Sex Steroid Hormone Levels May Not Explain Gender Differences in Development of Nephrolithiasis

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Abstract

Objectives: To determine whether serum sex steroid hormone levels, or the subsequent change in those levels over time, represent a risk factor for the development of nephrolithiasis in men.

Methods: We retrospectively identified patients participating in a long-term cohort study (Rochester Epidemiology Project) in Olmsted County, Minnesota. Patients had previously undergone baseline detailed clinical examination and sex steroid hormone studies, including estradiol, testosterone, and bioavailable testosterone. Patients were followed on a biennial basis. Records were then reviewed to assess for formation of nephrolithiasis.

Results: We identified 684 patients, with a median follow-up for stone formation of 12.8 years. All 684 patients had measurement of testosterone, of which 78.9% were in normal range. Five hundred eighteen men had baseline-free testosterone, of whom 88.6% were normal. Three hundred seventy-one patients had baseline estradiol, of whom 88.7% were normal. One hundred two men (14.9%) were found to have stones, with 61 of those (59.8%) occurring before first hormone measurement and 41 (40.2%) occurring after. On multivariate analysis, there was no significant association of serum hormones with nephrolithiasis, although a trend toward higher baseline testosterone and stones was seen (odds ratio [OR] 1.29; 95% confidence intervals [CI] 0.71, 2.33). Using a time-to-event for incident stone formation, we found no significant association of baseline hormones or percentage change in hormone levels over time with risk of stones.

Conclusion: We found no significant association of sex steroid hormone levels with the risk of nephrolithiasis formation in men, although a weak trend toward an increased risk with elevated testosterone was seen.

Introduction

NEPHROLITHIASIS IS A COMMON CAUSE of morbidity, with an average lifetime prevalence of about 5% in the American population.¹ Rates of nephrolithiasis have been found to be significantly higher among males vs comparable aged females, with prevalence rates as high as 13% in some age groups, although this gap appears to be narrowing.^{1,2} Nonetheless, males still comprise a significant majority of kidney stone patients.^{1–3} The causes of this gender difference in prevalence of nephrolithiasis are largely unknown. Several studies using animal models have examined the hypothesis that hormonal differences may impact stone risk, and in particular found an association between testosterone and increased oxalate excretion with decreased citrate excretion.^{4–8}

While animal models have demonstrated an association between sex steroid hormone levels and lithogenesis, this relationship remains less clear among humans. To date, a small number of studies have explored the impact of testosterone on stones, with limited number of patients.^{9–13} The

objective of our study, therefore, was to determine whether baseline serum sex steroid hormone levels or subsequent change in those levels represents a risk factor for the development of nephrolithiasis in men.

Materials and Methods

Overview

We conducted a retrospective cohort study to examine the association between serum sex steroid hormone levels, as well as changes in these levels and the subsequent risk of stone formation, among men participating in the long-term cohort study entitled: “Natural History of Prostatism: The Olmsted County Study.” Details related to the development of the study cohort have been previously published.^{14,15} In brief, a randomly sampled population-based group of white men between 40 and 79 years residing in Olmsted County, Minnesota, in 1990 was identified through the Rochester Epidemiology Project (REP).¹⁶ Men who had a history of

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prostate or bladder surgery, urethral surgery or stricture, or medical or other neurologic conditions that could affect normal urinary function were excluded. Subsequently, 3,874 men were asked to join the study and 2,115 (55%) agreed to participate. A 25% random subsample of men was also invited to participate in a detailed clinical urologic examination, which included provision of a blood sample for prostate-specific antigen and hormone measurements. All blood samples were drawn in the morning. A total of 475 (88%) men agreed to participate in this more intensive examination. The cohort was actively followed on a biennial basis for 16 years using a protocol similar to the initial examination. During the second and third round of visits, men who did not participate in the follow-up were replaced by men randomly selected from the community, after being screened for the exclusion criteria used at baseline ($n=332$). Of the replacement men, 158 were added to the clinic subset. Since that time, the study has been maintained as a closed cohort.

Methods for measuring sex steroid hormone levels have been previously described.^{17,18} Normal range values for estradiol were 10–40 pg/mL, for testosterone 240–950 ng/dL, and for bioavailable testosterone 61–213 ng/dL for ages 40–49, 50–190 ng/dL for ages 50–59, and 40–168 ng/dL for ages of 60 or older. Sex steroid hormone levels were available for 648 men.

