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Review

Testosterone, Urethral Vascularity, and Urethral Stricture Disease: A Review

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Abstract

Urethral stricture disease is one of the oldest described urologic pathologies and urethroplasty is associated with high success rates. Many urethral strictures are thought to arise from iatrogenic injury or radiation therapy which can create ischemic insults to the urethra. In developed countries, most urethral strictures are idiopathic; therefore, much is still unknown about the etiology and pathogenesis of this disease. Testosterone is known to mediate vasculogenesis through vascular endothelial growth factor (VEGF) and hypoxia inducible factor-1α (HIF-1α) pathways in various organs. Recently, testosterone has been shown to mediate urethral vasculogenesis. In the setting of testosterone deficiency, androgen supplementation can improve urethral vascularity. Further, there appears to be a high incidence of testosterone deficiency in men with urethral strictures. Despite many advances in our understanding of testosterone's association with the urethra over the past few years, there remains much to be learned about the mechanism of testosterone on urethral stricture etiology and whether testosterone deficiency and supplementation impact urethral reconstruction outcomes.

Keywords: urethral stricture; testosterone; testosterone deficiency; vasculogenesis

1. Introduction

Urethral stricture disease was described as early as the sixth century BC in ancient India and was treated with dilation from a reed catheter at that time [1]. Although it is one of the oldest described pathologies in urology and medicine, the etiology remains poorly understood in a significant number of patients. The most common etiologies for anterior urethral strictures are iatrogenic, infectious, traumatic, and lichen sclerosus (LS) disease (formerly known as balanitis xerotica obliterans). In developed countries, an idiopathic or unknown etiology accounts for 34%–41% of anterior urethral strictures [2–5]. Some idiopathic strictures may be the result of unrecognized perineal trauma; however, a lot remains poorly understood about the etiology of many strictures. Iatrogenic strictures are typically the result of transurethral instrumentation/catheterization, hypospadias surgery, or prostate cancer treatment. These insults typically result in an ischemic injury to the urethra leading to stricture formation.

Angiogenesis mediates wound healing following an ischemic insult. Multiple models have demonstrated the role of androgens in the regulation of ischemia induced angiogenesis [6,7]. Androgens have been shown to modulate angiogenesis through vascular endothelial growth factor (VEGF) and hypoxia inducible factor-1α (HIF-1α) pathways [7]. In animal models, testosterone deficiency (TD) impairs cytokine expression and homing of the stem cells that induce neovascularization within cardiac tissue following ischemic damage from myocardial infarction [8]. Further, it was suggested that testosterone replacement could restore neovascularization in TD mice [8].

Sex hormones have long been considered in the pathogenesis and treatment of urethral disorders, namely hypospadias. Exposure to estrogens has been shown to result in arrested urethral development. Alternatively, testosterone exposure to male mice in utero resulted in a more robust peri-urethral spongiosal tissue [9]. Androgen stimulation prior to hypospadias surgery was first used in 1971 [10]. Preoperative testosterone has several theoretical advantages including increased penile and glanular size as well as an increase in prepucial vascularity [11–15]. Theoretically, improved tissue quality and vascularity would result in better wound healing and outcomes. Results of hormonal stimulation on hypospadias outcomes are conflicting [16,17] and the use of preoperative testosterone remains controversial.

As the understanding of the role of testosterone in urethral development and angiogenesis has grown, it has spurred an interest beyond hypospadias and into other urethral pathologies including urethral stricture disease. The objectives of this review are to discuss the roles of (1) testosterone in urethral vascularity, (2) TD and urethral stricture disease, (3) testosterone supplementation on urethral vascularity, and (4) future directions of testosterone and stricture disease.

2. Testosterone and AUS Urethral Erosion

Over the last several years there has been a growing interest in testosterone and adult urethral pathologies. The first series that spurred this interest evaluated testosterone and urethral erosion following artificial urinary sphincter (AUS) placement [18]. The authors had noticed an increase

in AUS erosions in men with TD. In this paper, Hofer *et al*. [18] evaluated serum testosterone levels in 53 consecutive patients who presented for follow-up after AUS placement. They defined TD as <280 ng/dL. Twenty patients had an AUS erosion, of which 18 (90%) had TD [18]. Only 9% of men with normal serum testosterone had an erosion. In a multivariate analysis, TD was independently associated with AUS erosion [18]. Interestingly, on multivariate analysis, radiation was not associated with AUS erosion although a higher number of patients with erosion had prior radiation therapy (80% vs 51%, $p = 0.038$) [18]. The same group performed a larger retrospective review of all patients who underwent AUS by a single surgeon [19]. They identified 161 men who underwent AUS and had a perioperative serum testosterone level. Low serum testosterone levels were more common in those patients who had urethral erosion. Men with TD were more likely to have urethral erosion (OR 2.519, $p = 0.021$). Again, on their multivariate analysis, TD was the only factor associated with urethral erosion [19].

