Review Article

Hypogonadism and urologic surgeries: a narrative review

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Background and Objective: Previous studies indicated that the treatment of male hypogonadism can be beneficial for intraoperative and postsurgical outcomes. In this study, we aimed to determine the impact of male hypogonadism on urologic surgeries. We provided an overview of the key studies in the field with the focus on the outcomes of urologic surgeries in hypogonadal men with/without testosterone replacement therapy (TRT).

Methods: We performed a literature review in PubMed and Google Scholar databases for the most relevant articles pertaining to the outlined topics without placing any limitations on publication years or study designs. We included full-text English articles published in peer reviewed journals between January 1970 and March 2022.

Key Content and Findings: Androgen deficiency is a common finding after major urologic surgeries. Although guidelines recommend against TRT in men with prostate carcinoma, recent investigations showed no association between TRT and disease progression and recurrence. Indeed, recent evidence suggested that low androgen levels could be related to high grade prostate carcinoma and increased risk of upgrading from low to high grade disease. Investigations on the application of TRT in benign prostatic hyperplasia (BPH) patients also revealed contrasting results. While some studies suggested higher rates of prostate-related events in men who received TRT, others showed that TRT could alleviate urinary symptoms in hypogonadal men with BPH. Decreased testosterone level is commonly seen in bladder cancer patients. The treatment of perioperative androgen deficiency can reduce postoperative morbidities and lower the risk of recurrence in these patients. Low testosterone levels are observed in approximately half of the men who undergo artificial urinary sphincter (AUS) placement and can increase the risk of complications.

Conclusions: The role of testosterone treatment in patients with urologic diseases such as prostate carcinoma and BPH is controversial. Further investigations are needed to determine the impact of hypogonadism and TRT on the outcomes of urologic surgeries in patients with androgen deficiency.

Keywords: Hypogonadism; androgen deficiency; testosterone; urologic surgery

Submitted Apr 27, 2022. Accepted for publication Jul 01, 2022.
doi: 10.21037/tau-22-308
View this article at: https://dx.doi.org/10.21037/tau-22-308

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Introduction

Male hypogonadism is defined as decreased serum testosterone levels (total testosterone <300 ng/dL equivalent to 10.41 nmol/L) in the presence of symptoms and/or signs of androgen deficiency (1). It affects 5–10% of men above 30 years old and its prevalence increases with age (2,3). Several studies have reported a physiologic age-dependent decline of nearly 1–2% per year in total and free testosterone concentrations in men after the age of 30 years (4-6). The incidence rate of male hypogonadism is estimated as 481,000 new cases per year in the United States (US) men (7). American Urological Association (AUA) guidelines recommend male hormone profile assessment in male patients with signs and symptoms of testosterone deficiency such as decreased bone mineral density, loss of muscular mass, erectile dysfunction (ED), decreased libido, fatigue, and mood changes (1). There exist several challenges for diagnosis of hypogonadism (8). Although most patients become symptomatic at total testosterone levels below 300 ng/dL, studies have shown that there are no universal serum testosterone levels associated with hypogonadism symptoms forcing specialists to rely more on patient-reported symptoms than blood test values. Serum testosterone level is also fluctuating over the course of the day and from day-to-day (8). Previous investigations determined that approximately 15% of healthy men can have low testosterone at any hour of the day (9). Measurement of testosterone concentration widely depends on the process and protocol utilized by the laboratory. There are several methods to measure total testosterone concentrations including radioimmunoassay, immunometric assays, and liquid chromatography–tandem mass spectrometry (LC-MS/MS). These methods are associated with considerable interassay variations (3,10). LC-MS/MS generally provides higher specificity, sensitivity, and precision especially in low-range levels compared with other methods (3). Nonetheless, this technique is costly and is available to a limited number of care facilities. Therefore, the most commonly utilized methods to measure testosterone in non-reference hospitals and commercial laboratories are enzyme immunoassays (8). Serum total testosterone comprises unbound and protein-bound testosterone. Most of the serum testosterone is bound to sex hormone-binding globulin (SHBG) and albumin, and only 2–4% of the circulating testosterone is considered as unbound or free (11). Previous investigations revealed that men with low free testosterone levels are affected with testosterone deficiency symptoms regardless of their total testosterone levels (12). While total testosterone concentration is usually affected by conditions that modestly increase or decrease SHBG, free testosterone levels usually remain within the normal range limits in such conditions. Guidelines recommend measuring free testosterone concentration when total testosterone is mildly above or below the reference ranges (2,3). Free testosterone is mainly calculated upon accurate measurement of total testosterone, SHBG, and albumin using different available formulas based on the binding characteristics of testosterone to SHBG and albumin (3,13).

Low testosterone levels cause a wide range of pathophysiologic changes in various body systems. It is associated with increased risk of insulin resistance and metabolic syndrome (14,15). It has been demonstrated that long-term uncorrected testosterone deficiency is closely related to poor general health, hypercholesterolemia, and anemia (16,17). Furthermore, male hypogonadism can independently increase the risk of cardiovascular diseases and all-cause mortalities (18-20). Disease-specific investigations demonstrated that male hypogonadism is associated with higher mortality rates in patients with cardiovascular, respiratory and renal diseases, type 2 diabetes and malignancies (21,22). Also, male hypogonadism can increase postoperative complication rates and total costs of care after various orthopedic surgeries (23,24).

