Association between low-testosterone and kidney stones in US men: The national health and nutrition examination survey 2011–2012

Emre Yucel, Stacia DeSantis, Mary A. Smith, David S. Lopez

A R T I C L E   I N F O

Keywords:
Kidney stones
men's health
Testosterone
NHANES
Obesity
Diabetes
Race/ethnicity
Dyslipidemia

A B S T R A C T

The purpose of this study was to determine the association between low-testosterone (total testosterone ≤ 3 ng/mL) and prevalence of kidney stones (KS) in men 20 years and older, and whether this varies by comorbidities, and race/ethnicity, and age. This was a cross-sectional study with data from the National Health and Nutrition Examination Survey (NHANES) 2011–2012 cycle. We found that men with low-testosterone had 41% lower odds of KS as compared to men without low-testosterone after multivariable adjustment (OR: 0.59, 95% CI 0.40–0.86). When stratified by obesity, obese men with low-testosterone had 59% lower odds of KS. When stratified by HDL, men with HDL ≥ 40 mg/dL and with low-testosterone had 40% lower odds of KS. When stratified by diabetes, men without diabetes with low-testosterone had 39% lower odds of KS, but the association was not significant in diabetic men with low-testosterone and other comorbidities. There were significant differences when stratified by race/ethnicity. Finally, when stratified by age, only the subgroup of men ≥ 40–< 60 years old with low-testosterone had 68% lower odds of KS (OR: 0.32, 95% CI: 0.16–0.67). The association between low-testosterone and KS was inversely related. Similar associations were identified when stratified by obesity, diabetes, dyslipidemia, race/ethnicity and age.

1. Introduction

Kidney stones (KS) induce substantial disease burden on men's health (CDC, 2011; L. and S., 2012). For example, prevalence increased from 6.3% (1988–1994) to 10.6% (2007–2010) in men (4.1% and 7.1% in women, respectively) (Scales et al., 2012; Stamatakis et al., 2003), and annual costs associated with KS was estimated to range between $5 billion (Ghani et al., 2014) and $10 billion (Litwin and Saigal, 2012) in the U.S. Although prevalence of KS is historically higher in men than women (Scales et al., 2012; Shoag et al., 2015; Stamatakis et al., 2003), we lack further evidence if there is an association between testosterone concentrations and KS (Scales Jr et al., 2016). Because testosterone concentrations are biologically higher in men than women (Vesper et al., 2015) and are associated with KS (Naghii et al., 2014; Otucetemur et al., 2015), we aimed to determine the association between low-testosterone (total testosterone ≤ 3 ng/mL) and KS in men. TT is the combination of bioavailable and sex hormone-binding globulin (SHBG)-bound testosterone.

KS was considered a multifactorial disease due to role thought to play by demographics (eg age, race/ethnicity), and comorbidities (eg diabetes, obesity, dyslipidemia) (Scales et al., 2012; Shoag et al., 2015). Such factors were also associated with change in total testosterone (TT) concentrations in men (Al Hayek et al., 2013; Calderon et al., 2016; Peskoe et al., 2015; Rohrmann et al., 2007). Obesity was associated with TT concentrations and with KS. For example, 45% of obese men (BMI ≥ 30 kg/m²) had low-testosterone (Peskoe et al., 2015), and obese men were 55% more likely to report KS (Scales et al., 2012). Diabetes was associated with TT concentrations (Calderon et al., 2016) and with KS (Scales et al., 2012). For example, TT concentrations were negatively correlated with diabetes (Calderon et al., 2016), and diabetic men were 59% more likely to have a history of KS (Scales et al., 2012). Dyslipidemia was associated with low TT concentrations (Haring et al., 2011; Thirumalai et al., 2015), and with KS (Kang et al., 2014; Masterson et al., 2015; Torricelli et al., 2014). For example, testosterone was inversely associated with dyslipidemia (Haring et al., 2011).

Race/ethnicity was associated with both KS and TT concentrations. Prevalence of low testosterone (TT concentrations < 3 ng/mL) was 17.7% in White, 1.7% in Black, and 2.4% in Hispanic men (Peskoe et al., 2015), and Hispanic men had TT concentrations significantly higher than those in White men (Rohrmann et al., 2007). Black men and Hispanic men were 63% and 40% less likely to have a history of KS than White men respectively (Scales et al., 2012). Age was associated with...
KS (Perinpam et al., 2015; Scales et al., 2012). KS prevalence was 10.8% (2007–2010) in men, and varied when stratified by age groups (3.4% for 20–29, 6.9% for 30–39, 9.8% for 40–49, 13.1% for 50–59, and 19.1% for 60–69 years) (Scales et al., 2012). Increasing age was significantly associated with excretion of key urinary compounds related to kidney stones (Perinpam et al., 2015), and there was a reverse association between total testosterone concentrations and age (Feldman et al., 2002; Harman et al., 2001).

