



Is Polycystic Ovarian Syndrome a Risk Factor for Urinary Stone Disease?

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Abstract

Urinary stone disease is a multi factorial disorder and a complex process influenced by both intrinsic and environmental factors with an approximate prevalence of 1% to 15% worldwide that varies depending on elements such as age, sex, race, and genetic factors. In animal and human studies, testosterone has been shown to increase the formation of urinary stones. This suggests that sex hormones are involved in the pathogenesis of stone disease. Hyperandrogenism, the main feature of Poly Cystic Ovary Syndrome (PCOS), may trigger the urinary stone formation besides hirsutism, alopecia and acne. The present study was performed to investigate whether patients with PCOS were at risk in terms of urinary system stone disease. Forty patients with PCOS and 40 healthy controls were included in the study, after exclusions the study ended up with 38 patients (PCOS group n=23, control group n=15). 24-hr urinary composition, biochemical and hormonal levels were analyzed. 24-hr excretion of oxalate was statistically significantly higher in the PCOS subjects than control group. Patients with PCOS had higher urinary uric acid and lower citrate levels than control subjects. There was no difference for urinary calcium levels between the PCOS and control groups. PCOS may trigger the urinary stone disease.

Keywords: Urinary stone disease; Polycystic ovary syndrome; Urinary oxalate; Urinary uric acid; Urinary citrate; Urinary calcium

Introduction

Urinary stone disease is a multi factorial disorder and a complex process influenced by both intrinsic and environmental factors with an approximate prevalence of 1% to 15% worldwide that varies depending on elements such as age, sex, race, and genetic factors. Males have a three times higher incidence compared to females in the reproductive stage, but there is no gender difference in childhood or climacterium. In males it occurs in the third and fourth decades of life when the level of serum testosterone is also the highest [5]. In women during the sixth decade of life a time that corresponds to the onset of menopause with a fall of estrogen levels, the incidence of urinary stone disease increases [6].

Furthermore, men have higher urinary calcium, oxalate and uric acid excretions than women which promote lithogenesis and lower urinary citrate excretion which inhibits crystal growth and aggregation [15,20]. Compared with men, urinary calcium is lower in women until age 50 years, when it equals that of men. Citrate is equal in the genders until the age 60 years, when it tends to decrease in women [20]. Estrogen replacement increases urinary citrate excretion in postmenopausal women [4].

These all support the role of sex hormones in urinary stone formation. In animal and human studies, it has been shown that androgens appear to have a boosting effect and estrogens appear to have an inhibitory effect on urinary stone formation [7-10,12-14,16-19].

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders encountered in 5%-10% of reproductive- age women [11]. It is a heterogeneous condition, characterized by hyperandrogenism and ovulatory dysfunction that consists of anovulation or polycystic ovarian morphology. The principle features of PCOS are hyperandrogenism and insulin resistance which can augment hyperandrogenism [1]. It is a major cause of menstrual disturbances, female anovulatory infertility and clinical signs of androgen excess including hirsutism and acne [2]. Moreover, PCOS is associated with long-term health risks, including cardiovascular disease, diabetes mellitus, hypertension, endometrial carcinoma [2,3].

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Table 1: Demographic features of PCOS patients and healthy controls.

	PCOS (n=23)	Control (n=15)	p
Age (years)	24,09 ± 4,54	26,73 ± 3,20	0,08
Marital status			
Married	13 (%56.5)	13 (%86.7)	0,03*
Single	10 (%43.5)	2 (%13.3)	
Gravida	0.00 (1.00) (0-2)	2 (1) (0-3)	<0,001*
Parity	0.00 (1.00) (0-2)	1 (1) (0-3)	<0,001*
BMI (kg/m ²)	26,04 ± 7,42	23,10 ± 2,60	0,09

Data are means ± SD or median (IQR). *represents the significance.

Abbreviations: PCOS: Polycystic Ovary Syndrome; BMI: Body Mass Index; SD: Standard Deviation; IQR: Inter Quartile Ranges

Table 2: Biochemical and hormonal features of PCOS patients and healthy controls.