Testosterone replacement therapy (TRT) is extensively used to treat men with androgen deficiency and symptoms of hypogonadism (25). The main goals of TRT are to restore and maintain sexual function and body composition, in addition to improving mood, general health, and quality of life (14,15,17). Previous investigations demonstrated the benefits of preoperative testosterone administration, even at higher than physiological levels, to minimize postoperative adverse outcomes and improve recovery following major surgeries (26,27). Studies have also shown that low free testosterone concentration is associated with increased mortality rates after major surgeries (28).

To the best of our knowledge, no study has reviewed the role of androgen deficiency and TRT in urologic diseases and their surgical outcomes. In this narrative review, we aimed to determine the impact of male hypogonadism on urologic surgeries. We provide an overview of the key studies in the field with the focus on the outcomes of urologic surgeries in hypogonadal men with/without TRT. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-308/rc).

Table 1 The search strategy summary

Items	Specification
Date of search	• 03/01/2022
Databases and other sources searched	• PubMed • Google Scholar
Search terms used	• "male hypogonadism", "androgen deficiency", "testosterone", "testosterone replacement therapy", "androgen replacement" in combination with "urologic surgery" and "urologic intervention"
Timeframe	• January 1970–March 2022
Inclusion and exclusion criteria	Inclusion criteria: • Focus on urologic surgeries and interventions in hypogonadal men and the impact of testosterone therapies on surgical outcomes • English-language papers • Peer-reviewed, published literature including review papers Exclusion criteria: • Main topic not related to male hypogonadism or urologic surgeries/interventions • Editorials, letters to the editors, and abstracts • Non-English-language articles
Selection process	• First author conducted the selection and all the co-authors approved the included studies

Methods

We performed a literature review in PubMed and Google Scholar databases for the most relevant articles pertaining to the outlined topics without placing any limitations on publication years or study designs. The search keywords included "male hypogonadism", "androgen deficiency", "testosterone", "testosterone replacement therapy", and "androgen replacement" in combination with "urologic surgery" and "urologic intervention". We also manually reviewed the references lists of the articles to include other papers relevant to the topic. We included full-text English articles published in peer reviewed journals between January 1970 and March 2022 (*Table 1*).

Transient postoperative/post-illness hypogonadism

Androgen deficiency is a common finding among men with critical illness or cancer, and up to two-thirds of male patients with advanced or metastatic malignancies are affected with various degrees of symptomatic or asymptomatic low serum testosterone levels (29-31). A transient decline in testosterone concentration is detected in male patients after major surgeries, and the level of the decrease is related to the severity of the surgical stress (32-34). Stress-induced impaired adrenal and testicular function has been suggested as the underlying mechanisms for this decline (35).

Preoperative testosterone administration can be beneficial for intraoperative measures and postsurgical outcomes. Studies showed that preoperative testosterone treatment can increase patients' hematocrit and reduce the need for intraoperative blood transfusions (27). In the study by Amory *et al.*, 25 male patients received weekly intramuscular injections of 600 mg testosterone enanthate for four consecutive weeks prior to surgery (days 21, 14, 7, and 1 before surgery). Postoperative hematocrit levels were significantly increased in the testosterone-receiving group compared with the placebo-receiving group (32%±3.3% *vs.* 30%±4.8% on postop day 3 and 41%±4.4% *vs.* 38%±4.5% on postop day 35). The authors did not detect any complications attributable to testosterone therapy (27). Testosterone administration can positively affect postoperative recovery and rehabilitation by increasing protein synthesis and anabolism of muscle tissues, in addition to modulating the immune system (36,37) (*Table 2*).

Table 2 Hypogonadism symptoms, indications/contraindications for TRT

Parameters	Signs and symptoms for decreased levels	Indications for TRT	Contraindications for TRT
Total testosterone: 300–1,080 ng/dL	• Sexual symptoms, in particular low libido, decreased spontaneous and sex-related erections	• Testosterone deficiency is based on the presence of both abnormal laboratory measurements and clinical symptoms/signs	• History of breast or prostate cancer; elevated plasma levels of PSA (>4 ng/mL) and/or biopsy confirmed prostate cancer
	• Infertility	• Patients need to report symptoms of androgen deficiency and have a total serum T level lower than 300 ng/dL	• Abnormal findings at DRE of the prostate raising a suspicion of cancer
	• Anemia	• The threshold for low testosterone as being consistently <300 ng/dL on at least two serum total testosterone measurements obtained in an early morning fashion, preferably using the same laboratory with the same method/ instrumentation	• Hematocrit level of at least 52% at baseline
	• Bone mineral density loss		• Patient at risk of cardiovascular events
	• Diabetes mellitus		• MI or stroke within the past 3–6 months
	• Loss of muscle and increase in adiposity		• Severe diseases such as terminal cardiac disease, severe diabetes mellitus, severe obstructive LUTS (IPSS >19), polycythemia, or serious renal and liver disease that might be aggravated by T administration
	• Reduced energy, reduced endurance, diminished work and/or physical performance		• Young infertile men and patients who are interested in future fertility
	• Fatigue, especially in the afternoon		
	• Visual field changes (bitemporal hemianopsia)		
	• Anosmia		
	• Depression		
	• Poor concentration		
Free testosterone: 47–244 pg/mL	• Impaired memory		
Bioavailable testosterone: 131–682 ng/dL	• Irritability		

TRT, testosterone replacement therapy; PSA, prostate-specific antigen; MI, myocardial infarction; DRE, digital rectal exam; LUTS, lower urinary tract symptoms; IPSS, international prostate symptom score; T, testosterone.