Despite all these relationships, there is a paucity of evidence on the association between testosterone and KS and how this relationship varied when stratified by obesity, diabetes, dyslipidemia, race/ethnicity, and age.

2. Methods

2.1. Survey overview, study design, and subjects

This was a cross-sectional study. We analyzed data collected from the National Health and Nutrition Examination Survey (NHANES) 2011–2012. NHANES is a program of studies undertaken by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the US population. NHANES uses a multistage, stratified and clustered probability sampling in which Hispanics, non-Hispanic Blacks, and the elderly were oversampled to ensure adequate sample sizes and to represent the total US civilian, non-institutionalized population. (NCHS, 1994) The study population consisted entirely of male respondents, 20 years and older.

2.2. Outcome, exposure, and covariates

Data on KS, TT concentrations, demographics, comorbidities, and other covariates were gathered from the 2011–2012 cycle of NHANES. Low-testosterone is defined as TT concentrations < 3 ng/mL. Testosterone is the major male androgen, and free circulating concentrations are controlled by SHBG. Bioavailable testosterone is the concentration of non-SHBG-bound testosterone and is comprised of both free and albumin-bound testosterone. TT is the combination of bioavailable and SHBG-bound testosterone. Testosterone was isolated from 100 μL serum by 2 serial liquid–liquid extraction steps and quantified with 113C stable isotope-labeled testosterone as the internal standard. The method had a nonsignificant bias to established reference methods at National Institute for Standards and Technology and the University of Ghent. Imprecision over 2 years was < 4.8%, and the limit of detection was 0.3 ng/dL (0.01 nmol/L).

KS, age, and other covariates are self-reported (e.g. race/ethnicity, marital status, education, alcohol use, prescription drug use, comorbidities, and physical activity. Body Mass Index (BMI) was categorized as normal weight (BMI ≤ 24.9 kg/m²), overweight (25.0 ≤ BMI < 30.0 kg/m²), and obese (BMI ≥ 30.0 kg/m²). Diabetes was identified as one or more of the following: diabetes diagnosis, fasting plasma glucose levels ≥ 126 mg/dL, positive response to questions about medication treatment (e.g. “are you now taking insulin?” or “are you now taking diabetic pills to lower your blood sugar?”), glycated hemoglobin level of 6.5% or greater (A1C ≥ 6.5%). Race/ethnicity was collected for White, Non-Hispanic Black, and Hispanic. Prescription drug use, which is associated with KS (Daum et al., 2016; Shafi et al., 2016), included statins, angiotensin-receptor blockers, ACE inhibitors, beta blockers, calcium channel inhibitors, thiazide diuretics, loop diuretics, protease inhibitors, sulfonamides, and aminopenicillins. Other comorbidities included hypertension [diagnosis or an average of three systolic/diastolic blood pressure readings ≥ 130/85 mmHg], heart attack, stroke, congestive heart failure, coronary heart disease, angina pectoris, asthma, bladder cancer, gout, thyroid disease, and daily dietary laboratory data and behavioral data. Age was stratified into four groups for stratification: ≥ 20–< 40, ≥ 40–< 60,

