

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

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Abstract The aim of this study is to investigate the serum levels of parathyroid hormone (PTH), calcitonin, 1,25 (OH)₂ vitamin D₃, estradiol and testosterone in male patients with active renal calcium stone disease compared with controls and investigate their relationship with serum/urinary biochemistry. Male active renal calcium stone formers (ASF) were enrolled from December 2008 to April 2009. Controls were selected from age and sex matched individuals. Two 24-h urine samples and a blood sample were withdrawn from each participant while they were on free diet. Serum 1,25 (OH)₂ vitamin D₃ levels in the ASF and control groups were 127 ± 40 and 93 ± 35 pmol/l ($p < 0.001$). Serum levels of PTH, calcitonin, estradiol and testosterone were not statistically different between the ASF and control groups (all $p > 0.05$). Serum 1,25 (OH)₂

vitamin D₃ was associated with higher urinary excretion of calcium and phosphorus in ASF patients. Serum levels of calcitonin were related to less urinary excretion of calcium in the control group. Serum testosterone was related to higher urinary excretion of uric acid in ASF patients and to higher urinary excretion of oxalate in the control group. 1,25 (OH)₂ Vitamin D₃ is an important hormone in the pathogenesis of recurrent renal calcium stone disease and could increase renal stone risk by increasing the urinary excretion of calcium and phosphorus. There is a possibility of testosterone involvement in the pathogenesis of renal stones through higher urinary uric acid and oxalate excretion.

Keywords Nephrolithiasis · Vitamin D · Parathyroid hormone · Calcitonin · Estradiol · Testosterone

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Introduction

Renal calcium stones represent more than 80% of kidney stones [1]. Different metabolic, anatomic, nutritional, genetic and environmental factors are involved in the pathogenesis of renal calcium stones [2–6]. Hypercalciuria is considered as an important factor contributing to the formation of calcium based kidney stones [7]. Therefore, hormones involved in calcium homeostasis were one of the early factors that were investigated in urinary stone pathogenesis. Hormones can modulate their effect through changes in their serum levels or in the sensitivity or activity of their receptors. Several studies have been published on the relationship of the serum levels of parathyroid hormone (PTH), calcitonin and vitamin D with kidney calcium stone disease.

Studies on PTH were mainly focused on kidney stones in hyperparathyroidism. In the few published studies about

idiopathic renal stone formers, no relationship was reported between serum PTH and calcium stone disease [8–10]. Serum levels of calcitonin in active calcium stone disease have not been fully investigated [11–13]. Few published studies reported an association between serum calcitonin and calcium stone disease [13, 14]. Several studies investigated the relationship of vitamin D levels in serum with calcium stone disease. Some studies observed an association between serum vitamin D and urinary calcium and uric acid excretion [8, 15]. Other studies have failed to repeat such observations [15–17]. Since the serum levels of vitamin D is dependent on sunlight [18], we think that the significance of vitamin D contribution to calcium stone pathogenesis could be regionally dependent. Studies on the association of vitamin D with renal stones in the Middle East are scant.

As the prevalence of renal stones is different in males and females [19, 20], some studies have focused on the possible role of sexual hormones and their receptors in renal calcium stone disease. In animal studies serum estradiol was associated with increased urinary citrate and decreased urinary oxalate excretion [19, 21, 22] and castration in males was also associated with lower urinary oxalate excretion [2]. The clinical relevance of these observations in human subjects remains to be further elucidated.

In the Tehran Stone Study, we aimed at studying the hormonal profile of 1,25 (OH)₂ vitamin D₃, PTH, calcitonin, estradiol and testosterone and variations in their receptor genes in active stone formers versus normal controls. To the best of our knowledge, few studies have evaluated this complete set of hormones in a single study and such studies have not been completed in an endemic area for kidney stones such as Iran. We have presented the hormonal profile section of this study in this article.

Materials and methods

Subjects and settings

Male active stone formers (ASF) who were referred to the Labbafinejad Hospital urology clinic from December 2008 to April 2009 and agreed to participate and met the inclusion criteria were enrolled. The study protocol aimed at enrolling 109 ASF patients and 109 controls. ASF was defined as a patient with at least two episodes of stone relapse or increase in stone size during the previous 5 years. Inclusion criteria were: male gender, age of 30–55 years, absence of adrenal, hypophyseal or any systemic diseases such as sarcoidosis that alter calcium homeostasis, absence of cardiovascular, gastrointestinal, hepatic or renal disease. Patients with non-calcium stones, current use of medications namely calcium tablets, vitamin D,

levothyroxine, lithium, hormonal medications, diuretics, antacids, vitamin C, H₂ blockers, probenecid, allopurinol, indinavir, obesity (body mass index > 30), positive urine culture and patients with anatomical anomalies of the urinary tract were excluded from the study. The exclusion of non-calcium stone formers was based on either the stone analysis report or, if not available, the radiological appearance of the stone in KUB films.