Hypogonadism and kidney transplant

Male hypogonadism is frequently detected in end-stage renal disease (ESRD) patients, and nearly half of the patients are affected by some levels of androgen deficiency (38-40). Decreased prolactin renal clearance, abnormal luteinizing hormone (LH) secretion and function, and corticosteroid use are suggested as potential etiologies for testosterone deficiency in uremic patients (41-43). Carrero *et al.* found a significant negative correlation between serum levels of testosterone and inflammatory mediators such as CRP, IL-6, and fibrinogen in ESRD patients (38). In a randomized trial, androgen administration showed therapeutic effects similar to recombinant human erythropoietin for the treatment of anemia in men with chronic kidney disease. Additionally, androgen therapy was associated with improved anthropometric and biochemical nutritional status in these patients (44). Although renal transplants can restore androgen levels in a considerable proportion of the patients after 6–12 months, nearly 25% of ESRD patients remain hypogonadal even 24 months following transplantation (45). In the study by Lofaro *et al.*, testosterone deficiency was detected in nearly half of kidney transplant recipients. They detected significant relationships between low androgen levels and reduced estimated glomerular filtration rate, hemoglobin and serum albumin concentrations, in addition to increased C-reactive protein (CRP) and high-density lipoprotein cholesterol serum levels (46).

Shoskes *et al.* evaluated serum testosterone levels in 197 kidney transplant recipients and reported higher rates of graft loss and mortality in patients with low serum testosterone concentrations (43). Androgens can suppress inflammatory immune cells and antibody response while promoting the function of regulatory immune cells (47). Therefore, it has been suggested that TTR can reduce rejection rates and increase survival in graft recipients (43,45). The reason(s) for the positive impact of TRT on renal transplant recipients has been described through several mechanisms including hormonal, cardiovascular, and immunological means. Experimental studies showed that administration of exogenous testosterone in animal models can stimulate CD4 T cells and prolong graft survival (43,48). TRT can also ameliorate the adverse effects of immunosuppressive therapies such as insulin resistance, dyslipidemia, anemia, and reduced bone density in kidney transplant recipients (45). Administration of acute low-dose testosterone can be protective against renal ischemia-reperfusion injuries by modulating the immune response and reducing T-cell infiltration (49).

Hypogonadism and urolithiasis

Men are three times more susceptible to stone formation compared to women and this may stem from androgen production. Several investigations indicated increased risk of kidney stone formation in patients with either low or high androgen levels. While several studies demonstrated increased incidence of urolithiasis and stone-related events in men with high plasma androgen concentrations (25,50,51), others suggested increased risk of stone formation in hypogonadal men and patients with ED (52,53).

Naghii *et al.* reported increased serum concentrations of total testosterone, free testosterone, and dihydrotestosterone in male patients with idiopathic urolithiasis (50). Male stone formers show higher levels of testosterone than those without stones after adjusting for age and body mass index (BMI) (51). McClintock *et al.* reviewed the records of 26,586 hypogonadal men who received TRT, and found increased risk of stone-related events among them in comparison with those who did not receive this treatment (25). Testosterone therapy can suppress osteopontin expression and increase urinary oxalate excretion which could increase the risk of stone formation (54).

On the other hand, lower urinary testosterone concentration has been observed in male patients with urolithiasis. Van Aswegen *et al.* demonstrated a positive correlation between total urinary testosterone and urokinase activity (53). Otunctemur *et al.* investigated the prevalence of androgen deficiency and ED in 98 male patients with kidney stones. They detected ED in 29% and low testosterone levels in 13.3% of the patients (52). Further prospective investigations and randomized controlled trials (RCTs) are needed to determine the impact of androgen deficiency and TRT on kidney stone formation, symptoms, and the need for interventions.

Hypogonadism and bladder diseases

The prevalence and mortality rates of bladder carcinoma are considerably higher among men (55,56). The bladder is primarily derived from the urogenital sinus during embryogenesis, and there exists a well-established role for androgens in normal development and carcinogenesis of the bladder (57). Decreased testosterone concentration is commonly observed in bladder cancer patients especially

those who underwent radical cystectomy. Smelser *et al.* performed a prospective observational trial in male patients undergoing radical cystectomy for non-metastatic bladder cancer. They found that the treatment of perioperative androgen deficiency can reduce postoperative morbidities (58). They also detected low serum testosterone levels in 52.5% of the patients prior to the surgery which increased to 95% on postoperative days two and three. Although the prevalence of postoperative androgen deficiency decreased over time, serum testosterone concentrations remained low in 63% and 37.5% of the patients on postoperative days 30 and 90 (58). Previous studies revealed that declining androgen levels after cystectomy is a significant contributory factor to sarcopenia which can result in worsened outcomes. Also, it has been demonstrated that perioperative alterations in androgen concentration is associated with weight loss, frailty, immunosuppression, and infections. Therefore, decreased androgen levels can considerably impact morbidity in this group of patients (58). Nam *et al.* showed lower recurrence rates in transitional cell carcinoma with increased androgen receptor expression (59).