| Table 1 |
| --- |
| Prevalence estimates (%) for demographic, lifestyle, and clinical factors for 27,904 men, NHANES 2011–2012. |
| Factors | Kidney stones (N, %, or otherwise noted) | No kidney stones (N, %, or otherwise noted) | p-value |
| --- | --- | --- | --- |
| Age (Mean) | 58.58 | 48.75 | < 0.001* |
| Age categories | | | < 0.0001* |
| Age group ≥ 20 & < 40 years | 136 (15.51) | 2778 (35.85) | | |
| Age group ≥ 40 & < 60 years | 266 (30.33) | 2523 (32.56) | | |
| Age group ≥ 60 & < 80 years | 376 (42.87) | 1983 (25.59) | | |
| Age group ≥ 80 years | 99 (11.29) | 465 (6.00) | | |
| Education categories | | | 0.669 |
| Some college or equiv. | 409 (46.64) | 3669 (47.40) | | |
| High school or less | 468 (53.36) | 4072 (52.60) | | |
| Marital status | | | < 0.001* |
| Not married | 85 (34.96) | 1224 (49.18) | | |
| Married | 158 (30.68) | 1265 (50.82) | | |
| Race/ethnicity | | | < 0.0001* |
| White, non-Hispanic | 515 (58.72) | 3350 (43.23) | | |
| Black, non-Hispanic | 97 (11.06) | 1740 (22.45) | | |
| Hispanic | 215 (24.52) | 1949 (25.15) | | |
| Other | 50 (5.70) | 710 (9.16) | | |
| Overall obesity; BMI, (kg/m²) | | | < 0.0001* |
| < 25 (ref) | 161 (18.53) | 2134 (27.73) | | |
| ≥ 25–29.99 | 336 (38.67) | 2749 (35.72) | | |
| ≥ 30 | 372 (42.81) | 2812 (36.54) | | |
| Alcohol use (ALQ101) | | | 0.415 |
| Did not have at least 12 alcoholic drinks in one year | 182 (83.11) | 1821 (85.17) | | |
| Had at least 12 alcoholic drinks in one year | | | 0.138 |
| Physical activity | | | |
| No physical activity | 502 (57.24) | 4225 (54.53) | | |
| Moderate activity | 175 (19.95) | 1520 (19.62) | | |
| Vigorous activity | 200 (22.81) | 2003 (25.85) | | |
| Diabetes | | | < 0.0001* |
| No | 401 (74.81) | 4485 (86.40) | | |
| Yes | 135 (25.19) | 706 (13.60) | | |
| Heart attack | | | < 0.0001* |
| No | 219 (91.80) | 2388 (96.02) | | |
| Yes | 24 (9.88) | 99 (3.98) | | |
| Stroke | | | 0.001* |
| No | 224 (91.80) | 2398 (96.34) | | |
| Yes | 20 (8.20) | 91 (3.66) | | |
| Congestive heart failure | | | < 0.0001* |
| No | 221 (91.32) | 2416 (97.22) | | |
| Yes | 21 (8.68) | 69 (2.78) | | |
| Coronary heart disease | | | < 0.0001* |
| No | 215 (89.21) | 2381 (95.89) | | |
| Yes | 26 (10.79) | 102 (4.11) | | |
| Angina pectoris | | | < 0.0001* |
| No | 226 (93.00) | 2436 (98.15) | | |
| Yes | 17 (7.00) | 46 (1.85) | | |
| Hypertension | | | < 0.0001* |
| No | 259 (29.53) | 3396 (43.83) | | |
| Yes | 618 (70.47) | 4353 (56.17) | | |
| Asthma | | | 0.670 |
| No | 211 (86.48) | 2176 (87.42) | | |
| Yes | 33 (13.52) | 313 (12.58) | | |
| Bladder cancer | | | 0.038* |
| No | 874 (99.66) | 7742 (99.91) | | |
| Yes | 3 (0.34) | 7 (0.09) | | |
| Gout | | | < 0.0001* |
| No | 772 (88.23) | 7280 (94.03) | | |
| Yes | 103 (11.77) | 462 (5.97) | | |
| Thyroid disease | | | 0.137 |
| No | 228 (93.83) | 2385 (95.86) | | |
| Yes | 15 (6.17) | 103 (4.14) | | |

(continued on next page)
Table 1 (continued)

