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ORIGINAL ARTICLE

Testosterone replacement therapy is associated with an increased risk of urolithiasis

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Abstract

Purpose To determine whether TRT in men with hypogonadism is associated with an increased risk of urolithiasis.

Methods We conducted a population-based matched cohort study utilizing data sourced from the Military Health System Data Repository (a large military-based database that includes beneficiaries of the TRICARE program). This included men aged 40–64 years with no prior history of urolithiasis who received continuous TRT for a diagnosis of hypogonadism between 2006 and 2014. Eligible individuals were matched using both demographics and comorbidities to TRICARE enrollees who did not receive TRT. The primary outcome was 2-year absolute risk of a stone-related event, comparing men on TRT to non-TRT controls.

Results There were 26,586 pairs in our cohort. Four hundred and eighty-two stone-related events were observed at 2 years in the non-TRT group versus 659 in the TRT group. Log-rank comparisons showed this to be a statistically significant difference in events between the two groups ($p < 0.0001$). This difference was observed for topical ($p < 0.0001$) and injection ($p = 0.004$) therapy-type subgroups, though not for pellet ($p = 0.27$). There was no significant difference in stone episodes based on secondary polycythemia diagnosis, which was used as an indirect indicator of higher on-treatment testosterone levels ($p = 0.14$).

Conclusion We observed an increase in 2-year absolute risk of stone events among those on TRT compared to those who did not undergo this hormonal therapy. These findings merit further investigation into the pathophysiologic basis of our observation and consideration by clinicians when determining the risks and benefits of placing patients on TRT.

Keywords Hypogonadism · Male aging · Testosterone · Urinary calculi · Urolithiasis

Introduction

Male hypogonadism is a syndromic diagnosis characterized by low serum testosterone levels and at least one associated clinical sign or symptom of testosterone deficiency [1]. Sexual dysfunction, decreased muscle mass, decreased bone mineral density, and mood changes might accompany low testosterone and may affect up to a quarter of middle-aged and elderly men [2]. While testosterone replacement therapy (TRT) has historically been utilized in individuals

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with pathologic disruption of the pituitary–hypothalamus–gonadal axis, indications for TRT have more recently expanded to include men with symptoms of hypogonadism and serum testosterone levels below reference ranges for young men, but without evidence of testicular or pituitary disease. Much of this broadening has been driven by middle-aged and older men with age-related or obesity-related decline who have non-specific symptoms.

Broadening of TRT indications has given way to an industry on the scale of 2 billion dollars in annual sales, an astounding 100-fold increase in magnitude over the preceding three decades [3]. Coincident with this widespread increase in prescription rate has been controversy regarding the risks, benefits, and appropriate indications for TRT use [4–6]. While such conversations regarding adverse effects of TRT often involve such potential risks as cardiovascular events, exacerbation of underlying prostate cancer, or obstructive sleep apnea, it has also been suggested that there may be an association between endogenous serum testosterone levels and risk of urolithiasis [7].

The potential role of testosterone in urolithiasis can be rationalized by gender differences observed in ecological data, as indeed there exists a persistent male predominance among stone formers [8]. Animal models have also lent support to this idea. In rat models fed with lithogenic ethylene glycol, testosterone was associated with stone formation secondary to increased renal oxalate excretion and decreased citrate excretion [9]. Furthermore, rat models have also shown that testosterone mediates renal handling of calcium by inhibiting expression of TRPV5 channels, which play a key role in calcium reabsorption within the kidney [10]. Connecting these findings to a clinically significant association between testosterone and urolithiasis has proven more difficult, however, with correlations having been identified primarily among small patient populations [11]. Data utilizing large datasets are decidedly more limited, and no study to date has specifically studied the effect of TRT on urolithiasis. As a result, in this study, we set out to compare the incidence of urolithiasis in a cohort of men using TRT with a cohort of age- and comorbidity-matched controls.

Methods

Study population and variables

This was a retrospective matched cohort study utilizing data sourced from the Military Health System Data Repository (MDR), a large military-based database that includes beneficiaries of the TRICARE program. This program contains over 9 million individuals and comprises active members of the US Uniformed Services, retirees, and their family members, and is administrated by the Defense Health Agency. Only 20% of covered individuals are active US military personnel.