Prior pelvic radiation therapy, AUS surgery, and prior urethral reconstruction are known risk factors for AUS urethral erosion [20–22] and all impact periurethral vascularity. Radiation therapy creates an obliterative endarteritis, and prior urethral dissection places the urethra at risk of partial devascularization and atrophy [18]. Compromise to urethral vascularity appears to confer the risk of urethral sub-cuff atrophy and erosion. Since testosterone is known to mediate angiogenesis, this work stimulated further investigations regarding testosterone's impact on urethral vascularity [18].

3. Testosterone and Urethral Vascularity

Following the findings by Hofer *et al*. [18] in 2016, the same group explored androgen mediated vascularity in men with normal and low serum testosterone levels. They compared androgen receptor (AR) expression, its downstream target the angiopoietin-1 receptor (TIE-2), and the overall vascularity or vessel count in urethral stricture tissue of men who underwent urethroplasty. The cohort consisted of 11 men who had a serum testosterone level within 2 years of urethroplasty. They found decreased expression of AR (1.11% high power field [HPF] vs 1.62, $p = 0.016$), TIE-2 (1.84% HPF vs 3.08, $p = 0.006$), and overall vessel count (44.47 vessels/HPF vs 98.33, $p = 0.004$) in men with serum testosterone less than 280 ng/dL. They also noted a non-significant correlation between vessel count and serum testosterone [23]. This study consisted of a very select cohort of patients. During the study period, approximately 1200 patients underwent urethroplasty at this institution, but only 11 met inclusion criteria of having perioperative serum testosterone level which certainly introduces a degree of selection bias. Despite the limitations of this article, the authors suggest a mechanistic model of low serum testosterone on decreased urethral and corpus spongiosum vasculogenesis regulated through the AR and TIE-2 receptors [23]. AR mediated vasculogenesis is complex and there are likely additional factors involved in this process within the urethral and periurethral tissue such as VEGF or HIF-1α; however, no papers to date have explored the role of this mechanism.

Levy *et al*. [24] explored pathological markers in urethral stricture tissue of LS and non-LS patients. The authors' objective was to evaluate the pathophysiology of LS strictures by analyzing protein expression related to inflammation, cell cycle disruption, oxidative stress, hormone receptor status, and infection. Admittedly, the goal of this paper was not to explore androgen specific effects on urethral strictures. They examined tissue from 81 urethral strictures and found loss of AR in 43% of all strictures. There was no difference between LS and non-LS strictures. Interestingly, they also found that nearly two-thirds of strictures expressed high levels of VEGF [24]. This series did not assess the serum testosterone levels and therefore conclusions regarding the impact of serum testosterone on AR and VEGF cannot be drawn from this series. However, the results are interesting and add to the work by Hofer *et al*. [23] demonstrating alterations in the expression of the AR in urethral stricture disease.

4. Testosterone Deficiency and Urethral Stricture Disease

Spencer *et al*. [25] performed a retrospective review of patients undergoing urethroplasty by two surgeons at two institutions. Preoperative testosterone assessment was part of the standard practice of both surgeons. They excluded patients with a history of pelvic radiation, prostatectomy, or pelvic fracture urethral injury. Overall 157/202 met inclusion criteria of which 115 had preoperative testosterone. These authors found 56.5% of men undergoing urethroplasty had TD as defined by serum testosterone <300 ng/dL. BMI was associated with low testosterone levels ($p < 0.00001$). They compared this group to the National Health and Nutrition Examination Survey (NHANES) database. During 2011–2012 all males in the NHANES dataset had testosterone levels assessed and men >18 years were included as a comparison group. The NHANES group has 2575 men for analysis of which 28% had serum testosterone <300 ng/dL [25].