All men who participated in this study agreed to allow their medical records to be abstracted for details related to urologic disease. Dates of stone formation were routinely abstracted from the medical records using International Classification of Diseases, Ninth Revision (ICD-9) codes 592, 594, and 274.11. Comprehensive medical records were then reviewed by a dedicated nurse abstractor who validated stone formers and then collected details of their care. A validated incident symptomatic stone event had to either have documentation of stone recovery after passage or identification of a stone in the ureter or renal pelvis consistent with obstruction or intermittent obstruction.

Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC). Bivariate associations of

patient characteristics were tested by the Pearson chi-square or Fischer's exact test where appropriate. Multivariate analysis was performed to test the association of hormone levels with risk of nephrolithiasis.

Results

Clinical characteristics of the study population are shown in Table 1. Of the 684 men identified, 102 (15.7%) had a stone event. All 684 men with at least one measurement of sex steroid hormone levels had testosterone measured, 489 had estradiol measured, and 636 had bioavailable testosterone measured. Of 371 men with a baseline estradiol measure, 329 (88.68%) had levels within normal range. Baseline testosterone levels were available for all 530 men, of which 418 (78.87%) were within normal range. During the course of the study, there was a median annual increase in estradiol levels, and a median decrease in both testosterone and bioavailable testosterone levels among stone formers and nonstone formers. There was no significant difference between men who did and did not form stones with regard to mean baseline age, history of smoking, body-mass index, median baseline hormone levels, and median annual percentage change in hormone levels.

The median length of follow-up for assessment of stone formation was 12.8 years (interquartile [IQR] 5.4, 14.2). Among a total of 102 men who formed nephrolithiasis, 61 (59.8%) developed their first episode of nephrolithiasis before their first hormone measure and 41 (40.2%) had incident stone formation after hormone measurement. The odds of all-time occurrence of nephrolithiasis for age, smoking history, body-mass index greater than 30 kg/m², and baseline sex steroid hormone levels are summarized in Table 2. On multivariable analysis, there was no significant association of serum hormone levels with all-time risk of nephrolithiasis. However, there was a trend toward an increased risk for baseline testosterone levels (odds ratio [OR] 1.29; 95% confidence intervals [CI] 0.71, 2.33) as well as baseline

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

	<i>Nephrolithiasis (all time), N=102</i>		<i>No nephrolithiasis, N=546</i>		<i>p</i>
	<i>N or median</i>	<i>% or IQR</i>	<i>N or median</i>	<i>% or IQR</i>	
Baseline characteristic					
Age, years (<i>N</i> , %)					0.79
40–49	29	28.43	157	28.75	
50–59	25	24.51	152	27.84	
60–69	31	30.39	141	25.82	
70+	17	16.67	96	17.58	
Smoking history (<i>N</i> , %)	57	55.88	345	63.19	0.16
BMI (median, IQR), kg/m ²	28.35	25.49, 30.99	27.42	25.30, 30.26	0.21
BMI ≥30 kg/m ²	34	33.33	155	28.39	0.31
Estradiol (median, IQR), pg/mL	24.74	21.83, 32.27	24.02	21.83, 32.12	0.70
Testosterone (median, IQR), ng/dL	347.24	255.40, 454.89	332.07	261.88, 434.48	0.68
Bio-T (median, IQR), ng/dL	94.79	70.32, 122.23	92.47	66.82, 123.48	0.47
Annual percentage change					
Estradiol (median, IQR)	0.13	–0.32, 0.82	0.13	–0.33, 0.61	0.47
Testosterone (median, IQR)	–0.23	–0.51, 0.07	–0.19	–0.49, 0.12	0.58
Bio-T (median, IQR)	–1.68	–1.92, –1.45	–1.66	–1.92, –1.46	0.55

Bio-T=bioavailable testosterone; BMI=body mass index; IQR=interquartile range.

TABLE 2. ODDS OF NEPHROLITHIASIS (ALL TIME) FOR BASELINE CHARACTERISTICS AND SEX STEROID HORMONE LEVELS WHEN ANALYZED CONTINUOUSLY

Characteristic	Unadjusted	Multivariable adjusted ^a
	OR (95% CI)	OR (95% CI)
Age		
40–49	Reference	—
50–59	0.89 (0.50, 1.59)	—
60–69	1.19 (0.68, 2.07)	—
70+	0.96 (0.50, 1.84)	—
Smoking history	0.74 (0.48, 1.13)	—
BMI ≥ 30 kg/m ²	1.26 (0.80, 1.98)	—
Baseline estradiol	1.03 (0.45, 2.35)	0.93 (0.40, 2.16)
Baseline testosterone	1.15 (0.66, 2.02)	1.29 (0.71, 2.33)
Baseline Bio-T	1.28 (0.80, 2.05)	1.48 (0.87, 2.53)