General details of patient selection for this study have been published previously [12]. Briefly, inclusion criteria were men aged 40–64 with a clinical diagnosis of low testosterone who received continuous TRT during the study period of April 1, 2006, through March 31, 2014. To establish "continuous" treatment for outpatient administration, we assessed the time between first and last TRT prescription and ensured that the supply could not fall under 6 months. Exclusion criteria were TRICARE enrollment of less than 1 year, less than 180-day washout period (i.e., start of TRT prior to October 1, 2006), history of prior urinary stones, and use of oral testosterone given that it is not approved for use in the USA. This left 26,586 men in the treatment cohort, all of whom were matched with men of the same inclusion and exclusion criteria aside from use of TRT (Appendix 1). Matching was performed on the basis of common birth year, race, primary policy holder rank, marital status, residency region (Northeast, Midwest, West, and South) and comorbidities using the Charlson comorbidity index (CCI). Individuals who did not have a match based on these characteristics were dropped from the analysis. Relevant ICD-9 diagnostic and CPT procedural codes utilized for cohort selection and matching are detailed in Appendix 2. Because testosterone has a dose-dependent stimulatory effect on erythropoiesis and results in coincident rise in serum hemoglobin and hematocrit, we identified patients within our cohort with a diagnosis of secondary polycythemia to serve as an indirect indicator of higher on-treatment testosterone levels [13].

For each patient, age, race, marital status, and region were obtained. As has been done in prior military-based research, military rank was used as a proxy for socioeconomic status [14].

The primary outcome was 2-year absolute risk of a stone-related event. For this, we utilized a comprehensive list of diagnosis and procedure (extracorporeal shock wave lithotripsy, ureteroscopy with lithotripsy, or percutaneous nephrolithotomy) codes related to urolithiasis that is defined in Appendix 2 [15, 16]. We compared event-free survival (for urolithiasis) as a function of time and calculated 2-year absolute risk of event. Secondary outcomes related to stone events included time to first diagnosis of urolithiasis and total number of stone events during the study period.

Statistical analysis

A three-step process was utilized to define and match a non-TRT group to our experimental cohort. First, all eligible male TRICARE enrollees were matched to the TRT users in our cohort based on birth year to generate artificial "twin pairs." Second, for each pair, the starting point for creating the non-TRT pool was matching the date of the first

TRT prescription date. For eligible matched pairs, baseline comorbidities and risk factors were assessed. Lastly, the final cohort was generated on the basis of one-to-one match without replacement based on race, baseline conditions, and risk factors.

Unweighted Kaplan–Meier curves were employed to compare event-free survival between the treatment groups. We used a log-rank test to evaluate significance. Absolute 2-year risk of urolithiasis-related event was calculated, along with 95% confidence intervals. A sub-analysis was performed by therapy type, comparing incidence of stone events specifically among pellet, injection, and topical therapy types to incidence among their respective matched non-TRT controls. Incidence of overall stone events among TRT patients with and without diagnosis of secondary polycythemia was compared with the Chi-squared test.

All statistical testing was two-sided with a level of significance of 0.05. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina). Institutional review board approval was obtained from the Uniformed Services University of the Health Sciences, as well as the Center for Surgery and Public Health at Brigham and Women's Hospital. A data use agreement with the TRICARE Management Activity Privacy Office was also secured.

Results

Cohort characteristics

Prior to matching, there were 26,887 men who had undergone TRT and were eligible for the study, based on the aforementioned inclusion and exclusion criteria. Matching yielded 53,172 individuals (26,586 "twin pairs") who were appropriately matched on demographic parameters and CCI. The mean age was 52.03 years, with the majority being of white ethnicity. 90.04% were married, and 70.26% were located in the South. With respect to military rank, senior enlisted was the most common at 76.10%. 78.73% were characterized by a CCI of zero, while 15.69% had a CCI of one. Further details on the study cohort are given in Table 1. Median follow-up was 36 months in the TRT group and 37 months in the non-TRT group.

Method of stone diagnosis by procedural or diagnostic code is shown in Table 2. A total of 1853 stone events were diagnosed clinically—794 stone events in the no-treatment group and 1059 stone events in the TRT group. Procedural diagnosis of stones was performed most commonly either by extracorporeal shock wave lithotripsy (51 in the non-TRT group and 67 in the TRT group; total 118) or by ureteroscopy with lithotripsy (46 in the non-TRT group and 75 in the TRT group; total 121). The least common method of identifying stone events was percutaneous nephrolithotomy, which accounted for 4 stone occurrences in the no-treatment group and 1 in the TRT group.