The authors then analyzed stricture characteristics among men with low and normal testosterone levels. Men with low testosterone levels had higher BMI, 36 kg/m^2 vs 29 kg/m^2 ($p < 0.00001$). In men with low serum testosterone, stricture length was significantly longer than in the normal testosterone group, 7.2 cm vs 4.8 cm ($p = 0.02$). They found no difference in stricture etiology between groups with normal and low serum testosterone. On multivariate analysis, TD remained associated with stricture length ($p = 0.015$) [25]. Despite the obvious limitations of using a national database as the comparison group and

selection bias associated with the retrospective design, this study suggests that men with urethral stricture disease have a higher incidence of low serum testosterone. Further, this work questions whether TD has a role in the pathogenesis of urethral strictures leading to more severe disease as TD was associated with stricture length.

Bonilla *et al*. [26] recently published an abstract form a cross sectional case-control study of men presenting to one institution evaluating TD in men with urethral stricture disease. They compared serum testosterone levels in men presenting for urethral stricture evaluation to men presenting for non-voiding related complaints. They had 120 men with urethral stricture and 41 controls. There were no differences in demographics or comorbidities between groups. Mean serum testosterone levels were significantly lower (391 ng/dL vs 495 ng/dL, $p < 0.01$) in men with urethral strictures although the mean was above 300 ng/dL in both groups. Men with urethral stricture disease also had higher levels of follicle stimulating hormone (10.7 mIU/mL vs 5.01 mIU/mL, $p < 0.01$) and luteinizing hormone (6.2 mIU/mL vs 4.2 mIU/mL, $p < 0.01$). Serum testosterone was <300 ng/dL in significantly more men with urethral stricture disease (35.8% vs 14.6%, $p < 0.007$; OR 3.2, CI 1.27–8.33) [26]. These studies taken together demonstrate a growing body of evidence that TD is more common in men with urethral stricture disease. It is still, however, unclear if serum testosterone has a role in stricture pathogenesis.

5. Testosterone Supplementation and Urethral Vascularity

As the evidence supporting a link between low serum testosterone and urethral vascularity grows, efforts shifted toward determining if urethral vascularity could be improved with hormone supplementation. Yura and colleagues [27] first evaluated this in a rat model. They divided 24 Sprague Dawley rats into four groups: non-castrate control, castrate, castrate with testosterone supplementation, and castrate with estrogen supplementation. They compared AR, TIE-2, and CD31 expression between groups. CD31 is a sensitive marker for vascular tissue. CD31 was decreased in castrated rats compared to controls. AR and TIE-2 were not detected in the castrate group. Following supplementation with testosterone the overall vessel count, AR, and TIE-2 expression increased significantly. Testosterone restored CD31 and AR expression to higher levels than the non-castrate control group [27]. Estrogen supplementation improved CD31 but not AR or TIE-2 expression [27]. These findings demonstrate that testosterone supplementation restores periurethral vascularity in an animal model.

The same group then assessed the impact of hormone supplementation on urethral tissue following urethroplasty in a rat model [28]. They allocated 48 rats to the same groups (non-castrate control, castrate, castrate with testosterone supplementation, and castrate with estrogen supplementation). In each group half of the rats underwent a Heineke Mikulicz style urethroplasty. CD31 expression was used to assess tissue vascularity and it was increased post-operatively in the control group as well as the testosterone and estrogen arms compared to the castrate arm. AR expression was slightly decreased in those that received surgery compared to no surgery in the testosterone supplementation arm (5.21% vs 4.24%, $p = 0.042$). TIE-2 expression was increased in both the control (0.43% vs 0.85%, $p = 0.001$) and testosterone supplementation cohort (0.20% vs 0.70%, $p < 0.001$) following urethroplasty. They then found postoperative CD31 was correlated with TIE-2 ($r = 0.454$, $p < 0.001$) and AR ($r = 0.561$, $p < 0.001$) expression suggesting a mechanistic relationship [28].

The fascinating work by this group demonstrates that not only does testosterone supplementation improve urethral vascularity but that it is also true in a perioperative environment. They also suggest that postoperative angiogenesis is an androgen driven process. The rats who underwent surgery did not have urethral stricture disease and it remains unclear how urethral pathology would impact these results. Prior work has shown urethral stricture tissue has decreased vascularity [23]; therefore, it is reasonable to believe postoperative angiogenesis would still be improved with androgen supplementation. Additionally, the comparison group was not just TD, but castrate and it is possible that these results may not extrapolate to subjects with less degree of TD.