^aAdjusted for baseline age, smoking history, and BMI.
OR = odds ratio; CI = confidence interval.

bioavailable testosterone (OR 1.48; 95% CI 0.87, 2.53), while baseline estradiol showed a trend toward protection against nephrolithiasis (OR 0.93; 95% CI 0.40, 2.16). Similarly, when hormone levels were separated into normal (reference range), below normal, or above normal, no significant difference was identified with regard to all-time risk of nephrolithiasis (Table 3). However, again, a similar trend was found toward testosterone increasing the risk of nephrolithiasis and estradiol decreasing the risk of nephrolithiasis. Next, we analyzed the subset of 41 men who

TABLE 3. ODDS OF NEPHROLITHIASIS (ALL TIME) FOR BASELINE SEX STEROID HORMONE LEVELS WHEN COMPARING ELEVATED OR LOW LEVELS WITH NORMAL VALUES

Characteristic	Unadjusted	Multivariable adjusted ^a
	OR (95% CI)	OR (95% CI)
Baseline estradiol		
Within normal range	Reference	Reference
Below normal range	—	—
Above normal range	1.04 (0.47, 2.33)	0.95 (0.42, 2.12)
Baseline testosterone		
Within normal range	Reference	Reference
Below normal range	1.28 (0.77, 2.11)	1.22 (0.73, 2.04)
Above normal range	5.69 (0.35, 91.94)	5.73 (0.34, 96.66)
Baseline Bio-T		
Within normal range	Reference	Reference
Below normal range	0.33 (0.08, 1.39)	0.32 (0.08, 1.38)
Above normal range	1.59 (0.66, 3.81)	1.81 (0.74, 4.42)

^aAdjusted for baseline age, smoking history, and BMI.

formed incident nephrolithiasis after the first hormone measure. Using a time-to-event method (Cox model) in this subgroup, we assessed for risk of new stone formation (Table 4). We found no significant risk increase associated with baseline hormone levels or annual percentage change of hormone levels with regard to testosterone, bioavailable testosterone, and estradiol.

Discussion

Previous animal models have demonstrated a link between testosterone and stone formation, raising speculation that testosterone may contribute to the observed increased incidence of stones among men.^{4,5,7,8} This association among humans, however, has remained inadequately described. Watson et al., in their series of 55 patients, found that subjects with nephrolithiasis had a trend toward higher serum testosterone levels (423.48 vs 363.82 ng/dL, $p=0.19$), but not free testosterone levels (60.51 vs 58.61, $p=0.75$).¹¹ Although this trend toward the association of higher testosterone with stones was nonsignificant, they concluded that their findings largely supported the association of testosterone with lithogenesis.

Additional studies have identified a significant link between testosterone levels and urolithiasis.^{12,13} Li et al. investigated the relationship of renal stones with plasma free and total testosterone as well as the presence of upregulated androgen receptors on biopsy of renal tissue among 68 Chinese men.¹² Their study included men 22–39 years of age with stones who underwent percutaneous nephrolithotomy (PCNL) with an associated renal biopsy, and compared serum hormone levels with healthy controls of similar age, as well as compared biopsy specimens obtained at the time of PCNL with autopsy specimens of previously healthy patients of similar age to assess for upregulation of androgen receptors. Their group found that men who had developed nephrolithiasis had higher serum testosterone and free testosterone levels ($p<0.001$ for each) than normal controls. Furthermore, they found that androgen receptors were significantly upregulated among patients with stone formation. However, it is worth noting that their study group represented a healthy group of young men, and that the differences detected may become dilute in an older population such as ours with higher comorbidities.

In contradistinction to the findings by Li et al., a recent study by Otunctemur et al. evaluated 513 men over the age of 18 years, evaluating the relationship of urolithiasis with metabolic syndrome and testosterone levels.¹³ Using a cut-point for low serum testosterone of <285 ng/dL, they found that lower serum testosterone was associated with an increased risk of stone formation ($p=0.000$; OR 2.93). Given that both cohorts examined relatively young populations, it is striking to note the degree to which findings differed.