The controls were selected from similar age range and gender matched persons. The individuals were excluded from the control group if there was a positive history of urinary stone disease in them, their relatives, or if abdominal ultrasonography revealed the presence of urinary stones. The same exclusion criteria defined for the patients was also applied for the controls.

Blood and urinary sampling and analysis

Two 24-h urine collections and a blood sample were obtained from each subject. Participants were on a free diet with no restriction of their sodium or calcium intake when they were evaluated. Urine and blood samples were used to determine the blood, urinary biochemistry and serum hormonal levels. Serum biochemistry constituted total and ionized calcium, urea, creatinine, sodium, phosphorus, chloride, potassium, uric acid, bicarbonate and pH. The 24-h urinary biochemistry comprised phosphorus, creatinine, calcium, oxalate, sodium, uric acid, magnesium, urea, chloride, citrate and potassium. Hormonal profile investigation included PTH, calcitonin, 1,25 (OH)₂ vitamin D₃, estradiol and testosterone. The measurement of serum and urinary calcium, phosphorous and creatinine concentrations was carried out using selectra E autoanalyser (Vitalab, Merck, Germany). Urinary oxalate and citrate concentrations were measured by an enzymatic colorimetric method using standard kits (LTA s.r.l, Milan, Italy).

Serum PTH, testosterone and estradiol were measured by electrochemiluminescent method. (Elecys 2010 automatic analyzer, Roche Hitachi) The concentration of calcitonin was evaluated by ELISA method (IBL international GMBH). Serum 1,25 (OH)₂ vitamin D₃ measurement was performed by EIA Kit (IDS Ltd, UK) in which the first step is immunoextraction, followed by quantification completed by enzyme immunoassay.

Statistical analysis

SPSS ver. 16.0 software was used to enter and analyze the data subsequently. Logarithmic transformations of serum PTH, testosterone, calcitonin, urinary creatinine, calcium, oxalate, sodium, uric acid, chloride and citrate were used to make a near normal distribution. Other variables were analyzed without transformation. Independent samples *t*

test was used to compare quantitative variables between the ASF and control groups. To exclude the confounding effect of age, a logistic regression model was employed in which age was entered to the model and in the second step, predictor variables were introduced to the model. Bivariable scatter plots were used to judge the presence of evident nonlinear relationship between serum hormones and serum/urinary biochemistry. Pearson correlation coefficient was used to test the relationship of the serum levels of PTH, testosterone, calcitonin, estradiol and testosterone with serum or urinary biochemicals separately in ASF patients and controls. Two-sided p values less than 0.05 were considered statistically significant. In case of multiple comparisons, Bonferroni's adjustment for α was employed.

Results

106 ASFs and 109 controls were enrolled as final eligible candidates during the study period (3 ASF subjects were excluded because of inadequate blood/urinary samples). The mean \pm SD of age in ASF and the control subjects were 43.4 ± 6.9 and 38.4 ± 6.9 years, respectively ($p < 0.001$). The mean \pm SD of BMI in ASF and the control subjects were 26.3 ± 2.7 and 25.8 ± 3.0 , respectively ($p > 0.05$). A significant difference was observed between ASF and the control subjects regarding serum vitamin D3 and urinary 24-h calcium, oxalate, uric acid and citrate (Table 1). Mean (range) of serum PTH, calcitonin,

Table 1 Comparison of some serum and urinary biochemicals in male active calcium stone formers and controls

Characteristic	ASF ($n = 106$)	Controls ($n = 109$)	p value [†]
Serum			
Total calcium, mg/dl	10.1 ± 0.6	9.9 ± 0.7	0.02 [‡]
Uric acid, mg/dl	5.3 ± 1.2	5.0 ± 1.1	0.03 [‡]
24-h urine			
Chloride, mmol	197 ± 74	168 ± 52	0.004 ^{*‡}
Calcium, mg	221 ± 110	156 ± 73	<0.001 [*]
Oxalate, mmol	0.46 ± 0.19	0.34 ± 0.13	<0.001 [*]
Uric acid, mg	464 ± 239	352 ± 206	0.001 [*]
Citrate, mg	539 ± 285	411 ± 179	0.001 [*]

