome is still questionable.

Keywords: Urethral stricture disease, Testosterone levels, Urethroplasty.

INTRODUCTION

Urethral stricture is the narrowing of the urethra that results from scarring and may cause lower urinary tract obstruction.[1] Male urethral stricture disease (USD) is a heterogeneous disorder that is caused by a diversity of etiological factors and has a broad range of clinical presentations.[2] The most common cause is external trauma to the perinium. Other causes include iatrogenic USD from instrumentation of the urethra, , and radiation to the pelvis. In low income countries, USD can be caused by non-treated sexually transmitted infections.[3,4] Male USD is an underestimated cause of patient morbidity. It can lead to recurrent urinary tract infections (UTIs) and in severe untreated cases may result in renal failure.[5]

The male USD treatment is variable depending on several factors, such as the stricture site and severity, age, and functional status of the patient. Treatment options comprise simple dilation, endoscopic treatment that includes direct vision internal urethrotomy (DVIU), and open surgical treatment; urethroplasty.[3]

Urethroplasty is associated with a considerably superior long-term success rate compared to dilation and endoscopic treatment.[6] Several surgical techniques have been adopted for male USD. Excision and primary anastomosis (EPA) or end-to-end urethroplasty, has been assumed to be the top procedure in terms of long-term surgical success, with success rates reaching up to 93.8%.[7,8] However, EPA performance is restricted by the bulbar urethra limited elasticity. Indeed, EPA is suitable only for urethral strictures up to 3 cm since excising a longer portion impedes creating a tension-free and properly vascularized anastomosis, which is decisive for a successful outcome.[3] Testosterone has an important role in the development of the urethra and the smooth muscle integrity of the corpora cavernosa.[9] Sex hormones have long been implicated in the pathogenesis of urethral disorders.[10] An association of low testosterone levels with inflammation and fibrosis in various body systems has been documented.[11–14] There has been growing evidence linking low testosterone levels to the reduction of periurethral vascularization[15] and the occurrence of USD.[16]

The present study aimed to evaluate the impact of testosterone levels on the surgical outcome of patients undergoing urethroplasty for the treatment of urethral stricture.

PATIENTS AND METHODS

This is a multicentric prospective clinical observational study that was performed in two urological centres during the period from April 2020 to March 2022. The study was conducted per the Helsinki Declaration and commenced after approval by the Institutional Review Board.

Adult patients with primary USD who were scheduled for EPA were eligible for the study. Patients with diagnosed hypothalamic-pituitary axis disorders and those on testosterone replacement therapy were excluded. Patients with ASA physical status III or higher[17] and those with strictures longer than 3 cm and/or penile strictures were also excluded. Informed written consent was obtained from each patient included.

All patients were evaluated by history taking, general and urological examinations, including assessment of the International Prostatic Symptoms Score (IPSS),[18] and routine laboratory investigations. Patients with UTI underwent urine culture examination and were treated accordingly.

The serum total testosterone levels were assessed on the morning of the operation day (8–10 a.m.) using the human testosterone enzyme immunoassay (EIA) kit by Ansh Labs, Webster, U.S.A., according to the manufacturer, with a detection range of 0–1500 ng/dL. The free testosterone levels were estimated using a widely used web calculator (http://www.issam.ch/freetesto.htm), based on the serum albumin and sex-hormone binding globulin (SHBG) measures. Total testosterone levels <300 ng/dL and free testosterone levels < 6 ng/dL were considered hypogonadism.[19]

Retrograde and voiding urethrography to assess the features and location of the urethral stricture and pelvi-abdominal ultrasound to assess the post-voiding residual volume (PVR). The urine flow rate (Q-max) was estimated via uroflowmetry using a wired multiple-task urodynamic system, Laborie Medical Technologies, version.[12]

Surgical Procedure

An inverted U perineal incision was made. Circumferential dissection of the urethra and sorrounding corpus spongiosum was done down to the stricture site which was identified using a 16 Fr nelaton catheter. Dissection was continued and the urethra was divided through the stricture site. The proximal urethra was identified with the aid of a metal urethral dilator passed through the suprapubic catheter site and into the bladder neck. Excision of the strictured urethra and all sorrounding fibrous tissues was done until we reach healthy urethral mucosa. Both urethral ends were spatulated and anastomosed using tension free 6 interrupted 4-0 vicryl sutures. A 16Fr silicone urethral catheter was left in the urethra and a periurethral suction drain was applied if indicated.