Event-free survival

The constructed Kaplan–Meier curves in Fig. 1 illustrate event-free survival in both the TRT and non-TRT groups. Four hundred and eighty-two incident stone events were observed at 2 years in the non-TRT group versus 659 in the TRT group ($p < 0.0001$ by log-rank test). Median time to stone diagnosis was 544 days in the non-TRT group versus 528 days in the TRT group.

Stone events and testosterone formulation

Table 3 shows the proportion of patients with urolithiasis of stone events according to type of TRT. Nine individuals with stone events (5.39%) were observed in the group receiving testosterone pellets compared to those who did not receive pellets ($p = 0.27$ by Chi-squared test). There were 218 (5.12%) events in the testosterone injection group, and 655 (3.47%) in the topical formulation group, which corresponded to a statistically significant increased risk of stone events among those who received testosterone injections or topical testosterone formulations compared to those who did not receive injections or topical formulations ($p < 0.05$ by Chi-squared test).

Secondary polycythemia sub-analysis

Secondary polycythemia was diagnosed in 493 patients receiving testosterone replacement therapy. Twenty-six patients in the secondary polycythemia group experienced stone events (5.27%) versus 1035 (3.97%) in the no polycythemia group (Appendix 3). This did not correspond to a statistically significant difference in stone episodes based on polycythemia diagnosis ($p = 0.14$).

Discussion

TRT is indicated in men with organic hypogonadism but is widely prescribed for age-related decline in serum testosterone levels even though benefits are modest [17] and risks of TRT, such as erythrocytosis, obstructive sleep apnea, exacerbation of prostate cancer and cardiovascular disease, remain [18–20]. Association between testosterone and urolithiasis is an emerging field and focus of research [11]. In this first study to characterize the association of TRT with incidence of urolithiasis in men with low testosterone, we report a statistically significant increase in risk of stone events in men on testosterone. In particular, there were 659 stone events at 2-year follow-up in our TRT group versus 482 in a cohort of

Table 1 Characteristics of 26,586 men in TRICARE diagnosed with hypogonadism who underwent testosterone replacement therapy between 2006 and 2014

Mean (SD)		Range
Age		
52.03 (6.89)		40–64
	Frequency	Percent
Race		
White	18,581	69.89
Asian	774	2.91
African-American	4581	17.23
Hispanic	867	3.26
Native American	210	0.79
Other	467	1.76
Missing	1106	4.16
Rank		
Junior enlisted	400	1.50
Senior enlisted	20,233	76.10
Junior officer	686	2.58
Senior officer	4230	15.91
Warrant officer	1037	3.90
Marital status		
Married	23,939	90.04
Single	2647	9.96
Region		
Midwest	2141	8.05
Northeast	540	2.03
South	18,679	70.26
West	5156	19.39
Missing	70	0.26
Charlson comorbidity index		
0	20,932	78.73
1	4172	15.69
2	844	3.17
3	435	1.64
4	59	0.22
5	63	0.24
6	34	0.13
7	13	0.05
8	25	0.09
9	6	0.02
10	3	0.01

matched controls. This difference persisted for topical and injection therapy-type subgroups.

Stone formation is influenced by a milieu of epidemiologic and environmental factors, including age, sex, ethnic background, fluid intake, medical conditions, and diet. Despite this broad range of influencing factors, studies historically report up to a 3.2:1 male predilection for urolithiasis. A contemporary cross-sectional analysis of National Health and Nutrition Examination Survey (NHANES) data showed overall stone prevalence of 8.8% in the USA, with 10.6% (95% CI 9.4–11.9%) prevalence among men and 7.1% (6.4–7.8%) among women [8]. Specific associations between hyperandrogenicity and nephrolithiasis have been noted at the case study level and subsequently suggested or validated in small studies [7, 11, 21, 22]. In a pilot study conducted among 55 Americans, a difference in total serum testosterone was suggested in patients with urolithiasis versus controls, though the observed difference did not meet the threshold of statistical significance (median serum testosterone = 384 vs. 346 ng/dl; $p = 0.051$) [7]. A similar case–control study of 108 Indian men that compared 78 individuals with urolithiasis to 30 controls did find significantly higher testosterone levels in the urolithiasis group compared to controls ($p = 0.02$) [22].