6. Future Directions

Over the last 5–6 years, much has been learned regarding the impact of testosterone on urethral vascularity and stricture disease (Table 1, Ref [18,19,23–28]). However, there is still more work to be done as this emerging area translates into clinical practice. First, the role of testosterone on urethral stricture etiology remains unclear. Is there a direct pathogenesis where low serum testosterone creates an ischemic environment leading to urethral strictures in men? If so, what portion of idiopathic urethral strictures are secondary to TD? Does TD and poor urethral vascularity prevent wound healing following an insult from iatrogenic or straddle trauma? If this is true, then is testosterone supplementation protective against urethral stricture disease?

Second, it is important to understand if TD impacts surgical outcomes. It is plausible that urethral stricture recurrence following surgery could be reduced by improving urethral vascularity and subsequently wound healing. Further, sexual side effects following urethroplasty have gained significant attention in the literature and are thought to be the result of vascular insults during surgery. The role of transecting vs non-transecting anastomotic urethroplasty is a highly debated topic in reconstructive urology. This debate focuses on the benefits of preserving the antegrade blood supply to the corpus spongiosum. A recent random-

Table 1. Summary to studies evaluating testosterone and urethral vascularity.

Study (year)	Subjects (n)	Design	Main finding	Additional findings
Hofer *et al.* [18]	Human (53)	Retrospective cohort study	AUS erosion independently associated with TD*	90% of men with AUS erosion had TD*
Wolfe *et al.* [19]	Human (161)	Retrospective cohort study	TD* associated with AUS erosion on multivariate analysis	OR = 2.519 for AUS erosion with TD*
Hofer *et al.* [23]	Human (11)	Retrospective cohort study	Urethral stricture tissue in TD* men had less AR expression	TIE-2 and vessel count also decreased in men with TD*
Levy *et al.* [24]	Human (81)	Retrospective cohort study	AR loss in 43% of all strictures	VEGF upregulated in 66% of strictures.
Spencer *et al.* [25]	Human (115)	Retrospective review from 2 centers	TD present in 56.5% of men with urethral stricture	Strictures were significantly longer in men with TD
Bonilla *et al.* [26]	Human (161)	Case control, cross-sectional analysis	TD was more common in men with urethral stricture (35.8 vs 14.5%, $p < 0.0007$)	FSH (10.7 vs 5.01 mIU/mL, $p < 0.01$) and LH (6.2 vs 4.2 mIU/mL, $p < 0.01$) were higher in stricture patients
Yura *et al.* [27]	Sprague-Dawley Rats (24)	Multi-arm study	Testosterone supplementation improved AR and CD31 expression compared to castrate rats	Estrogen supplementation only improved CD31
Yura Gerbie *et al.* [28]	Sprague-Dawley Rats (48)	Multi-arm study	AR and TIE-2 increased in testosterone supplementation group following urethroplasty	AR and TIE-2 correlated with postoperative vascularity suggesting mechanistic relationship

*TD defined by serum testosterone <280 ng/dL; TD, testosterone deficiency; AUS, artificial urinary sphincter; FSH, follicle stimulating hormone; LH, luteinizing hormone.

ized controlled trial comparing excision and primary anastomosis (EPA) and buccal mucosa graft urethroplasty found a higher rate of reduced glans filling in the EPA group [29]. As we learn more about the impact of testosterone on urethroplasty outcomes, it will be interesting to see if testosterone not only changes outcomes but also approaches to urethral reconstruction.

7. Conclusions

Vascularity within the urethra and corpus spongiosum is mediated through androgen pathways. Further, it appears a large number of men with urethral stricture disease have TD. Supplementation with testosterone appears to improve urethral vascularity within animal models. As this area of study continues to emerge, we will hopefully learn more about urethral stricture etiologies and the impact of testosterone on surgical outcomes.

Author Contributions

MAMH, FAY, DWB all contributed to design, data analysis, writing, and reviewing of the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of Interest

MAMH—no conflicts of interest; FAY—on the advisory board and is a consultant for Coloplast, a speaker for Antares Pharma, a speaker for Clarus Therapeutics, on the advisory board for Promescent, and a research investigator for Viome; DWB—no conflicts of interest. FAY is serving as one of the Guest editors of this journal. We declare that FAY had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to TA.

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