Post-Operative Management

Patients were observed for 24 hours postoperatively. Analgesics (NSAIDs) and/or narcotics were given if needed. On the next day, the drain if applied was removed and the patient was discharged and oral antibiotics were continued for 5-7 days. The catheter was removed after 14 days.

The patients' follow-up included assessment of the IPSS, Q-max, and PVR at 1 month postoperatively.

The Study Outcomes

The primary outcome was the potential association of the preoperative testosterone levels with the surgery success rate. The secondary outcome was their association with the operative events, the postoperative complications, and the length of hospital stay (LOS).

The procedure was considered successful if the patients had a Q-max greater than 15 ml/sec, and IPSS score of 0-7.[18]

Post-operative complications were categorized according to the Clavien-Dindo grading system of surgical complications.[20]

Statistical Analysis

Information was coded and entered into the SPSS Statistical Software for Windows, Version 26.0. Armonk, NY, IBM. After normality testing, the numerical data were expressed and compared using the independent t-test, Mann-Whitney test, paired t-test, or Wilcoxon Rank test, as appropriate. Categorical variables were expressed as numbers and percentages and compared using the chi-square test or Fisher exact test according to the cells' predicted count. The correlation of the testosterone levels with other numerical variables was done using Spearman's test. A binary logistic regression analysis was performed to identify predictors of surgery failure, and risk factors for postoperative complications.

RESULTS

The current study included 70 male patients undergoing EPA urethroplasty for urethral stricture disease. The patients' ages ranged from 18 to 84 years, with a mean of 42.94 ± 21.33 years. Eleven patients (15.7%) were smokers, twenty patients (28.6%) had dyslipidaemia, twenty-nine patients had hypertension (41.4%), and sixteen patients had diabetes mellitus (22.9%) (Table 1).

The preoperative assessment revealed that the stricture etiology was iatrogenic (29 cases; 41.4%), traumatic (26 cases; 37.1%), and inflammatory (15 cases; 21.4%). Fifty patients (71.4%) were of ASA I and 20 patients were of ASA II (28.6%). IPSS, PVR and uroflowmetry were performed in only 47 patients since the remaining patients had complete obstruction with a suprapubic catheter inserted. The IPSS scores ranged from 24 to 35, with a mean of 30.16 ± 2.65. The PVR ranged from 49.4 to 456 cm3, with a mean of 152.8 ± 114.1 and the Q-max ranged from 1.6 to 15.6 ml/sec, with a mean of 6.3 ± 5.5. Concerning the stricture location, the majority of patients (58 cases; 82.8%) had bulbar strictures, 6 patients (8.6%) had membranous strictures, and the remaining 6 patients (8.6%) had bulbo-membranous strictures (Table 1).

Table (1): The patients' clinical characteristics

Item		Mean ± SD / Median (IQR)
Age (years)		42.94 ± 21.33
BMI (Kg/m2)		32.1 ± 7.1
Preoperative PVR (cm)		152.8 ± 114.1
Preoperative Q-max (ml/sec)		6.3 ± 5.5
Preoperative IPSS		30 (29-32)
Total Testosterone (ng/dL)		684.16 ± 339.99
Free Testosterone (ng/dL)		8.34 ± 2.4
Stricture length (cm)		1.68 ± 0.52
operative time (min)		120.57 ± 13.61
		N (%)
Smokers		11 (15.7%)
Comorbidities	Dyslipidemia	20 (28.6%)
	Hypertension	29 (41.4%)
	DM	16 (22.9%)
ASA	I	50 (71.4%)
	II	20 (28.6%)
Etiology	Traumatic	26 (37.1%)
	Inflammatory	15 (21.4%)
	Iatrogenic	29 (41.4%)
Stricture site	Bulbar	58 (82.8%)
	Membranous	6 ((8.6%)
	Bulbo-membranous	6 ((8.6%)
Low serum testosterone		19 (27.1%)
Drain insertion		15 (21.4%)

Preoperative serum testosterone analysis revealed that the total testosterone levels ranged from 212 to 1093.7 ng/dL, with a mean of 684.16 ± 339.99, and the serum free testosterone ranged from 3.54 to 12.9 ng/dL, with a mean of 8.34 ± 2.4. Based on the total testosterone levels; 19 patients (27.1%) had low testosterone levels (Table 2).