Laboratory-based investigations of the molecular processes underlying calcium oxalate stone formation have furthered the notion that testosterone may indeed play a role in the promotion of lithogenesis. In 24-h urine studies of mice with and without orchiectomy and testosterone replacement, testosterone has been shown to increase urinary calcium excretion via inhibition of TRPV5-mediated active renal calcium transport [10]. Furthermore, studies of mice with altered levels of sex hormones and ethylene glycol loading have shown that testosterone enhances the activity of glycolate oxidase (GO) to increase urinary oxalate levels, while concurrently decreasing excretion of crystal inhibitors citrate and magnesium [23, 24]. While differences in GO activity between male and female rats are not thought to be clinically significant, animal studies have reported a greater degree of hyperoxaluria and urolithiasis in normal versus castrated male rats [23, 25, 26]. In addition to promoting a lithogenic urinary environment, testosterone also promotes lithogenesis by modulating renal expression of osteopontin

Table 2 Occurrence of stone events by diagnosis or procedure among testosterone replacement therapy (TRT) and non-TRT groups of men in TRICARE, 2006–2014

Stone event	Non-TRT group	TRT group	Total
Extracorporeal shock wave lithotripsy	51	67	118
Ureteroscopy with lithotripsy	46	75	121
Percutaneous nephrolithotomy	4	1	5
Clinical diagnosis	794	1059	1853

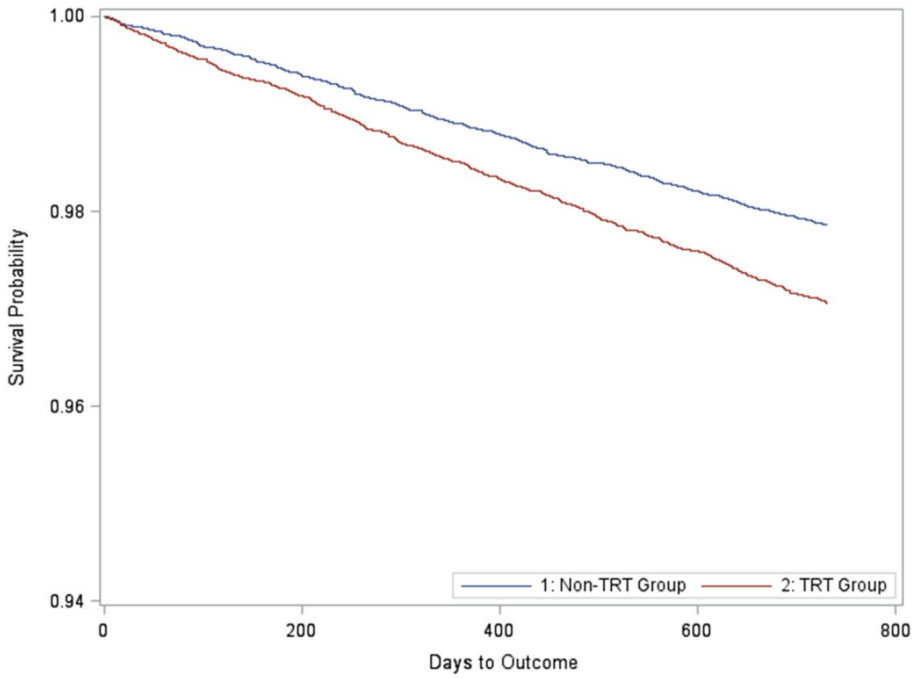

Fig. 1 Event-free survival relative to incident stone event for 26,586 men in TRICARE diagnosed with hypogonadism who underwent testosterone replacement therapy (TRT) between 2006 and 2014, compared to a matched non-TRT group

Table 3 Occurrence of stone events by testosterone therapy type for men diagnosed with hypogonadism in TRICARE, 2006–2014

Testosterone replacement therapy type	Individuals receiving therapy	Individuals with stone event	Percent with stone event (%)	*p* value
Pellet	167	9	5.39	0.27
Injection	4259	218	5.12	0.004
Topical	18,895	655	3.47	< 0.0001

and alpha-enolase, resultantly aiding in calcium oxalate crystal formation and adhesion, respectively [27–30].