In a prospective study by Kafkasli *et al.* on 257 bladder cancer patients, total testosterone levels were not related to tumor aggression parameters (60). Several investigations reported negative associations between androgen receptor expression and increased pathologic stage of bladder carcinoma (57,51,62). Previous studies suggested that androgen receptor signaling can increase *de novo* carcinogenesis and bladder cancer recurrence (63,64). It has been demonstrated that androgen receptor signaling can suppress detoxification through expressional regulation of uridine 5'-diphospho-glucuronosyltransferases which can affect the removal of carcinogens. Previous investigations reported that androgen treatment down-regulates NF-κB mediated IL-6 expression by human transitional carcinoma cells in response to bacille Calmette-Guérin (BCG) which can significantly affect BCG treatment efficacy (65).

Experimental investigations on androgen deprivation animal models showed that TRT can improve bladder capacity and smooth muscle content (66,67). In addition, in a prospective study on hypogonadal men, TRT improved bladder functions by increasing bladder capacity and compliance and decreasing detrusor pressure at maximal flow (68). Nonetheless, several studies showed increased androgen receptors in bladder cancer and prominent impact of androgen signaling pathways in oncogenesis, progression, and resistance to chemotherapy in bladder carcinomas (69-73). Izumi *et al.* demonstrated reduced recurrence rates and higher 5-year recurrence-free survival in bladder cancer patients who received androgen deprivation therapy (71).

In the study by Tyagi *et al.*, androgen receptor expression was detected in nearly 60% of bladder carcinomas. This study depicted the efficacy of administration of androgen receptor inhibitors as monotherapy or in combination with cisplatin to inhibit bladder cancer progression (74). Shiota *et al.* suggested the application of androgen suppression therapy for prophylaxis for intravesical recurrence of bladder cancer (63). Tripathi and Gupta also demonstrated androgen receptor inhibition as a promising method to inhibit urothelial carcinoma growth (69).

Hypogonadism and prostate cancer

According to current guidelines, TRT is contraindicated in the presence of hormone-responsive tumors including prostate carcinoma (15,75); however, the impact of hypogonadism and TRT on prostate cancer progression and disease course is controversial (76,77). In 1996, Gann *et al.* demonstrated the association between high serum testosterone concentration and enhanced risk of prostate carcinoma (78). Furthermore, Porcaro *et al.* suggested increased preoperative total testosterone level as a predictor of positive surgical margins in prostate carcinoma patients (79).

Increased preoperative total testosterone is also associated with increased risk of lymph node invasion in prostate cancer patients (80). Androgen-deprivation therapy has been successfully used to control advanced and localized prostatic carcinoma (81). Hugosson *et al.* evaluated the efficacy of neoadjuvant hormone treatment by triptorelin and cyproterone acetate prior to radical prostatectomy which resulted in reduced risk of malignancy in surgical margins (82). On the contrary, several investigations suggested that TRT is not related to increased risk of developing prostate cancer (76,77). Also, androgen deficiency is associated with insulin resistance and increased leptin levels which could ultimately lead to higher mortality, recurrence, and metastasis in prostate carcinoma patients (83).

Morales *et al.* demonstrated the efficacy of TRT in hypogonadal men after external beam radiotherapy for localized prostate carcinoma. They suggested that prostate-specific antigen (PSA) levels should reach a nadir prior to TRT (84). A retrospective study by Morgentaler *et al.* showed higher prevalence of biopsy-detectable prostate

cancer in patients with low total or free testosterone concentrations. The outcomes of this study suggested that PSA testing and digital rectal examination could be insensitive indicators for prostate cancer screening in hypogonadal men (85). Kaplan and Hu reviewed records of 149,354 men with prostate cancer using Medicare data and demonstrated that TRT at the time of diagnosis was not associated with aggressive features of the disease and mortality rates (86). Furthermore, Khera *et al.* showed that TRT can be safely used in hypogonadal men who underwent radical prostatectomy without increasing PSA levels (87). The study by Coward *et al.* indicated that hypogonadism and TRT do not increase the incidence of prostate carcinoma. They evaluated PSA serum concentration for 144 months and concluded that TRT did not alter PSA levels (76).

In a prospective study by Pichon *et al.* on 937 patients who underwent radical prostatectomy, low serum testosterone was an independent risk factor for high grade prostate carcinoma and upgrading from low to high grade disease between biopsied and postoperative specimens (88). Gao *et al.* also showed that lower preoperative serum testosterone is associated with increased rate of upgrading and upstaging in prostate carcinoma patients (89). Botto *et al.* showed a correlation between preoperative low serum testosterone levels and tumor aggressiveness in prostate cancer patients who underwent radical prostatectomy (90). Preoperative androgen deficiency is also correlated with increased rates of extraprostatic invasion, biochemical recurrence, and postoperative progression in prostate carcinoma patients who undergo radical prostatectomy (91,92).