| Factors | Kidney stones (N, %, or otherwise noted) | No kidney stones (N, %, or otherwise noted) | p-value |
|---------|----------------------------------------|---------------------------------------------|---------|
| Statin use | < 0.0001 | 592 (67.50) 6231 (81.57) | |
| No | 285 (32.50) 1428 (18.43) | |
| Angiotensin-renin blocker use | 0.680 | 242 (99.18) 2475 (99.40) | |
| No | 2 (0.41) 15 (0.60) | |
| ACE Inhibitor use | 0.184 | 232 (95.08) 2408 (96.71) | |
| No | 12 (4.92) 82 (3.29) | |
| Beta blocker use | 0.015** | 234 (95.90) 2445 (98.19) | |
| No | 10 (4.10) 45 (1.81) | |
| Ca Channel use | 0.206 | 242 (99.18) 2441 (98.03) | |
| No | 2 (0.82) 49 (1.79) | |
| Thiazide use | 0.062 | 217 (88.93) 2299 (92.33) | |
| No | 27 (11.07) 191 (7.67) | |
| Loop diuretic use | 0.346 | 242 (99.18) 2480 (99.60) | |
| No | 2 (0.82) 10 (0.40) | |
| Protease Inhibitor use | 0.036*** | 242 (99.18) 2486 (99.84) | |
| No | 2 (0.82) 4 (0.16) | |
| Sulfonamide use | 0.548 | 242 (99.18) 2477 (99.48) | |
| No | 2 (0.82) 13 (0.52) | |
| Amino-penicillin use | 0.436 | 241 (98.77) 2471 (99.24) | |
| No | 3 (1.23) 19 (0.76) | |
| Total plain water drank yesterday (g) (mean) | 0.0403 | 1847.16 2029.95 | |
| Dietary calcium (mg) (mean) | 0.0196* | 925.40 1030.87 | |
| Dietary sodium (mg) (mean) | 0.006* | 1971.58 4102.48 | |
| Dietary protein (g) (mean) | 0.0006* | 85.12 96.04 | |
| Dietary fat (g) (mean) | 0.0454* | 26.35 28.83 | |
| Dietary vitamin D (mcg) (mean) | 0.8966 | 5.09 5.16 | |
| Dietary caffeine (mg) (mean) | 0.8825 | 156.31 158.51 | |
| Serum vitamin B12 (pg/ml) (mean) | 0.1107 | 552.10 593.98 | |
| Serum HDL-D cholesterol (mg/dl) (mean) | 0.0029 | 45.46 48.21 | |
| Low salt/low sodium diet | 0.142 | 870 (99.20) 7715 (99.56) | |
| No | 7 (0.80) 34 (0.44) | |
| Doctor’s orders to lose weight | < 0.0001* | 156 (99.20) 1983 (79.64) | |
| No | 88 (8.00) 507 (20.36) | |
| Diet to reduce fat | 0.211 | 112 (45.90) 1247 (50.10) | |
| No | 132 (34.10) 1242 (49.90) | |
| Diet to reduce salt | 0.052 | 109 (44.67) 1274 (51.19) | |
| No | 135 (55.33) 1215 (48.81) | |
| Increasing exercise | 0.539 | 112 (45.90) 1092 (43.86) | |

Chi-square test is used for categorical variables, and t-test is used for continuous variables.
KS: Kidney Stones, Low-testosterone: total testosterone concentrations < 3 ng/mL, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker. Multivariable adjusted. OR: Odds ratio, 95% CI: 95% Confidence Intervals, NE: Not Estimable; ng/mL: nanograms per milliliter.

Table 2

| Variable | KS |
|----------|----|
| Testosterone ≥ 3 ng/mL | Odds Ratio (OR) 95% CI p-value |
| Yes | 132 (54.10) 1398 (56.14) | 0.78, 0.40, 0.21 |
| No | 552 (44.67) 2441 (48.81) | 1.00, N/A, N/A 1.00, N/A, N/A 1.00, N/A, N/A |
| Testosterone (ng/mL) | 1.01 0.93, 0.86, 0.71 |

KS: Kidney Stones, Low-testosterone: total testosterone concentrations < 3 ng/mL. Adjusted for age, education, marital status, race/ethnicity, overall obesity, alcohol use, physical activity, diabetes, heart attack, stroke, congestive heart failure, coronary heart disease, angina pectoris, hypertension, asthma, bladder cancer, gout, thyroid disease, prescribed drug use (a separate dichotomous variable for each drug use), 7567 statin, angiotensin-renin blocker, ACE inhibitor, beta blocker, calcium channel, thiazide diuretic, loop diuretic, protease inhibitor, sulfonamide, aminopenicillin), total plain water drank yesterday (g), dietary calcium (mg), dietary sodium, dietary protein, dietary fat, dietary vitamin D (mcg), dietary caffeine (mg), serum B12 (pg/ml), serum HDL-D cholesterol (mg/dl), low salt/low sodium diet (y/n), doctor’s orders to lose weight (y/n), diet to reduce fat (y/n), diet to reduce salt (y/n), increasing exercise (y/n). Multivariable adjusted. OR: Odds ratio, 95% CI: 95% Confidence Intervals, NE: Not Applicable. Type I Error: p-value threshold set at 0.05; α < 0.05, (ng/mL: nanograms per milliliter).