In comparison, we found in a study of over 600 men a trend toward higher testosterone being lithogenic (OR 1.48; 95% CI 0.87, 2.53). While our study yielded negative results, namely that we did not find any significant association of sex hormones with the risk of nephrolithiasis, it offers an important contribution to the literature. While Li et al. found a significant association of testosterone with stone formation among a select population,¹² these results were not confirmed by Watson et al. in their series of 55 patients¹¹ and were contradicted by Otunctemur and colleagues.¹³ While it is

TABLE 4. RISK OF INCIDENT NEPHROLITHIASIS

Characteristic	Unadjusted	Multivariable adjusted ^a
	HR (95% CI)	HR (95% CI)
Age		
40–49	Reference	—
50–59	0.51 (0.20, 1.31)	—
60–69	1.34 (0.64, 2.80)	—
70+	1.04 (0.40, 2.68)	—
Smoking history	0.69 (0.37, 1.27)	—
BMI ≥30 kg/m ²	1.01 (0.51, 2.03)	—
Estradiol		
Baseline estradiol	0.35 (0.07, 1.80)	0.31 (0.06, 1.64)
Baseline testosterone	1.00 (0.45, 2.20)	1.01 (0.44, 2.34)
Baseline Bio-T	0.77 (0.40, 1.50)	0.86 (0.40, 1.85)
Estradiol annual percentage change	0.71 (0.40, 1.24)	0.74 (0.42, 1.31)
Testosterone annual percentage change	0.79 (0.42, 1.49)	0.49 (0.11, 2.17)
Bio-T annual percentage change	1.61 (0.63, 4.14)	2.09 (0.46, 9.46)
Estradiol annual percentage change (upper 25th percentile)	0.63 (0.22, 1.82)	0.67 (0.23, 1.96)
Testosterone annual percentage change (upper 25th percentile)	1.01 (0.52, 1.96)	1.07 (0.38, 2.97)
Bio-T annual percentage change (upper 25th percentile)	1.39 (0.69, 2.77)	1.25 (0.52, 2.99)
Estradiol annual percentage change		
Lower 20th percentile	Reference	Reference
Middle 60th percentile	0.80 (0.33, 1.95)	0.83 (0.34, 2.05)
Upper 20th percentile	0.50 (0.13, 1.91)	0.55 (0.14, 2.20)
Testosterone annual percentage change		
Lower 20th percentile	Reference	Reference
Middle 60th percentile	0.99 (0.43, 2.30)	1.35 (0.24, 7.45)
Upper 20th percentile	0.78 (0.29, 2.11)	0.87 (0.12, 6.24)
Bio-T annual percentage change		
Lower 20th percentile	Reference	Reference
Middle 60th percentile	1.33 (0.60, 2.96)	1.53 (0.60, 3.90)
Upper 20th percentile	1.73 (0.67, 4.51)	1.84 (0.51, 6.64)
Baseline testosterone <300 ng/dL	1.07 (0.57, 2.00)	1.06 (0.56, 2.01)

^aAdjusted for baseline age, smoking history, and BMI.
HR = hazard ratio.

possible that their study was unable to detect a difference because of the number of patients enrolled, we similarly were unable to detect a significant difference with over 600 patients. This reinforces that, although sex steroid hormones may play a role in stone formation, it either extends beyond the simple measurement of serum values or represents a small-enough risk factor that it remained undetectable in our population and therefore would likely be clinically insignificant as a contributing factor. Based on this we feel that the evidence currently available would not support a role for the clinical manipulation of hormones to alter the risk of stone formation; namely, men with stones and hypogonadism should not be recommended to avoid testosterone replacement simply because of their history of stones.

We recognize the limitations of our study. First, it is retrospective in nature. Second, it included only patients as part of the REP study within Olmstead County, Minnesota, and the patients were exclusively Caucasian and, therefore, caution must be taken when generalizing to the overall population. Third, as the study used an existing data source from a population-based study, we were unable to expand our variables beyond those previously defined. Importantly, our study did not include men under the age of 40 nor assess the role of dihydrotestosterone and sex hormone binding globulin

in the development of urolithiasis. In addition, our cohort lacks an identification of stone type (calcium oxalate, calcium phosphate, uric acid) or any urinary parameters such as oxalate, which would be important to characterize with future studies. Finally, despite having a relatively large cohort of patients, we find that the power to detect a relative risk less than 2.2 was limited because of the fixed size of the cohort and subsequent number of events. Nonetheless, we feel our study adds clarity to the role of sex steroid hormones in urolithogenesis.

Conclusion

We found no significant association of sex steroid hormone levels with risk of nephrolithiasis formation in men. Although a weak trend was seen for an increased incidence of stones among men with elevated testosterone, such association, if true, is likely to be clinically insignificant and would not explain the increased incidence in nephrolithiasis seen in men.

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Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

CI = confidence interval
 IQR = interquartile range
 OR = odds ratio
 PCNL = percutaneous nephrolithotomy
 REP = Rochester Epidemiology Project