Values are expressed as mean \pm SD

* Analysis was performed on the logarithmic transformations of these variables

[†] Based on 20 comparisons for serum and urinary biochemicals between stone formers and controls (all biochemicals are not displayed), the p value should be less than 0.0025 for a difference to be statistically significant according to Bonferroni correction for multiple comparisons

[‡] Difference NOT statistically significant after Bonferroni's correction for multiple comparisons

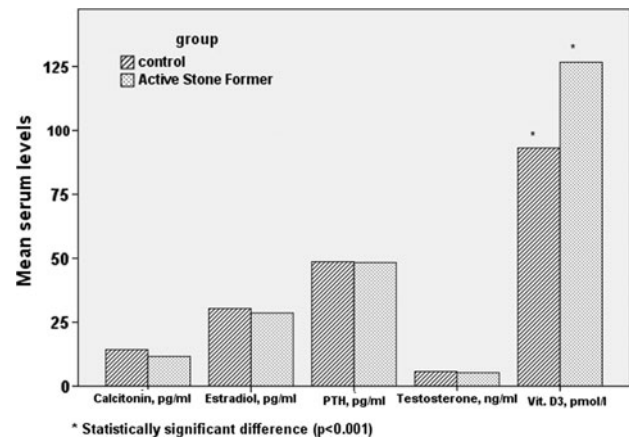


Fig. 1 Comparison of the serum levels of PTH, calcitonin, 1,25 (OH)₂ vitamin D3, estradiol and testosterone in active stone formers with the controls

testosterone, estradiol and 1,25 (OH)₂ vitamin D3 in ASF individuals were 48.3 (24–117), 11.6 (0.2–121.9) pg/ml, 5.2 (2.3–13.2) ng/ml, 28.6 (12–45) pg/ml and 126.7 (48–193) pmol/l, respectively. The above figures for the controls were 48.6 (19.5–102), 14.3 (0.2–87.8) pg/ml, 5.7 (2.3–13.6) ng/ml, 30.3 (14–62) pg/ml and 93.1 (40–191) pmol/l, respectively. The comparison of serum hormonal levels with the subjects' status of stone disease is shown in Fig. 1. The only statistically significant difference was for serum 1,25 (OH)₂ vitamin D3 ($p < 0.001$) and this existed after adjusting for age. The odds ratio for the probability of active calcium stone disease with each pmol/l increase in serum vitamin D3 after adjusting for the effect of age was 1.024 (CI 95% 1.015–1.034).

As several serum and urinary parameters were different between ASF and the control subjects, we tested the hypothesis of association between serum levels of investigated hormones and urinary biochemicals separately in the ASF and the control groups (Table 2).

The associations between serum vitamin D3 and urinary phosphorus, magnesium, calcium, oxalate, uric acid, potassium, sodium and chloride, between calcitonin and urinary calcium and citrate, and between testosterone and urinary uric acid were observed in the whole sample of ASFs and the controls. Other associations were only observed in either the ASF or the control groups. As explained in Table 2, after adjusting α for multiple comparisons only the associations of (1) serum 1,25 (OH)₂ vitamin D3 with urinary phosphorus, magnesium and calcium in ASF patients, (2) serum calcitonin with urinary calcium in controls, (3) serum testosterone with urinary uric acid in ASF patients and (4) serum testosterone with urinary oxalate in controls were statistically significant.

The associations of age with urinary calcium, citrate and oxalate were also tested (Data not provided). Positive

Table 2 Pearson correlation coefficient for the relationship of serum hormonal levels of PTH, calcitonin, vitamin D3, estradiol and testosterone, and 24-h urinary biochemistry

Urinary 24-h biochemistry	Estradiol		Vitamin D3		Ln(PTH)		Ln(calcitonin)		Ln(testosterone)	
	ASF	Con	ASF	Con	ASF	Con	ASF	Con	ASF	Con
Phosphorus	-0.12	0.09	0.29 ^{†,‡}	0.02	0.02	0.08	0.04	-0.11	0.04	0.07
Magnesium	-0.07	0.15	0.30 ^{†,‡}	0.10	0.02	0.09	0.03	-0.19*	0.08	0.07
Potassium	-0.21*	-0.01	0.21*	-0.09	0.05	-0.10	0.05	0.02	-0.06	0.01
Ln(calcium)	-0.11	0.03	0.44 ^{†,‡}	0.24*	0.08	0.11	0.03	-0.29 ^{†,‡}	0.13	-0.02
Ln(oxalate)	-0.06	0.09	-0.05	0.17	-0.06	0.01	0.20*	0.01	0.04	0.28 ^{†,‡}
Ln(sodium)	-0.03	0.17	0.25 [†]	-0.04	0.02	0.15	0.09	-0.12	0.11	0.09
Ln(uric acid)	0.03	0.08	0.24*	0.19*	-0.03	-0.01	-0.02	0.13	0.29 ^{†,‡}	0.23*
Ln(chloride)	-0.08	0.17	0.22*	0.19*	-0.04	0.03	0.23*	0.04	0.11	0.14
Ln(citrate)	-0.07	0.03	0.02	-0.03	-0.05	-0.01	-0.06	-0.25 [†]	0.04	-0.11