Table 3

| Overall obesity; BMI, kg/m² | ≥ 30 | 25-29.99 | < 25 |
|-----------------------------|------|----------|------|
| Testosterone ≥ 3 ng/mL | OR, 95% CI p-value | OR, 95% CI p-value | OR, 95% CI p-value |
| Yes | 1.00, N/A, N/A | 1.00, N/A, N/A | 1.00, N/A, N/A |
| No | 0.41, 0.21-0.78, 0.009 | 0.82, 0.36-1.83, 0.613 | 0.53, 0.10-2.84, 0.442 |

KS: Kidney Stones Low-testosterone: total testosterone concentrations < 3 ng/mL. Adjusted for the same confounders as in model presented in Table 2.

© 2018 E. Yucl et al. Preventive Medicine Reports 10 (2018) 248-253

250
KS: Kidney Stones. Low-testosterone: total testosterone concentrations < 3 ng/mL. Multivariable adjusted. OR: Odds ratio, 95% CI: 95% Confidence Intervals. N/A: Not applicable. Type I Error: p-value threshold set at 0.05; *α < 0.05. (ng/mL: nanograms per milliliter; mg/dL: milligram per deciliter) Adjusted for the same number of confounders as in model presented in Table 2.

Table 4

| Total testosterone concentration | Comorbidity | Yes | No |
|----------------------------------|-------------|-----|----|
| ≥ 3 ng/mL (ref)                  | OR, 95% CI, p-value | OR, 95% CI, p-value |
| Low-testosterone                  | Diabetes     | 0.62, 0.18–2.10, 0.425 | 0.61, 0.42–0.90, 0.017* |

KS: Kidney Stones. Low-testosterone: total testosterone concentrations < 3 ng/mL. Multivariable adjusted. OR: Odds ratio, 95% CI: 95% Confidence Intervals. N/A: Not applicable. Type I Error: p-value threshold set at 0.05; *α < 0.05. (ng/mL: nanograms per milliliter; mg/dL: milligram per deciliter) Adjusted for the same number of confounders as in model presented in Table 2.

2.3. Statistical analysis

NHANES analytical reporting guidelines were followed, adhering to the complex survey design. (NHANES, 2015) Sampling weights were applied to account for selection probabilities, over-sampling, non-response, and differences between the sample and the total US population. Descriptive statistics for participants’ characteristics were reported with t-tests for continuous variables and Chi-square for categorical. Adjusted odds ratios (OR) and 95% confidence intervals (CI) using logistic regression models were estimated in relation to total testosterone concentrations with multiple covariates, and stratified by age groups and comorbidities (NHANES, 2014). Outcome was defined as Kidney Stones Exposure was TT concentration < 3 ng/mL, (Low-testosterone).

Statistical significance of tests is set at p values < 0.05 (Type I Error). Software utilized for analysis was Stata/IC version 12.1.

3. Results

Descriptive statistics are reported in Table 1. Mean age of men were 48.75 (SD 17.83, 95% CI 48.35–49.14) for those without KS, and 58.58 (SD 15.89, 95% CI 57.53–59.63; p-value < 0.001). We found that men 20 years and older with Low-testosterone had 41% lower odds of KS than men without Low-testosterone after multivariable adjustment (OR: 0.59, 95% CI 0.40–0.86, Table 2).

When stratified by obesity, men with BMI ≥ 30 kg/m² and low-testosterone had 59% lower odds of KS versus men without low-testosterone (OR: 0.41, 95% CI: 0.21–0.786), but this association was not statistically significant in BMI levels < 30 kg/m² (Table 3). When stratified by diabetes, there was no association in men with diabetes and low-testosterone, but men without diabetes and with low-testosterone had 39% lower odds of KS (OR: 0.61, 95% CI: 0.42–0.90 (Table 4). When stratified by high density lipid (HDL) levels, men with HDL > 40 mg/dL and low-testosterone had 40% lower odds of have KS (OR: 0.60, 95% CI: 0.40–0.90), but this association was not significant in men with low-testosterone and with HDL ≤ 40 mg/dL (Table 5).

None of the associations was significant in other lipid levels; i.e. low density lipid (LDL) (cut-off = 120 mg/dL), total glycerides (TG) (cut-off = 150 mg/dL), total cholesterol (cut-off = 200 mg/dL or 240 mg/dL) (Table 5).

When stratified by race/ethnicity, white men with low-testosterone had 48% lower odds of KS (OR: 0.52, 95% CI: 0.30–0.89) (Table 6). Hispanic men with low-testosterone had 2.36 times higher odds of KS (OR: 2.36, 95% CI: 1.03–5.38), and there was no significant association in Black (non-Hispanic) men (Table 6). There was no other significant association when stratified by other comorbidities and prescription drug use, (Supplementary tables).