	PCOS (n=23)	Control (n=15)	p
Hemoglobin gr/dl	13,53 ± 1,05	12,61 ± 0,97	0,01*
Fasting insulin (mIU/ml)	86,00 (79,00 - 100,00)	82,00 (67,00 - 97,00)	0,06
OGTT 120. minute(mg/dl)	98,00 (66,00 - 153,54)	82,50 (71,00 - 118,00)	0,06
İnsulin (uIU/ml)	11,42 (5,22 - 46,43)	6,84 (5,02 - 11,62)	0,01*
HOMA_IR	2,51 (1,20 - 13,35)	1,47 (1,05 - 2,27)	<0,01*
Creatinine (0,5-1,2 mg/dl)	0,65 (0,47 - 0,80)	0,60 (0,50 - 0,90)	0,40
Uric acid (2,6-6 mg/dl)	4,20 (3,50 - 6,00)	3,61 (2,50 - 5,00)	0,12
Urea (10-50 mg/dl)	19,00 (3,70 - 31,00)	22,50 (18,00 - 25,00)	0,07
Calcium (8,4-10,2mg/dl)	9,58 ± 0,33	9,48 ± 0,49	0,49
Magnesium (1,7-2,55mg/dl)	2,00 (1,70 - 2,30)	2,00 (1,70 - 2,10)	0,90
Total Cholesterol <200mg/dl)	191,00 (161,40 - 250,78)	173,00 (119,00 - 236,00)	0,02*
HDL (35-60 mg/dl)	49,00 (35,00 - 85,00)	54,00 (51,10 - 88,00)	0,02
LDL (0-130 mg/dl)	111 (84,80 - 156,80)	90,00 (60,00 - 163,00)	0,02*
VLDL (<40 mg/dl)	18,30 (8,40 - 36,20)	19,80 (7,61 - 37,80)	0,95
Triglyceride (<200 mg/dl)	89,00 (38,00 - 181,00)	99,00 (38,00 - 189,00)	0,99
FSH (mIU/ml)	6,05 (3,62 - 8,26)	6,60 (4,00 - 19,37)	0,34
E2 (pg/ml)	30,34 (15,74 - 361,00)	33,60 (14,85 - 82,22)	0,70
LH (mIU/ml)	8,69 (4,67 - 24,48)	5,23 (2,69 - 10,06)	0,001*
TSH (0,27-4,2 uIU/ml)	1,95 (1,13 - 4,20)	1,73 (0,83 - 2,87)	0,21
PRL (4,79-23,2 ng/ml)	11,61 (6,22 - 23,10)	12,28 (8,00 - 20,64)	0,58
Total Testosterone (8-50 ng/dl)	36,08 (8,46 - 94,24)	17,98 (0,48 - 1,69)	0,02*
17-OH Progesteron (0,4-4,28 ng/ml)	1,39 ± 0,53	1,01 ± 0,46	0,04*
DHEAS (98,8-340 ug/dl)	203,10 (75,57 - 423,50)	87,60 (72,07 - 265,2)	0,001*
PTH (15-65 pg/ml)	53,20 (31,52 - 64,50)	49,65 (26,90 - 60,70)	0,15
25 OH Kolekalsiferol (ug/L)	16,50 (4,50 - 140)	13,50 (5,30 - 32,90)	0,47

Data are means ± SD or median (minimum-maximum). *represents the significance

Abbreviations: PCOS: Polycystic Ovary Syndrome; OGTT: Oral Glucose Tolerance Test; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein; FSH: Follicle Stimulant Hormone; E2: Estradiol; LH: Luteinizing Hormone; TSH: Thyroid Stimulating Hormone; PRL: Prolactin; DHEA-S: Dehydroepiandrosterone Sulphate; PTH: Parathormone; SD: Standard Deviation

It's a known fact for many years that urinary stone disease is more frequently seen in men depending on the hyperandrogen levels. However it's not studied in patients with PCOS which is associated with high serum androgen levels. It is hypothesized that PCOS accompanied by hyperandrogenism may be a risk factor in the formation of urinary stone disease.

Materials and Methods

This cross sectional study was performed at the Medical School of Turgut Özal University, Ankara, Turkey between 2013 and 2016

years. A total of 23 newly diagnosed patients were identified as PCOS cases according to the Androgen Excess Society (AES) criteria [1], while 15 healthy volunteer women (regularly menstruating, non-hirsute, normo-ovulatory, without any infertility) were recruited in the study as the control group.