Ahlering *et al.* investigated the risk of biochemical recurrence after radical prostatectomy in 850 hypogonadal patients with prostate cancer and found that the patients on TRT were at lower risk for recurrence, and TRT was not associated with any complications, and (93). Pastuszak *et al.* demonstrated that TRT is not related to increased recurrence rates, even in patients with high risk prostate carcinoma (94). A recent study by Ferro *et al.* showed that low levels of circulating total testosterone can predict worse prognosis and outcomes following radical prostatectomy (95). Also, a significant correlation has been observed between low preoperative testosterone and ED after radical prostatectomy for prostate cancer (96). Conclusively, prospective multi-institutional studies on large populations and RCTs are needed to carefully evaluate the effects of androgen deficiency and TRT in prostate carcinoma patients, in addition to the outcomes of radical prostatectomy and postoperative complications.

Hypogonadism, benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS)

Investigations on the application of TRT in BPH patients show contrasting results. Although endocrine society guideline recommends against TRT in patients with severe LUTS and International Prostate Symptom Score (IPSS) above 19, several prospective trials studies failed to demonstrate any association between TRT and higher incidence or severity of LUTS and increased prostate volume (75,97).

While some studies suggested higher rates of prostate-related events including acute urinary retention and increased IPSS in men who received TRT (98), others showed that TRT could alleviate urinary symptoms in hypogonadal men with BPH (99). The AUA and European Association of Urology (EAU) guidelines acknowledged lack of associations between TRT in BPH patients and increased IPSS or urinary retention. Nonetheless, EAU guidelines indicated that testosterone administration can increase prostate volume especially during the first year of the treatment (100).

The investigation by Behre *et al.* showed no increase in prostate volume following androgen therapy in hypogonadal men (101). These findings were confirmed in a multi-center study by Meikle *et al.* which demonstrated that hypogonadal men on TRT showed prostate volume comparable to normal men (102). The absence of adverse effects of TRT in BPH patients is explained by low prostatic uptake of exogenous testosterone (103,104). Furthermore, investigations showed that LUTS and prostate volume are not correlated with endogenous testosterone levels as well (105,106).

Increased expression and activity of nitric oxide synthase and smooth muscle relaxation has been proposed as other mechanisms for the positive impact of TRT in this group of patients (107). Studies have also suggested that treating hypogonadism can reduce inflammatory processes that lead to BPH symptoms (99). An RCT by Marks *et al.* showed no alterations in prostate volume, voiding symptoms, and urinary flow following six months of TRT. They also found that androgen replacement did not increase intraprostatic testosterone and dihydrotestosterone concentrations (108). In 2007, a pilot study by Kalinchenko *et al.* showed that testosterone administration significantly improved

symptoms of LUTS (109). The authors subsequently performed an RCT using testosterone undecanoate in 184 men with hypogonadism and metabolic syndrome; however, they did not detect any significant differences in prostate volume and IPSS between treatment group and those who received placebo (110). Haider *et al.* demonstrated that TRT in hypogonadal men with metabolic syndrome can improve IPSS and residual bladder volume (111).

The efficacy of TRT in reducing LUTS has been confirmed by several RCT investigations (68,112,113). A prospective study on 656 patients with eight years of follow-up showed long-term benefits of TRT on IPSS and post-void bladder volume (114). Debruyne *et al.* carried out a prospective study on 999 hypogonadal men and determined the positive outcomes of TRT in alleviating LUTS and lowering patients' IPSS (115). An observational investigation by Yassin *et al.* revealed that while TRT can improve IPSS, residual bladder volume, and bladder wall thickness, interruptions in androgen therapy can worsen these parameters (116). Altogether, the current data suggest that the treatment of androgen deficiency in BPH patients could alleviate urinary symptoms and ultimately reduce the need for surgical interventions.

Hypogonadism and urethral surgeries

Hofer *et al.* retrospectively evaluated 1,200 men who underwent urethroplasty and concluded that androgen deficiency (<280 ng/dL) is associated with lower androgen receptor and angiopoietin receptor expression, decreased peri-urethral vascularity, and urethral atrophy in patients with strictures (117). Testosterone supplementation in experimental hypogonadism models positively affected periurethral vascularity and postoperative regeneration following urethroplasties (118).

Androgen supplementation and high testosterone levels in experimental models resulted in increased and prolonged inflammatory response, myofibroblast proliferation, and delayed urethral healing (119,120). Also, Low testosterone levels can increase the risk of complications after artificial urinary sphincter (AUS) implantation surgeries. Studies showed AUS erosion will affect 90% of men with androgen deficiency (121,122). Also, McKibben *et al.* demonstrated that low androgen levels are observed in approximately 50% of men who undergo AUS placement (123). In the study by Bailey *et al.*, androgen deprivation therapy within two years before AUS placement showed no impact on the outcomes and complications (124).