ASF active stone former, Con control, PTH parathyroid hormone, Ln natural logarithm

* p value < 0.05

[†] p value < 0.01

[‡] p value statistically significant after Bonferroni correction for multiple comparisons (9 comparisons reducing α to 0.0055)

correlation was observed between age and urinary citrate excretion. However, this difference is not statistically significant if we adjust α level for multiple comparisons according to Bonferroni (partial Pearson correlation coefficient after controlling for disease status: $r = 0.17$, $p = 0.02$). Furthermore, the associations of age with serum PTH, calcitonin, 1,25 (OH)₂ vitamin D3, estradiol and testosterone were evaluated after controlling for disease status. No statistically significant association was observed (all $r < 0.1$, all $p > 0.05$).

As supersaturation of urinary CaO_x, CaHPO₄ and uric acid are confirmed risk factors for calcium stones; we tested the relationship between serum PTH, calcitonin, 1,25 (OH)₂ vitamin D3, estradiol and testosterone with urinary supersaturation of the aforementioned crystals. There were statistically significant relationships between the serum levels of 1,25 (OH)₂ vitamin D3 and the urinary supersaturation of CaO_x ($p = 0.001$) and CaHPO₄ ($p < 0.001$) after controlling for disease status.

Discussion

The results of the current study confirm that serum vitamin D plays an important role in active idiopathic renal calcium stone disease and suggest a role for calcitonin and testosterone in the pathogenesis of the disease which are covered separately below under respective topics. Patients and controls were similar regarding demographic characteristics except for age. We used age range matching for controls in 10-year intervals. For example, each ASF subject from the 30–39-year age group was matched with a control from the same age range. This can explain the statistically

significant difference in age between ASFs and controls. Nevertheless, we cannot exclude the possibility of selection bias.

Vitamin D3

In this study, serum 1,25 (OH)₂ vitamin D3 levels were 30% higher in ASF patients compared to the controls (Fig. 1). 1,25 (OH)₂ Vitamin D3 was the only investigated hormone that was related to the participants' status of stone disease. The relationship of vitamin D3 with calcium stone disease has been previously reported in some studies while this relationship was not observed in certain other studies. We think that part of this inconsistency is environmental dependent as different levels of sunlight exposure result in different serum levels of vitamin D3 [18]. In fact, serum levels of 25 OH vitamin D3 were reported to be related to the latitude and seasons of the year [23]. If we consider 39–193 pmol/l as the reference range for serum 1,25-dihydroxyvitamin D [24], no participant in the current study had subnormal serum levels. All subjects' serum 1,25 (OH)₂ vitamin D3 fell within the reference range. The frequency of subnormal serum levels of 25-hydroxyvitamin D in Spanish and Finnish reports were within the range of 26–29% in the healthy adult population [25, 26]. The variation in the serum vitamin D3 in different regions and/or climates may result in varied contributions of vitamin D3 to stone pathogenesis. Other explanations could be the effect of calcium restriction on serum vitamin D3 [16, 27] which was exerted in some studies and polymorphisms in the gene for vitamin D receptor which can result in augmented response to the lower serum levels of vitamin D3 [3–5].

1,25 (OH)₂ vitamin D₃ was the only hormone in the current study that was associated with several urinary biochemicals (phosphorus, magnesium and calcium after correction by Bonferroni and also with uric acid, potassium and sodium if not considering the correction by Bonferroni). These associations could increase the possibility of calcium stone disease as urinary calcium and phosphorus are risk factors for renal calcium stone formation. The associations of serum vitamin D₃ with urinary calcium and uric acid have been previously demonstrated [15]. Moreover, higher excretion of urinary oxalate has been reported after vitamin D₃ consumption [28] and a positive association has been observed between the two [8]. In the current study, however, no relationship was observed between serum vitamin D₃ and urinary oxalate excretion in either the ASF or the control groups. It should be noted that high intake of calcium in free diet with no restriction on calcium intake, practiced in the current study, could result in lower intestinal absorption of oxalate and less excretion of urinary oxalate [8, 29]. Therefore, it is possible that such a relationship which could be observed in calcium restricted diets has been overlooked in the current study.