Age was a statistically significant factor in the association between testosterone and KS (Supplementary tables). When stratified by age, men in the age group ≥ 40– < 60 years and with low-testosterone had 68% lower odds of KS (OR: 0.32, 95% CI: 0.16–0.67, Table 7) but this association was not statistically significant in other age groups, i.e., ≥ 20– < 40, ≤ 60– < 80, and ≥ 80 years.

4. Discussion

We found that men who were 20 years and older and with Low-testosterone had 41% lower odds of KS as compared to men without low-testosterone. Contrary to our finding, Otuncetur et al. (Otuncetur et al., 2015) found that men with testosterone concentrations < 2.85 ng/mL had three times higher odds of KS (OR: 2.93, 95%CI: 1.88–4.56). This could be due to insufficient adjustment for confounders, small sample size, and Berksonian bias in Otuncetur et al.’s study (Otuncetur et al., 2015). Furthermore, our finding was consistent with earlier studies. For example, higher testosterone levels were found in KS patients (3.30 ng/mL, SE: 2.50) as compared to controls (2.41 ng/mL, SE: 1.06; p = 0.003) (Naghii et al., 2014). There was a significant and positive Pearson correlation between free serum testosterone levels and urinary oxalate concentrations (R = 0.297, p-
value = 0.040) (Nath et al., 2013). Serum testosterone levels were significantly associated with higher urinary excretion of uric acid in patients with KS versus those without (Shakhssalim et al., 2011). Furthermore, kidney stones were consistently reported more often in men than women, and men biologically carry higher testosterone levels than women (Scales et al., 2012; Stamatelou et al., 2003). The association between testosterone and KS in men could be explained by the upregulation of calcium oxalate biosynthesis by androgen receptors (Li et al., 2010; Li et al., 2014), and testosterone could have a biologic role in KS formation (Naghi et al., 2014).

We found that the association between low-testosterone and KS differed by race/ethnicity. Our findings were consistent with the recent findings. For example, Vesper et al. (2015) demonstrated significant variation in total testosterone levels among race/ethnicity. Non-Hispanic Black and Hispanic were 63% and 40% less likely to have KS as compared to Non-Hispanic White, respectively (Scales et al., 2012).

We found that men who were obese (BMI ≥ 30 kg/m²) had 59% lower odds of KS when with low-testosterone (Table 3). Obesity was strongly associated with KS (Bos et al., 2016; Jabbar et al., 2015; Taylor et al., 2005), and low testosterone (Tajar et al., 2010; Wang et al., 2011). Our finding suggests low-testosterone could prevent KS in obese men despite increased urinary excretion of calcium, oxalate, and uric acid (Taylor et al., 2005).

We found men with low-testosterone and with HDL ≥ 40 mg/dL had 40% lower odds of KS. Our finding is consistent with prior literature. Men with HDL < 45 mg/dL were 30% more likely to develop KS than men with HDL ≥ 45 mg/dL (HR: 1.30, 95% CI: 1.1–1.7) (Masterson et al., 2015). Furthermore, patients with dyslipidemia were 20% more likely to develop KS as compared to patients without dyslipidemia (HR: 1.20, 95% CI: 1.01–1.51). (Masterson et al., 2015).

Despite the strengths of our study (e.g.; NHANES is a validated representative sample of the civilian noninstitutionalized U.S. male population, and there is oversampling of minorities and the elderly), our findings should be evaluated with caution because NHANES is a cross-sectional study; therefore, causality cannot be inferred in any of the observed associations or suggest any clinical practice change. There could be an inherent bias in the use of surveys, and measurements were largely obtained at a single-time point.

In conclusion, we found men with low-testosterone had significantly 41% lower odds of KS. This finding should be further studied in cohort studies that control for confounding and bias and with longitudinal follow-up of patients.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study complies with current ethical considerations. No informed consent was required for this investigation because all data is from the publicly available database of the National Health and Nutrition Examination Survey, which complied with all of the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the privacy rights of human subjects.

Conflict of interest

Authors have no conflict of interest for this manuscript.