The operative time ranged from 98 to 157 minutes, with a mean of 120.57 ± 13.61. Drain insertion was indicated in 15 patients (21.4%). No intraoperative adverse events were encountered.

A statistically significant improvement was evident in the postoperative PVR and Q-max compared to the preoperative measures (p<0.001). The postoperative PVR decreased to range from 15 to 75 cm3, with a mean of 33.79 ± 13.14, and the Q-max increased to range from 13 to 40 ml/sec, with a mean of 21.00 ± 3.73 (Table 2).

Similar improvement was shown in the IPSS scores, which was reduced significantly (p<0.001) to show ranges of 0–10 with means of 5.10 ± 1.61 (Table 2).

The serum total testosterone levels showed a statistically significant negative correlation with the patient's age (r= -0.52, p<0.001), BMI (r=0.-52, p<0.001), preoperative PVR (r=-0.53, p<0.001), and significant positive correlation with Q-max levels (r=0.42, p=0.001). Similarly, the serum free testosterone levels showed a statistically significant negative correlation with the patient's age (r=-0.35, p=0.006), BMI (r=-0.44, p<0.001), and preoperative PVR (r=-0.45, p=0.005), and a significant positive correlation with Q-max levels (r=0.51, p=0.008).

The overall surgery success rate was 90% (63 cases). Comparing the baseline data of patients with the successful procedure to those of patients with the failed procedure demonstrated a statistically significant difference in the serum testosterone levels, preoperative PVR, preoperative Q-max, and the prevalence of diabetes mellitus (Table 3). No significant difference was found in the other tested parameters (p>0.05).

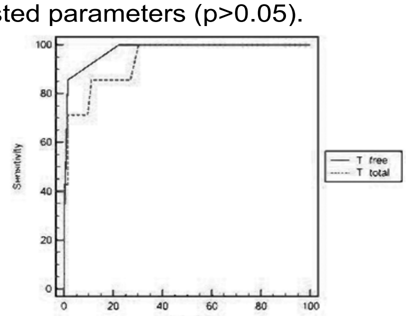

Figure 1: Prediction of failure results in correlation of total and free T.

Table (2): Comparison between preoperative and postoperative patients' clinical data

Item		Pre No. = 47	Post No. = 70	Wilcoxon Rank test	P-value
PVR (cm^3)	Mean ± SD	152.8 ± 114.1	33.79 ± 13.14	5.721	<0.001*
Q max (ml/sec)	Mean ± SD	6.3 ± 5.5	21.00 ± 3.73	7.273	<0.001*
IPSS	Median (IQR)	30 (27 - 32)	5 (4 - 6)	76.46	<0.001*

* Statistically significant.

Table 3: Comparison between patients with successful procedure and those with failed procedure