AES criteria are based on two abnormalities: hyperandrogenism and ovarian dysfunction after the exclusion of other pathologies with a similar clinical presentation such as congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumours, hypothyroidism and hyperprolactinemia. Hyperandrogenism was defined either

Table 3: 24-hour urinary composition of PCOS patients and healthy controls.

	PCOS (n=23)	Control (n=15)	p
Calcium 100-320mg/day	106,20 (18,90 - 283,50)	115,63 ± 70,80	0,63
Chloride (110-250 mEq/day)	155,70 (18,56 - 528,24)	173,74 (64,82 - 263,20)	0,87
Urea (12-20g/day)	16,27 ± 6,23	15,40 ± 4,04	0,64
Potassium (25-125 mEq/day)	52,96 (7,50 - 140,94)	51,40 (26,90 - 21,80)	0,59
Cysteine (2,16-30,9 mg/day)	8,05 (0,91 - 162,73)	14,80 (2,22 - 29,20)	0,20
Uric acid 0-400 mg/day)	408,71 (84,00 - 1039,50)	385,50 (259,60 - 609,00)	0,07
Magnesium (50-150 mg/day)	82,12 ± 45,16	81,39 ± 20,35	0,95
Sodium 40-220 mEq/day)	162,84 ± 84,91	146,06 ± 60,84	0,52
Creatinine 600-1600 mg/day)	1061,53 (231 - 5600)	1069,50 (622,60 - 1338)	0,37
Phosphorus (400-1300 mg/g creatinine)	655,93 (87,75 - 1782,20)	585,00 (183,00 - 897,60)	0,33
Oxalate (4-31 mg/day)	116,92 ± 121,94	12,97 ± 10,82	0,04*
Citrate 250-1153 mg/day)	805,78 ± 423,73	911,45 ± 529,33	0,55

Data are means ± SD or median (minimum-maximum). *represents the significance
Abbreviations: PCOS: Polycystic Ovary Syndrome; SD: Standard Deviation

clinical (hirsutism with a modified Ferriman-Gallwey score of >6, acne, alopecia) and/or biochemical (free serum testosterone level of >2.7 pg/mL and/or total testosterone level of >80 ng/dL) signs of hyperandrogenism. Oligo and/or anovulation (cycle length irregular, >35 days or <8 periods per year), or polycystic ovary morphology (presence of at least one ovary of more than 10 ml size and/or with at least 12 follicles of 2 mm to 9 mm diameter) is accepted the two manifestations of ovarian dysfunction.

Exclusion criteria were as follows: pregnancy, hypothyroidism, hyperprolactinemia, congenital adrenal hyperplasia, cushing syndrome, androgen-secreting tumors, hypertension, diabetes, hyperparathyroidism, adrenal, hypophyseal or any systemic diseases such as sarcoidosis that alter calcium homeostasis, hypercalcemia, current or previous (within the last 6 months) use of calcium, vitamin D supplementation, hormonal medications, diuretics, antacids, H2 blockers, antihypertensive drug, obesity (body mass index [BMI] >30), smokers. Positive history or positive family history of urinary stone disease, so no graphically proven urinary stones, positive urine culture, incomplete 24 hr urine collection, impaired renal function (serum creatinine >1.5 mg/dL) and patients with anatomical anomalies of the urinary tract were also other exclusion criteria.

This study was approved by the Turgut Ozal University Ethical Committee and complied with the Helsinki Declaration. All women signed written informed consent before the start of the study. This work is supported by the Scientific Research Fund of Turgut Ozal University under project number 2013_04_006.

A complete physical examination was performed on all subjects. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m²) for all subjects.

Hormonal assays and transvaginal ultrasonography were performed during the early follicular phase, between the 3rd and the 5th days of the patients' spontaneous or progestin-induced menstrual cycle. The sonographic evaluations of the kidneys and urinary tract systems and the diagnosis and detection of urinary stone were performed by the same radiologist. Venous blood samples of the participants were collected in the morning subsequent to an overnight fast from the antecubital vein, and 24-hr urine was collected (after 3 days of diet restricting strawberry, chocolate, ice cream, meat, fish, spinach, asparagus, tomato, cucumber) and calcium,

sodium, potassium, chloride, oxalate, urea, citrate, cysteine, uric acid, magnesium, creatinine, and phosphorus levels were measured. 24-hr urine analysis and fasting serum biochemistry (creatinine, uric acid, urea, calcium, magnesium) as well as intact PTH and 1,25(OH)₂D₃ was performed at the same time.