Presurgical administration of topical and parenteral testosterone is used to increase size before reconstructive surgeries on the urethra. Gearheart and Jeffs described the positive surgical benefits of preoperative testosterone treatment in hypospadias, epispadias, and urethral fistulas (125). Prospective randomized studies on patients with mid to distal hypospadias who underwent tubularized incised plate surgery showed that preoperative testosterone can reduce post-op complications and requirement for reoperation (126,127).

Adverse events associated with testosterone therapy

Testosterone therapy is associated with several adverse outcomes such as edema and polycythemia (41). Also, several cases of thromboembolism have been reported following treatment with androgens (128-130). A retrospective study on 947 patients on TRT, treatment with androgens did not increase thromboembolic events after non-cardiac surgeries (131). Testosterone treatment can result in progression of metastatic prostate cancer (132), and some guidelines recommend against testosterone administration in patients with hormone-dependent cancers (3).

The outcomes of testosterone therapy in hypogonadal patients with urologic disorders merits further evaluations. The impacts of androgen deficiency and TRT on patients with transitional cell carcinoma, prostate cancer, BPH, and urethral surgeries are still controversial. Although current guidelines recommend against the application of TRT in men with prostate carcinoma and severe BPH, recent studies showed no association between TRT and worsened outcomes in these patients. Further investigations, especially RCTs, are needed to determine the impact of testosterone therapy on disease progression and surgical outcomes in urologic disorders. The impacts of testosterone treatment on the need for surgical interventions and costs of care are to be determined. Future studies should be focused on evaluation of postoperative adverse effects of testosterone administration, particularly in patients with cardiovascular diseases and thrombophilia. In this study, we reviewed the literature on the impact of low androgen levels on the outcomes of various general urologic surgeries and the role of preoperative TRT in patients who were hypogonadal at the time of the surgery. Therefore, we did not include surgeries that would directly influence testosterone levels such as testicular related surgeries (partial orchiectomy/radical orchiectomy). We suggest future research is conducted on the impacts of TRT on disease progressions,

treatment outcomes, and rehabilitation in such conditions. Several studies reported an inverse relationship between the severity of metabolic syndrome and plasma testosterone concentrations (110,133,134). Although some investigations reported no significant differences in testosterone-related outcomes after adjusting for BMI as a potential confounding variable (51), patients with multiple comorbidities and metabolic syndrome often fare poorer after surgery and many of them are affected with variable degrees of hypogonadism. Therefore, future studies should take these important cofounders into account and determine their impact on the surgical outcomes (*Table 3*).

Conclusions

Androgen deficiency is a common finding after major urologic surgeries. Testosterone administration in hypogonadal men can positively affect post-op outcomes and improve recovery. Also, androgen therapy can modulate the immune system and increase graft survival following transplant surgeries. The role of testosterone treatment in prostate cancer and BPH patients is controversial. Although guidelines recommend against the application of these treatments in men with prostate carcinoma, recent investigations showed no association between TRT and disease progression or recurrence. Low androgen levels are related to high grade prostate carcinoma and increased risk of upgrading from low to high grade disease. Testosterone therapy in hypogonadal men can alleviate urinary symptoms of BPH and reduce the need for surgical interventions. Decreased testosterone level is commonly seen in bladder cancer patients and perioperative treatment. The treatment of perioperative androgen deficiency can reduce postoperative morbidities and lower recurrence rates. Further investigations, especially RCTs, are needed to determine the impact of hypogonadism and TRT on the outcomes of urologic surgeries in patients with androgen deficiency. The findings from this review shows that urologists should more frequently screen for testosterone deficiency, and further evaluate the impact of correction of pre-existing hypogonadism on different outcomes such as quality of life, comorbidities, and frailty. The outcomes of this review are in favor of more regular testosterone evaluation before and after implantation and transplant surgeries. The current evidence shows that diagnosis and treatment of hypogonadism could be associated with prominent positive outcomes in these conditions. The need for more regular preoperative and postoperative testosterone assessment and TRT in certain urological disorders such as BPH merits further investigations.

Table 3 Studies on the impact of hypogonadism/testosterone replacement therapy on the outcomes of urologic surgeries