Our study significantly adds to the available literature regarding testosterone and stone incidence given it is the first to specifically study TRT, utilizes a large population relative to prior studies, and employs matched cohort methodology that utilizes demographic, socioeconomic, and comorbidity variables to achieve appropriate comparative pairs. Certain limitations in our study, however, should be acknowledged. First, because this is a study exclusively of TRICARE data, our findings may lack some degree of generalizability outside of former (and current) service members and their immediate families. Second, we lack certain relevant pieces of patient-level data that influence stone formation such as body mass index, etiology of low testosterone, family history of stones, degree of physical activity, and medications. Because CCI was used in matching as a proxy for underlying health status, however, the impact of medications was minimized. Third, though we attempted to control for as many possible variables in our matching process, unmeasured confounders may exist, and our design remains inferior to a study of true randomized design. Fourth, while the primary endpoint of this study was time to first diagnosis of urolithiasis, it can be argued that stones requiring surgical intervention are more meaningful to patients rather than clinical stone diagnosis. However, the present study was not powered to assess the relationship of testosterone with surgical stone episodes alone. Fifth, though patients with a prior history of urolithiasis were excluded from the study, it cannot conclusively be determined that testosterone therapy implementation preceded stone formation given that patients did not systematically undergo imaging prior to starting therapy. Sixth, given that men on testosterone therapy may comparatively receive more healthcare services and undergo additional diagnostic tests, they may be more likely to have subclinical stones detected and therefore bias our results. Seventh, we were unable to determine testosterone dosing or correlate to specific serum testosterone levels. However, we did not find an association between our indirect indicator of higher on-treatment testosterone levels (secondary polycythemia) and stone incidence. Lastly, our follow-up was limited and clinically meaningful differences may emerge beyond the time period considered in this study.

In conclusion, controversy regarding the various risks of TRT persists. However, in this large retrospective cohort study, we establish a statistically significant association

between TRT and stone events at 2-year follow-up. Given this is the first study to specifically examine the relationship of TRT with stone events, these data should be considered alongside other known risks and benefits as clinicians select appropriate patients for implementation of TRT.

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Author contributions TRM, M-TI, TK, SB, and Q-DT developed the protocol/project, were involved in data collection or management, analyzed and interpreted the data, and wrote/edited the manuscript. NKK developed the protocol/project, was involved in data collection or management, analyzed the data, and wrote/edited the manuscript. APC, MNK, NB, GEH, and AHH analyzed and interpreted the data and wrote/edited the manuscript. WJ analyzed the data and wrote/edited the manuscript.

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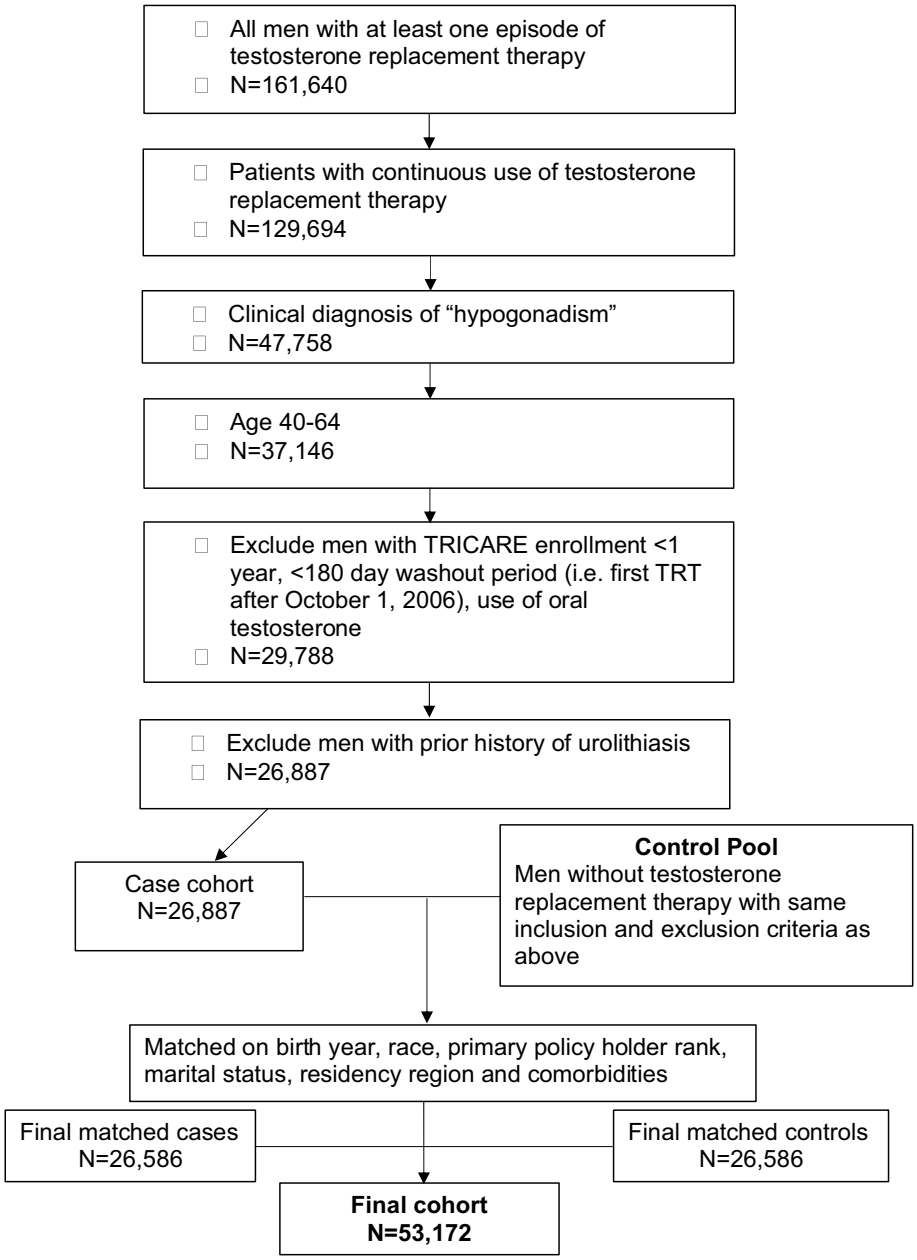
Compliance with ethical standards