Complete Blood Count (CBC), fasting blood glucose, fasting insulin, hormone profile, lipid profile, were measured. IR was determined from fasting glucose and insulin as homeostasis model assessment-insulin resistance (HOMA-IR) index: HOMA-IR = [glucose (mmol/l) × insulin (mIU/l)]/22.5. Oral glucose tolerance test (OGTT) with 75 gr glucose was applied to all patients.

CBC analysis was performed in a Beckmann-Coulter analyzer model LH -780 with optical scattering method. Blood glucose, total cholesterol, High-Density Lipoprotein (HDL) and Triglyceride (TG), serum creatinine, uric acid, urea, calcium and magnesium were measured by spectrophotometric method on a Roche Cobas 6000 series-c501 device (Roche Diagnostics, Tokyo, Japan). Low-Density Lipoprotein (LDL) was calculated with use of the Friedewald formula. Insulin, Follicle Stimulant Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Dehydroepiandrosterone Sulphate (DHEAS), Total Testosterone (TT), Thyroid Stimulating Hormone (TSH), and prolactin (PRL) were determined by Electrochemiluminesans (ECLIA) method using a Roche Cobas 6000 series-e601 device (Roche Diagnostics, Tokyo, Japan). 17-OH Progesterone was measured by a radioimmunoassay (RIA) method with DiaSource (Catalog No. KIP1409) kit in Ankalab Laboratory. 25OH cholecalciferol was measured by HPLC method using a UV detector on Zivak ONH-100A device (Istanbul, Turkey).

Urine calcium, sodium, potassium, chloride, urea, uric acid, magnesium, creatinine, and phosphorus were measured by spectrophotometric method on a Roche Cobas 6000 series-c501 device (Roche Diagnostics, Tokyo, Japan). Urine oxalate, citrate, cysteine were measured by spectrophotometric method on a Roche MIRA Plus analyzer (Roche Diagnostic Systems Welwyn Garden City, Herts) using a commercial kit in Ankalab Laboratory.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.0 for Windows XP. Continuous variables were first inspected for normality of statistical distribution graphically and by Shapiro-Wilk test. The data are presented as

mean \pm Standard Deviation or median with inter quartile ranges, as appropriate. Clinical characteristics, serum laboratory parameters and urinary biochemical parameters were compared in each group. The data were analyzed using the Student's t-test or Mann-Whitney test to determine whether differences were significant. The correlation between variables was investigated using Pearson correlation test (Spearman test). $P < 0.05$ was considered statistically significant.

Results

A total of 80 cases including 40 PCOS and 40 control patients were taken into the study. Seventeen cases were lost to follow-up ($n=5$, PCOS group, $n=12$ control group). Two cases had hemolysis in the blood ($n=1$, PCOS group, $n=1$ control group). Two cases had abnormal biochemical levels ($n=2$ control group). Twelve cases had abnormal hormonal levels ($n=5$, PCOS group, $n=7$ control group). Nine cases had inadequate or incorrect urine collection ($n=6$, PCOS group, $n=3$ control group). As a result, the study ended up with 38 subjects (PCOS group $n=23$, control group $n=15$).

There were no differences in age and BMI between the analyzed groups. Biochemical and endocrine features of PCOS and control groups are summarized in Table 1. As expected, serum LH, TT, 17-OH Progesterone, DHEAS, fasting insulin HOMA-IR, total cholesterol and LDL cholesterol levels were significantly higher in the PCOS group ($p = 0.001, 0.02, 0.04, 0.001, 0.01, <0.01, 0.02, 0.02$; respectively) (Table 2).

The urinary comparison of the subjects in both groups is shown in Table 3. When we compare the urinary composition of the groups, 24-hr excretion of oxalate levels were significantly higher in the PCOS subjects than control group ($p=0.04$). While urinary oxalate levels were found above the normal reference range in 3 PCOS patients, only 1 woman in control group had higher levels. Patients with PCOS had a higher urinary uric acid and lower citrate levels than control subjects, but there was no statistical significance ($p > 0.05$). While urinary citrate levels were found above the normal reference range in 1 PCOS patients, 6 woman in control group had higher levels. No difference was determined between the groups for 24-hr urinary excretion of calcium, sodium, potassium, chloride, urea, magnesium, creatinine, phosphorus, and cysteine levels ($p > 0.05$).