Table 7

| Age groups | ≥20– < 40 years | ≥40– < 60 years | ≥60– < 80 years | ≥80 years |
|------------|----------------|----------------|----------------|----------|
| Testosterone | OR, 95% CI, p-value | OR, 95% CI, p-value | OR, 95% CI, p-value | OR, 95% CI, p-value |
| ≥3 ng/mL (reference) | 1.00, N/A, N/A | 1.00, N/A, N/A | 1.00, N/A, N/A | 1.00, N/A, N/A |
| <3 ng/mL | 1.29, 0.45–3.64, 0.606 | 0.32, 0.16–0.67, 0.004 | 1.44, 0.43–4.80, 0.526 | 2.44, 0.13–4.47, 0.524 |

KS: Kidney Stones. Low-testosterone: total testosterone concentrations < 3 ng/mL. Multivariable adjusted. OR: Odds ratio, 95% CI: 95% Confidence Intervals. Type I Error: p-value threshold set at 0.05; α < 0.05 (ng/mL: nanograms per milliliter), Men (≥20 years) Adjusted for the same number of confounders as in model presented in Table 2.

- Denotes statistical significance at p < 0.05.

References

Al Hayek, A.A., Khader, Y.S., Jafal, S., Khawanji, N., Robert, A.A., Ajlouni, K., 2013. Prevalence of low testosterone levels in men with type 2 diabetes mellitus: a cross-sectional study. J. Family Commun. Med. 20, 179–186.

Bos, D., Dason, S., Matsumoto, E., Pinthus, J., Allard, C., 2016. A prospective evaluation of obesometric parameters associated with renal stone recurrence. Can. Urol. Assoc. J. 10, 254–258 Journal de l’Association des urologues du Canada.

Calderon, B., Gomez-Martín, J.M., Vega-Pinero, B., et al., 2016. Prospective evaluation of male secondary hypogonadism in moderate to severe obesity and its relationship with insulin resistance and excess body weight. Andrology 4, 62–67.

CDC. 2011. Health disparities and inequalities report - United States. 2011. MMWR Morb. Mortal. Wkly Rep. 60.

Dawu, C.A., Yi, Y., Bierlein, M.L., et al., 2016. Factors associated with preventive pharmacological therapy adherence among patients with kidney stones. Urology 93, 45–49.

Feldman, H.A., Longcope, C., Derby, C.A., et al., 2002. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J. Clin. Endocrinol. Metab. 87, 589–598.

Ghani, K.R., Raghavan, P., Sammon, J.D., et al., 2014. Emergency department visits in the United States for upper urinary tract stones: trends in hospitalization and charges. J. Urol. 191, 90–96.

Haring, R., Baumeister, S.E., Volzke, H., et al., 2011. Prospective association of low total testosterone concentrations with an adverse lipid profile and increased incident dyslipidemia. Eur. J. Cardiovasc. Prev. Rehabil. 18, 86–96.

Harman, S.M., Metter, E.J., Tobin, J.D., Pearson, J., Blackman, M.R., Baltimore Longitudinal Study of Aging. J. Clin. Endocrinol. Metab. 86, 724–731.

Jabbar, F., Asif, M., Dutani, H., et al., 2015. Assessment of the role of general, biochemical and family history characteristics in kidney stone formation. Saudi J. Biol. Sci. 22, 65–68.

Kang, H.W., Lee, S.K., Kim, W.T., et al., 2014. Hypertriglyceridemia and low high-density lipoprotein cholesterolemia are associated with increased hazard for urolithiasis. J. Endourology. 28, 1001–1006.

L., M.S., S., C.S., 2012. Urolologic Diseases in America. US Government Printing Office, Washington, DC.

Li, J.Y., Zhou, T., Gao, X., et al., 2010. Testosterone and androgen receptor in human nephrolithiasis. J. Urol. 184, 2360–2363.

Li, L., Li, L., Tian, J., et al., 2014. Androgen receptor enhances kidney stone-CaOx crystal formation via modulation of oxalate biosynthesis & oxidative stress. J. Mol. Endocrinol. 28, 1291–1303.

Li, J.B., Saigal, C.S., 2012. Table 14–47: Economic impact of urolithic disease. In: Urollogic Diseases in America. NIH Publication, Washington, DC (Nationalally representative charges for treatment of upper urinary tract stones, by site of service, charges, percent).

Masterson, J.H., Woo, J.R., Chang, D.C., et al., 2015. Dyslipidemia is associated with an increased risk of nephrolithiasis. Urolojis 43, 49–53.

Naghi, M.R., Babaei, M., Hedayati, M., 2014. Androgen involvement in the pathogenesis of renal stones formation. Phil. One 9, e93790.

Noth, S.J., Sarma, D., Bagchi, P.K., Baruah, S.K., Putheventil, R.T., Baruah, S.J., 2013. The role of serum testosterone as a lithogenic factor and its correlation with stone and urine composition amongst male stone formers. Ur. Today Int. J. 06.