Study	Population	Design	Type of surgery	Dosages, routes, types of testosterone/androgen suppression therapy	Duration of treatment	Outcomes
Thirumavalavan *et al.*, *Int J Impot Res*, 2022 (45)	87	Cohort	Organ transplant (36 kidney transplants)	Topical T preparations (n=31), injectable T (n=21), and subcutaneous T pellets (n=1) and non-testosterone therapies (i.e., HCG and clomiphene) n=5	–	Treatment of hypogonadism in solid organ recipients did not increase the risk for adverse effects related to treatment of hypogonadism or solid organ transplant. There was no difference in prostate cancer diagnoses, erythrocytosis, rejection, infections, number of unplanned admissions per patient. While there was no difference in the proportion of deaths in untreated (21%; n=6) and treated transplant recipients (7%; n=4; P=0.08), the median survival was longer in men treated with T (P=0.03)
Lofaro *et al.*, *J Nephrol*, 2018 (46)	112	Cross sectional	Kidney transplant	–	–	T deficient patients had lower estimated glomerular filtration rate and hemoglobin, higher values of C-reactive protein and fat tissue index/adipose tissue mass, and lower values of serum albumin and high-density lipoprotein-cholesterol levels. Significant differences were found in the number of patients on mammalian targets of rapamycin inhibitors immunosuppressant therapy
Shoskes *et al.*, *J Urol*, 2014 (43)	197	Cross sectional	Kidney transplant	–	–	Low T at transplant is associated with patient death and graft loss. If due to causality, T therapy may impact survival. Without causality, low T may still be a marker for post-transplant risk
McClintock *et al.*, *J Urol*, 2019 (25)	53,172	Cohort	Urolithiasis	Topical (n=18,895), injection (n=4,259), and pellet (n=167)	24 months	There was a statistically significant difference in urolithiasis between the TRT and Non-TRT patients. This difference was observed for topical and injection therapy-type subgroups, though not for pellets. There was no significant difference in stone episodes based on secondary polycythemia diagnosis, which was used as an indirect indicator of higher on-treatment T levels
Otunctemur *et al.*, *Arch Ital Urol Androl*, 2014 (52)	98	Case control	Erectile dysfunction & urolithiasis	–	–	Serum T levels were detected at the level of biochemical hypogonadism in 13 patients with stones (13.3%) and T levels were detected at the lower limit in 18 (18.3%) patients. ED and low T were significantly associated with urolithiasis
Smelser *et al.*, *Urol Oncol*, 2021 (58)	25	Cross sectional	Radical cystectomy	–	–	A pre-op, immediate postop, 30- and 90-day postoperative prevalence of low total T of 52%, 95%, 63%, and 37.5%, respectively. Significant changes in baseline weight were noted, although no significant changes in psoas muscle cross-sectional area were observed, limiting conclusions regarding a link between changes in androgens and sarcopenia in this setting
Shiota *et al.*, *J Urol*, 2017 (63)	228	Case control	Bladder cancer	5α-reductase inhibitor (Dutasteride 0.5 mg; n=20), Androgen deprivation therapy using a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprorelin acetate) and/or an antiandrogen agent bicalutamide (n=13)	Median of 2.4 years (IQR 1.2–3.5),	Multiple tumors (HR =1.82, P=0.027), large tumor (HR =2.13, P=0.043) and ever smoking (HR =2.45, P=0.020) as well as the presence of AST (HR =0.36, P=0.024) were independent risk factors for intravesical recurrence. Tumor progression to muscle-invasive bladder cancer occurred in six (3.1%) men without AST, while no case progressed to muscle-invasive bladder cancer in men with AST

Table 3 (*continued*)

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Study	Population	Design	Type of surgery	Dosages, routes, types of testosterone/androgen suppression therapy	Duration of treatment	Outcomes
Kafkasli *et al.*, *Aging Male*, 2021 (60)	257	Case control	Bladder cancer	–	–	T level was not found to be associated with any of the categories that determine tumor aggressiveness (P>0.05). There was no correlation between any categories that determine tumor aggressiveness of BCa and total T levels in adult men
Karazindiyanoğlu *et al.*, *Aging Male*, 2008 (68)	25	Cross sectional	Bladder outlet obstruction	Transdermal T, 50–100 mg gel per day	12 months	T therapy may improve LUTS/bladder functions by increasing bladder capacity and compliance and decreasing detrusor pressure at maximal flow in men with symptomatic late onset hypogonadism
Yassin *et al.*, *Aging Male*, 2016 (116)	262	Case control	Obesity and prostate indexes	Long-acting parenteral TU 1,000 mg in 12-week intervals	Maximum of 126 months (10.5 years)	TRT improved residual voiding volume, bladder wall thickness, IPSS and obesity parameters while PSA and prostate volume increased. TRT interruption reduced total T to hypogonadal levels in patients and resulted in worsening of obesity parameters, IPSS, residual voiding volume and bladder wall thickness, and PSA while CRP and prostate volume were unchanged until treatment resumed
Khera *et al.*, *J Sex Med*, 2009 (87)	57	Cross sectional	Radical prostatectomy	T gel replacement therapy with either Testim or AndroGel	36 months	Men received TRT for an average of 36 months following RP (range, 1–136 months). The mean T values increased from 255 ng/dL before TRT to 459 ng/dL after TRT (P<0.001). There was no increase in PSA values after initiation of TRT and thus no patient had a biochemical PSA recurrence
Marks *et al.*, *JAMA*, 2006 (108)	44	RCT	Prostate disease	Testosterone enanthate (150 mg), biweekly or saline placebo by intramuscular injection	6 months	Median prostate tissue levels of T (0.91 ng/g) and dihydrotestosterone (6.79 ng/g) did not change significantly in the TRT group. No treatment-related change was observed in prostate histology, tissue biomarkers, gene expression, or cancer incidence or severity. Treatment-related changes in prostate volume, serum prostate-specific antigen, voiding symptoms, and urinary flow were minor
Debruyne *et al.*, *BJU Int*, 2017 (115)	999	Prospective registry	Prostate cancer	Mostly topical gels (68%) or injectables (31%), only 2% receiving orally-administered drugs	16% received T at only one visit, 75% received T at two or more consecutive visits	Of 999 patients with clinically-diagnosed hypogonadism, 750 (75%) initiated TRT. The proportion of positive biopsies was nearly identical in men on T (37.5%) compared to those not on T (37.0%) over the course of the study. No differences were observed in PSA levels, total IPSS score, or IPSS obstructive sub-scale score by T treatment status. Lower IPSS irritative sub-scale scores were reported in treated men compared to untreated men
Haider *et al.*, *Andrologia*, 2009 (111)	117	Cohort	LUTS & metabolic syndrome	1,000 mg parenteral TU	12 months	Along with the improvements of the metabolic syndrome, there was a significant decline of the values of the IPSS, RBV and CRP. There was a (low) level of correlation between the decline of waist circumference and residual volume of urine but not with IPSS and prostate size. Along with the improvement of the metabolic syndrome upon T administration, there was also an improvement of the IPSS and of RBV of urine and CRP. The mechanism remains to be elucidated
Haider *et al.*, *J Urol*, 2018 (114)	656	Controlled registry	Urinary and sexual function	Parenteral TU 1,000 mg/12 weeks	Maximum of 10 years	Significant decreases in IPSS and post-voiding bladder volume in patients receiving TRT but not in the untreated group. They recorded a decrease in the AMS in the T treated group but not in the untreated group. They also recorded significant improvement in the IIEF-EF in the T-treated group, but not in the untreated group, and was maintained throughout the follow-up period