Conflict of interest Dr. Basaria reports receiving consulting fees from Eli Lilly and Takeda Pharmaceuticals. Dr. Trinh reports receiving consulting fees from Bayer, Astellas, and Janssen. All other authors have nothing to disclose.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

Appendix 1: Study cohort selection and matching



Appendix 2: Codes for diagnoses and procedures

Diagnosis	ICD-9 diagnosis	
Testicular dysfunction	257.1–257.9	
Procedure	ICD-9 procedure	HCPCS/CPT
Testosterone pellet; 75 mg		S0189/11980
Injection, testosterone enanthate and estradiol valerate, up to 1 cc		J0900
Injection, testosterone cypionate and estradiol cypionate, up to 1 ml		J1060
Injection, testosterone cypionate, up to 100 mg		J1070
Injection, testosterone cypionate, 1 cc, 200 mg		J1080
Injection, nandrolone decanoate, up to 50 mg		J2320
Injection, testosterone enanthate, up to 100 mg		J3120
Injection, testosterone enanthate, up to 200 mg		J3130
Injection, testosterone suspension, up to 50 mg		J3140
Injection, testosterone propionate, up to 100 mg		J3150
Unclassified drug (Testopel)		J3490
Topical formulations *(by name)*		
AndroGel		
Axiron		
Fortesta		
Testim		
Vogelxo		
Oral formulations *(by name)*		
Android		
Methitest		
Oxandrin		
Oxandrolone		
Testred		

Indicators of urolithiasis	ICD-9	CPT
ESWL	98.5 Extracorporeal shock wave lithotripsy	50590 Lithotripsy, extracorporeal shock wave
	98.51 Extracorporeal shock wave lithotripsy of the kidney, ureter and/or bladder	S0400 Global fee for extracorporeal shock wave lithotripsy treatment of kidney stone(s)
Lithotripsy		52352 Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with removal or manipulation of calculus
		52353 Cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy
Nephrolithotomy (percutaneous and open)	55.03 Nephrostomy	50060 Nephrolithotomy; removal of calculus
		50065 Nephrolithotomy; secondary surgical operation for calculus
		50070 Nephrolithotomy; complicated by congenital kidney abnormality
		50075 Nephrolithotomy; removal of large staghorn calculus filling renal pelvis and calices
		50080 Percutaneous nephrostolithotomy or pyelostolithotomy, up to 2 cm
		50081 Percutaneous nephrostolithotomy or pyelostolithotomy, over 2 cm
Urinary calculi	274.11 Uric acid nephrolithiasis	
	592 Calculus of kidney and ureter	
	592.1 Calculus of ureter	
	592.0 Calculus of kidney—nephrolithiasis not otherwise specified	
	592.9 Urinary calculus, unspecified	

Appendix 3: Occurrence of stone events among those diagnosed with secondary polycythemia within the testosterone replacement therapy cohort of hypogonadal men in TRICARE, 2006–2014

	Number of individuals	Individuals with stone event	Percent with stone event
No polycythemia diagnosis	26,093	1035	3.97
Polycythemia diagnosis	493	26	5.27

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