Discussion

In the present study, we found that 24-hr urinary excretion of oxalate levels were higher in PCOS group than healthy controls. Oxalate is a metabolic end product excreted in urine with no known useful biological function in human. Glycolate is metabolized to glyoxylate in liver peroxisomes, then metabolized to oxalate by glycolate oxidase, the most important enzyme in the pathway. Sex hormones have long been suspected of being etiologically important in the formation of calcium oxalate stones.

Several previous experimental studies have disclosed that androgens play a role in the etiopathology of urinary stone disease, for reason stone disease is more common in men than in women. Yoshihara et al. reported a gender-related difference in the metabolic conversion of glycolate to oxalate in rats, a process dose-dependently promoted by testosterone [17]. Their results also showed that estrogen decreases glycolate oxidase activity in male rats. Lee et al. Have shown that castrated male rats have a remarkable reduction in stone formation after drinking an ethylene-water solution and have indicated that testosterone promotes renal crystal deposition because

glycolic acid oxidase is involved in the metabolism of ethylene glycol to oxalate which may be enhanced by testosterone [10], resulting in hyperoxaluria, which in turn may be responsible for the increased predisposition to calcium oxalate urolithiasis [7]. In the rat ethylene glycol model of urolithiasis Dihydrotestosterone (DHT) is believed to be partially responsible for exaggerated hyperoxaluria [8]. Yagisawa et al. investigated the effect of castration on urinary lithogenic factors and renal osteopontin expression in rats treated with ethylene glycol and reported that while testosterone increased oxalate excretion in urine by suppressing osteopontin expression in the kidneys and promote stone formation, estrogen decreased oxalate excretion in urine by increasing osteopontin expression [16]. In another rat study Yoshioka et al. showed that sex hormones increased endogenous oxalate synthesis by affecting hepatic peroxisomal enzymes and renal tubular epithelial cells exposed to excessive oxalate causes oxidative stress injury that results in DNA damage to cells and initiates crystal formation [18].

In clinical studies Watson et al. reported that male stone formers ($n=30$) have higher serum total testosterone levels than stone-free controls ($n=25$) [19], Nath et al. Reported a positive correlation between serum testosterone with urinary oxalate in male stone formers [14]. Naghii et al. Analyzed the effect of steroid sex hormones in the plasma samples including testosterone, free testosterone, dihydrotestosterone, estradiol, and sex hormone binding globulin in renal stone patients and found higher androgen levels that indicate a possibility of a substantial pathogenic role of testosterone, free testosterone, and dihydrotestosterone in the pathogenesis of renal stones formation [13].

Androgenic hormone can modulate their effect through changes in their serum levels, or in the sensitivity or activity of their receptors. Defined an up-regulation in androgen receptors in the kidneys of patients with urolithiasis and linked the intergender difference of incidence to this condition [12].

Increased urinary excretion of uric acid is another risk factor for calcium stone disease that can form the nidus for calcium stone configuration. Heller et al. found lower daily excretion of urinary uric acid in women than men [9]. Unlike in another study, Shakhssalim et al. found no significant difference for testosterone and estradiol between the male active renal calcium stone formers and control groups serum testosterone was related to higher urinary excretion of uric acid in patients so postulated the possibility of testosterone involvement in the pathogenesis of renal stones through higher urinary uric acid and oxalate excretion [15]. In the present study 24-hr urinary excretion of oxalate levels were higher in PCOS group than healthy controls but we found no statistical significance ($p=0.07$).

Urinary citrates have a chelating activity against calcium ions regarded as an inhibitor of calcium-containing stone formation. Urinary citrate levels are clearly lower in stone formers than in healthy adults and in women than men [15]. In our study we found lower urinary citrate levels in PCOS group than healthy subjects.

As a result in our study we found statistically significantly higher urinary oxalate levels, higher urinary uric acid levels and lower urinary citrate levels which promote lithogenesis in PCOS patients than healthy controls suggesting the effect of testosterone. Small sample size of our study may have caused non-significant results in urinary uric acid and citrate levels. Hyperandrogenism, the main feature of PCOS, may trigger the urinary stone formation besides

hirsutism, alopecia and acne. Early identification of the situation will help to take protective measures in the PCOS patients.

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