Parathyroid hormone

In this study, serum PTH was not related to the status of calcium stone disease. Serum levels of PTH were not related to any serum or urinary biochemistry evaluated in this study. This finding is in accordance with the results of previous studies. It has been suggested that PTH is not directly involved in urinary stone pathogenesis in idiopathic stone formers [30]. Other studies have also reported that serum levels of PTH were not different in renal stone formers versus the controls and between hypercalciuric and normocalciuric stone formers [9, 10].

It does not seem that PTH plays an important role in idiopathic active kidney calcium stone disease.

Calcitonin

In this study serum calcitonin levels were not related to the status of calcium stone disease. A previous study by Fuss et al. [14] reported higher baseline levels of calcitonin in recurrent kidney calcium stone formers who were on a low calcium diet. He reported higher response of calcitonin to calcium infusion in recurrent stone formers. Later D'Angelo et al. [30] demonstrated that the relationship of calcitonin with urinary stones is dependent on calcium intake.

We observed an association between the serum levels of calcitonin and higher urinary excretion of oxalate in the ASF group and less urinary magnesium, calcium and citrate in the controls. After considering Bonferroni's

correction for multiple comparisons, only the association of calcitonin with less urinary excretion of calcium in controls was statistically significant (Table 2). All these associations except for less urinary calcium in the controls can theoretically increase stone formation risk. Since in this study, no restriction was applied on calcium intake it is possible that effects dependent on calcium restriction have been overlooked.

Estradiol

Estrogen has been demonstrated to inhibit bone resorption and increase renal absorption of calcium [31, 32] and urinary citrate levels [19, 21]. In some studies, the possibility of stone prevention after menopause through estrogen supplementation was suggested through decreased urinary saturation of calcium crystals [21, 22], but clinical studies failed to observe decreased incidence of urinary stones in women treated with supplemental exogenous estrogen [33, 34].

In this study, no association was found between serum estradiol levels and the studied urinary risk/protective factors of stone formation. It should be noted that our study population was restricted to men with a narrow window of range for estradiol levels. Nevertheless, it seems that serum estradiol does not play an important role in recurrent idiopathic calcium stone pathogenesis in the male patients.

Testosterone

In the current study, serum levels of testosterone were not associated with the status of renal stone disease. The two to three times higher prevalence of renal stones in males [22] in comparison with females formed the rationale for hypothesizing a possible role for sexual hormones in urinary stone pathogenesis. Animal studies have found that stone incidence severely decreases from 71 down to 14% after castration in ethylene glycol-treated male rats [35, 36]. A human study reported higher levels of testosterone and FSH in stone forming males relative to the controls [37].

In bivariable analyses of the current study, we observed that serum levels of testosterone were related to urinary excretion of uric acid in both the ASF and the control groups and to urinary oxalate excretion in the control group. After implementing Bonferroni's correction, only the association of testosterone with urinary uric acid in ASF patients and oxalate in controls were statistically significant. Animal studies have confirmed that androgens increase and estrogens decrease urinary and serum oxalate levels and oxalate crystal deposition in rat kidneys [38]. It was observed that estrogen supplementation in castrated rats treated with ethylene glycol did not result in stone

formation whereas testosterone supplementation did [38]. Yagisawa et al. studied both castrated and normal male rats also treated with ethylene glycol. They observed less urinary oxalate excretion in castrated male rats [39]. Furthermore, human studies have revealed that in men urinary excretion of uric acid and oxalate is higher than females [40, 41]. Increased urinary excretion of uric acid is another risk factor for calcium stone disease [3] as uric acid can form the nidus for calcium stone formation.

At last the following points should be kept in mind when studying the results of this study. We assert that in this study only male active calcium stone formers were studied and that the results are only pertinent to male patients. We implemented Bonferroni's correction for multiple comparisons. Such a correction in this study with relatively small sample size makes this study inadequately powered to detect small to moderate differences in serum/urinary biochemicals between study groups.

Conclusion

In this study on a Middle Eastern male population as an endemic area for renal stones, we observed that in adult men aged 30–55-year-old 1,25 (OH)₂ vitamin D₃ is an important hormone in the pathogenesis of recurrent renal calcium stone disease and could increase renal stone risk by increasing urinary excretion of calcium and phosphorus. There is a possibility of testosterone involvement in the pathogenesis of renal stones through higher urinary uric acid and oxalate excretion.

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