		Successful procedure (N = 63)	Failed procedure (N = 7)	Test	p-value
Age (year)	Mean ± SD	41.32 ± 20.67	57.57 ± 23.21	-1.951[a]	0.055
BMI (Kg/m^2)	Mean ± SD	32 ± 7.1	33.2 ± 6.8	-0.43[a]	0.67
Etiology	Traumatic	23 (36.5%)	3 (42.9%)	0.564[b]	0.754
	Inflammatory	13 (20.6%)	2 (28.6%)		
	Iatrogenic	27 (42.9%)	2 (28.6%)		
ASA	I	47 (74.6%)	3 (42.9%)	3.111[b]	0.078
	II	16 (25.4%)	4 (57.1%)		
Smoking		9 (14.3%)	2 (28.6%)	- 0.985[c]	0.23
Dyslipidemia		17 (26.98%)	3 (42.9%)	- 0.882[c]	0.379
Hypertension		25 (39.68%)	4 (57.1%)	- 0.889[c]	0.373
DM		12 (19.05%)	4 (57.1%)	- 2.28[c]	0.023*
Preoperative PVR (cm^3)	Mean ± SD	133.4 ± 97.2	310.9 ± 125.2	- 4.4[a]	<0.001*
Preoperative Q-max (ml/sec)	Mean ± SD	6.8 ± 5.6	2.4 ± 2.6	3.5[a]	0.003*
Preoperative IPSS	Median (IQR)	30 (29-32)	29 (26-30.5)	121[d]	0.094
Preoperative Free Testosterone (ng/dL)	Mean ± SD	8.6 ± 2.4	5. 5 ± 2.7	3.2[a]	0.002*
Preoperative Total Testosterone (ng/dL)	Mean ± SD	724.3 ± 330.2	357.6 ± 237.1	3.7[a]	0.005*
Stricture length (cm)	Mean ± SD	1.65 ± 0.53	1.79 ± 0.39	0.654[a]	0.515
Stricture site	Membranous	5 (7.9%)	1 (14.3%)	3.182[b]	0.364
	Bulbo-membranous	6 (9.5%)	0 (0.0%)		
	Bulbar	52 (82.6%)	6 (85.7%)		

a: independent t-test, b: Chi-square test, c: Z test for proportion, d: Mann-Whiteny test, * statistically significant.

Binary logistic regression revealed that the predictors for procedure failure were the presence of DM (p=0.039; OR: 0.179, 95% CI: 0.035-0.92), the levels of PVR (p=0.002; OR: 1.013, 95% CI: 1.005-1.021), serum total testosterone levels (p=0.026; OR: 0.996, 95% CI: 0.993-1), and serum free testosterone levels (p=0.009; OR: 0.56, 95% CI: 0.37-0.87). Implementing these variables in a multivariate regression analysis showed that only the levels of PVR (p=0.018; OR: 1.018, 95% CI: 1.03-1.033) was significant predictor of the surgery outcome.

Nine cases (12.8%) developed postoperative complications of Clavien-Dindo grade I in terms of surgical site infection (SSI), with one case (1.4%) having a perineal hematoma. Binary logistic regression revealed that the risk factors for postoperative complications were the patients' age (p=0.017; OR: 1.1, 95% CI: 1.02-1.2), ASA state (p=0.007; OR: 20.3, 95% CI: 2.24-184.2), presence of DM (p=0.002; OR: 0.031, 95% CI: 0.003-0.29), the serum free testosterone levels (p=0.021; OR: 0.617, 95% CI: 0.41-0.93), serum total testosterone levels (p=0.027; OR: 0.996, 95% CI: 0.993-1) and drain insertion (p=0.014; OR: 0.122, 95% CI: 0.023-0.653). Multivariate regression analysis of the described variables demonstrated only drain insertion (p=0.032; OR: 0.048, 95% CI: 0.003-0.772) to be significant risk factor for the postoperative complications.

DISCUSSION

A urethral stricture is one of the oldest urological disorders, and it is still challenging for urological surgeons.[21] Testosterone is a mainstay in the performance of various organs in the male body. Recent studies have highlighted the potentiality of testosterone involvement in the pathophysiology of urethral stricture.[15,16]

In this study, 27.1% of the patients had low testosterone levels. This finding denotes a high prevalence of low testosterone in patients with USD when compared to the rates found in general populations across the globe that were reported in the systematic review conducted by

Anaissie to be ranging from 2.1 to 12%.[22] Likewise, Puche-Sanz et al. reported a low testosterone rate of 26% in patients with USD.[23]

The present study showed a negative correlation between the testosterone level and the PVR and the Q-max in patients with USD. This finding supports the assumption that testosterone levels are associated with the severity of the condition. Urethral stricture is mainly caused by spongiofibrosis. Low testosterone levels were assumed to be implicated in the occurrence of fibrosis in various organs.[12–14] Testosterone exhibited the ability to impede the differentiation of fibroblasts into myofibroblasts.[14] Similarly, testosterone levels may be affecting the fibrosis process in the spongy tissue surrounding the male urethra, which could be a plausible explanation for the current study finding.