Table 3 (*continued*)

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Study	Population	Design	Type of surgery	Dosages, routes, types of testosterone/androgen suppression therapy	Duration of treatment	Outcomes
Yassin *et al.*, *J Sex Med*, 2014 (135)	261	Longitudinal registry	Metabolic syndrome	Intramuscular injections of 1,000 mg TU at day 1, at week 6, and every 3 months thereafter	Mean 4.25 years, with a maximum of 7 years	Long-term TRT in men with late-onset hypogonadism and ED reduced obesity parameters, improved metabolic syndrome and health-related quality of life
Rastrelli *et al.*, *Sex Med Rev*, 2019 (99)	423	Longitudinal registry	Sexual life	24.0% T gels, 41.5% injectable TU, 9.4% injectable T short acting, 4.9% chorionic gonadotropin, 1.2% mester-olone, 1.2% TU oral, 0.4% a selective estro-gen receptor modulator	–	After starting T, they reported an increase in all the domains of the IIEF-15, in the sexual and physical subdomains of the AMS as well as in the IPSS. Conversely, the untreated group reported a significant improvement, although lower than the treated group, only in the erectile function domain of the IIEF-15
Shigehara *et al.*, *Aging Male*, 2011 (113)	46	RCT	LUTS & BPH	250 mg of testosterone enanthate every 4 weeks	12 months	IPSS showed a significant decrease compared with baseline in the ART group. No significant changes were observed in the control group. The ART group also showed improvement in maximum flow rate and voided volume, whereas no significant improvements were observed in the controls. PVR showed no significant changes in either group. ART group showed significant enhancement of mean muscle volume, whereas no significant changes were seen in the controls
Hofer *et al.*, *Urology*, 2016 (121)	53	Cross sectional	AUS	–	–	Men with low T levels are at a significantly higher risk to experience AUS cuff erosion. Appropriate counseling before AUS implantation is warranted and it is unclear whether T supplementation will mitigate this risk
Wolfe *et al.*, *Neurourol Urodyn*, 2021 (122)	161	Cross sectional	AUS	–	–	Low T concentration is an independent risk factor for AUS cuff erosion. Men with low T are more likely to present with cuff erosion, but there is no difference in time to erosion
McKibben *et al.*, *Urology*, 2018 (123)	113	Cross sectional	AUS	–	–	Nearly half of men with stress urinary incontinence undergoing AUS placement present with low serum T. While AUS cuff erosion appears to be more common in men with low T, further study is needed to determine if treating low serum T will reduce cuff erosion rates
Hofer *et al.*, *Urology*, 2017 (117)	1200	Case control	Urethral stricture	–	–	Men with low T levels showed reduced AR expression and lower vessel counts in periurethral tissue samples of urethral strictures. The results indicated a mechanistic relationship between low T levels and decreased periurethral vascularity that may contribute to urethral atrophy in patients with urethral strictures

TRT, testosterone replacement therapy; ED, erectile dysfunction; HR, hazard ratio; AST, androgen suppression therapy; BCa, bladder cancer; LUTS, lower urinary tract symptoms; CRP, C-reactive protein; IPSS, international prostate symptom score; PSA, prostate specific antigen; RP, radical prostatectomy; T, testosterone; TU, testosterone undecanoate; RBV, residual bladder volume; AMS, aging males' symptoms scale; IIEF-EF, international index of erectile function – erectile function domain; IIEF-15, international index of erectile function-15; ART, androgen replacement therapy; PVR, post-void residual; AUS, artificial urinary sphincter; AR, androgen receptor.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-308/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-308/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-308/coif). JMH serves as an unpaid editorial board member of *Translational Andrology and Urology* from August 2021 to July 2023. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Fendereski K, Ghaed MA, Calvert JK, Hotaling JM. Hypogonadism and urologic surgeries: a narrative review. Transl Androl Urol 2022;11(7):1045-1062. doi: 10.21037/tau-22-308