NCHS, 1994. Plan and Operation of the Third National Health and Nutrition Examination Survey, which complied with all of the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the privacy rights of human subjects.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2018.04.002.

Author contribution

Conception and design- Drs. Lopez and Yucel. Data analysis and interpretation- Drs. Lopez, Yucel, DeSantis, and Smith. Manuscript writing, drafting and reviewing- Drs. Yucel, Lopez, DeSantis, and Smith. Final approval of manuscript- Lopez and Yucel.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2018.04.002.
Survey, 1988–94. Natl Ctr for Health Statistics.
NHANES, 2014. Key concepts About Setting Up A Logistic Regression in NHANES. NCHS/
NHANES, 2015. About the National Health and Nutrition Examination Survey.
Otnurtemur, A., Onbek, E., Cakir, S.S., et al., 2015. Urolithiasis is associated with low
serum testosterone levels in men. Arch. Ital. Urol. Androl. 87, 83–86.
Perinpam, M., Ware, E.B., Smith, J.A., Turner, S.T., Kardia, S.L., Lieske, J.C., 2015. Effect
of demographics on excretion of key urinary factors related to kidney stone risk.
Urology 86, 690–696.
Pesko, S.B., Joshu, C.E., Rohrmann, S., et al., 2015. Circulating total testosterone and
PSA concentrations in a nationally representative sample of men without a diagnosis
of prostate cancer. Prostate 75, 1167–1176.
Rohrmann, S., Nelson, W.G., Rifai, N., et al., 2007. Serum estrogen, but not testosterone,
levels differ between black and white men in a nationally representative sample of
Americans. J. Clin. Endocrinol. Metab. 92, 2519–2525.
Scales Jr., C.D., Smith, A.C., Hanley, J.M., Saigal, C.S., Urologic Diseases in America, P,
2012. Prevalence of kidney stones in the United States. Eur. Urol. 62, 160–165.
Scales Jr., C.D., Tasian, G.E., Schwaderer, A.L., Goldfarb, D.S., Star, R.A., Kirkali, Z.,
2016. Urinary stone disease: advancing knowledge, patient care, and population
health. Clin. J. Am. Soc. Nephrol. 11, 1305–1312.
Shafii, H., Moazzami, B., Pourghasem, M., Kaseaian, A., 2016. An overview of treatment
options for urinary stones. Caspian J. Intern. Med. 7, 1–6.
Shakhssalim, N., Gilani, K.R., Parvin, M., et al., 2011. An assessment of parathyroid
hormone, calcitonin, 1,25 (OH)2 vitamin D3, estradiol and testosterone in men with
active calcium stone disease and evaluation of its biochemical risk factors. Urol. Res.
39, 1–7.
Shang, J., Tasian, G.E., Goldfarb, D.S., Eisner, B.H., 2015. The new epidemiology of ne-
phrolithiasis. Adv. Chronic Kidney Dis. 22, 271–278.
Stamatelou, K.K., Francis, M.E., Jones, C.A., Nyberg, L.M., Curhan, G.C., 2003. Time
trends in reported prevalence of kidney stones in the United States: 1976–1994.
Kidney Int. 63, 1817–1823.
Tajar, A., Forti, G., O’Neill, T.W., et al., 2010. Characteristics of secondary, primary, and
compensated hypogonadism in aging men: evidence from the European male ageing
study. J. Clin. Endocrinol. Metab. 95, 1810–1818.
Taylor, E.N., Stampler, M.J., Curhan, G.C., 2005. Obesity, weight gain, and the risk of
kidney stones. JAMA 293, 455–462.
Thirumalai, A., Rubinow, K.B., Page, S.T., 2015. An update on testosterone, HDL and
cardiovascular risk in men. J. Clin. Lipidol. 10, 251–258.
Torricelli, F.C., De, S.K., Gebreellassie, S., Li, L., Sarkissian, C., Monga, M., 2014.
Dyslipidemia and kidney stone risk. J. Urol. 191, 667–672.
Vesper, H.W., Wang, Y., Vidal, M., Botelho, J.C., Caudill, S.P., 2015. Serum Total tes-
tosterone concentrations in the US household population from the NHANES
2011–2012 study population. Clin. Chem. 61, 1495–1504.
Wang, C., Jackson, G., Jones, T.H., et al., 2011. Low testosterone associated with obesity
and the metabolic syndrome contributes to sexual dysfunction and cardiovascular
disease risk in men with type 2 diabetes. Diabetes Care 34, 1669–1675.