In alignment with our study, the testosterone levels were shown to be an indicator of the stricture severity in the study by Spencer and colleagues. However, this was in terms of the stricture length rather than its effect as shown in our study.[16]

The present study confirmed the previously established impacts of age, BMI, and diabetes mellitus on testosterone levels.[30] The aging-related impairment of testicular function has been attributed to various age-related events, such as muscle mass and strength reduction, sexual activity and virility decline, and glucose metabolism impairment.[31] It has been estimated that the levels of circulating testosterone decline after the age of nineteen by 100 ng/dL per year, or at an average rate of 1%.[32–34] Concerning obesity, it has been documented that increased body fats impede the hypothalamic axis (HPT) via multiple mechanisms, including stimulation of the secretion of pro-inflammatory cytokines and predisposition to insulin resistance and DM. On the other hand, low testosterone enhances visceral and total fat accumulation by promoting the inhibition of gonadotropins.[35]

Despite investigating the association between testosterone levels and USD in various studies, to our knowledge, its effect on the urethroplasty outcome has not been assessed.

In the present work, the overall success rate was 90%. Serum testosterone levels were found to be significantly different according to the procedure outcome and significantly predicting failed cases. Serum testosterone levels were also found to be independently associated with postoperative complications, which were mainly wound infections. This is concordant with what has previously been reported that androgens protect against oxidative stress and inflammation[24] and that proper testosterone levels modulate the immune system.[25] Androgens are known to increase tissue vascularity. This should promote healing and decrease complications.[25] In consistency with these findings, low testosterone levels were found to be associated with the artificial urinary sphincter (AUS) surgery complications risk.[26,27] In addition, low testosterone was found to be related to the postoperative complication rates following orthopedic surgeries.[28,29]

Other than serum testosterone levels; the patient's age, ASA state, DM, and drain insertion were found to be risk factors for postoperative complications. Given that all patients with postoperative complications had surgical site infection, age is understandable to be a risk factor, with the documented aging-related immunosuppression.[36] In agreement, Dégbey et al study described that patients aged over 60 years were at higher risk of SSI than those aged 30–60.[37] Supporting our findings, the recent review of Shiferaw demonstrated that patients with an ASA score above 1 had more than double the chance to develop SSI compared to those with an ASA score of 1. In addition, the authors also investigated the association of DM with the risk for SSI and found that patients with DM were more than triple as likely to develop SSI than patients without DM.[38] This is likely that all these factors reflect the overall patient condition and immune status. Despite the potential advantages of drain insertion in certain surgical conditions, drains are supposed to behave as a conduit of bacteria into the wound and hence may increase the risk of SSI.[39]

It is important to note that, in the multivariate regression analysis, both the free and total testosterone levels failed to show significant association with the surgery outcome or the postoperative complications. This might be due to high collinearity of the investigated variables. Also, may be the small sample size contributing to this lack of significance. Therefore, still questionable whether the testosterone levels affect the surgery outcome or, they are just a reflection for the preoperative condition severity. Further studies including a larger population sample could unshed light on such an assumption.

CONCLUSION

The present study supports the impact of low testosterone levels on the presence and severity of USD. However, its impact on the surgery outcome is still questionable. We acknowledge that this work is limited by the small sample size, the short-term follow-up and the fact that the outcome of urethroplasty is affected by other variables. However, to our knowledge this study is the first to address the effect of testosterone levels on USD and the outcome of urethroplasty. Further studies are recommended to provide more insights into this relation.

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- **Availability of the data: Data is available upon a reasonable request.**

Declarations

1. Ethics approval and consent to participate: Ethical committee of urology department and Cairo university approved the research. Informed written consent was obtained from each patient included

2. Consent for publications: All authors approved the manuscript for submission.

3. Availability of data and material: Data is available upon a reasonable request.

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6. Authors contributions:

MA design of the study, revised the manuscript and approved this manuscript for submission

MK was responsible for data collection, drafted the manuscript and approved this manuscript for submission

AR did the surgical procedures, revised the statistics and approved this manuscript for submission

ML design of the study, revised the whole manuscript and approved this manuscript for submission

AE did the surgical procedures and revised the manuscript and approved this manuscript for submission.

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