ORIGINAL PAPER

UROLITHIASIS

The relationship between insulin, insulin resistance, parathyroid hormone, cortisol, testosterone, and thyroid function tests in the presence of nephrolithiasis: a comprehensive analysis

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Introduction Previous studies have shown that hormonal factors such as levels of insulin, cortisol, testosterone, and insulin resistance are related with increased nephrolithiasis (NL). However, no previous study has evaluated the relationship between insulin, insulin resistance, thyroid hormones, cortisol, intact parathyroid hormone and testosterone levels with the presence of NL in a comprehensive manner.
Materials and methods All patients underwent the following procedures: history taking, physical examination, biochemical analysis [including measurement of levels of insulin, thyroid hormones, cortisol, and total testosterone (for male patients only)], urine analysis, 24–hour urine collection to measure urinary protein, sodium excretion, and creatinine clearance. Insulin resistance was evaluated by the homeostasis model assessment index (HOMA–INDEX). The presence of NL was determined by ultrasonography.
Results The study was composed of 136 patients. In total, 30 patients had NL. Patients with NL were more likely to be older, male, obese, and smokers. Uric acid and HOMA–INDEX were also higher in patients with NL. In the whole group, only insulin (Odds ratio:1.128, CI:1.029–1.236, P:0.01) but not other hormones, and HOMA–INDEX were related with the presence of NL. In males, none of the hormones including total testosterone were associated with NL.
Conclusions Only levels of insulin, but not other hormones were associated with the presence of NL in a group of patients with suspicion of NL. More studies are needed to highlight the mechanisms regarding NL and hormone levels.

Key Words: cortisol ‹› insulin ‹› nephrolithiasis ‹› parathyroid ‹› thyroid

INTRODUCTION

Kidney stones are a common disease worldwide and lead to a major comorbidity in industrialized countries. Risk factors for kidney stones include age, gender, ethnicity, nutritional factors and genetic properties [1]. Previous studies have shown that hormonal factors play a role in the development of nephrolithiasis (NL). For instance, insulin resistance [2, 3] and testosterone [4, 5, 6] were found to be related with increased NL. Ando et al. showed that insulin resistance was higher in stone formers of Japanese descent [7]. On the other hand, van Aswegen et al. showed that persons with urinary stones have lower testosterone levels compared to healthy persons [8]. Fan et al. experimentally showed that testosterone increased the urinary oxalate excretion and kidney calcium oxalate crystal deposition [9]. Patients with hypercortisolism such as Cushing's disease, also have increased prevalence of NL [10]. Last but not least, increased parathyroid hormone levels and hyperparathyroidism are well known risk factors for NL [11, 12, 13]. Thus, it is of no doubt that hormonal factors play a role for the development of NL. However, the comprehensive evaluation of the relationship with hormones and NL is scarce in the literature. Ad-

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ditionally, no previous study has evaluated the relationship between levels of insulin, thyroid hormones, cortisol, intact parathyroid hormone, testosterone, and insulin resistance, in a comprehensive manner. Thus in light of the aforementioned data, the aim of this study was three–fold. Firstly, to determine general parameters related with ultasonographically detected urinary stones. Secondly, to investigate the relationship between different hormones (thyroid, parathyroid, insulin and cortisol) and NL. Thirdly, to investigate whether total testosterone levels were independently associated with NL in male patients.

MATERIAL AND METHODS

The current cross sectional study was conducted in the departments of internal medicine and nephrology. The study was in accordance with the declaration of Helsinki and local approval and informed consent was obtained before enrolment of the patients. The inclusion criteria involved: i) patients over 18 years old ii) patients referred to nephrology clinic with suspiscion of NL (low back pain, costovertebral angle tenderness, hematuria) iii) patients willing to participate. The patients were excluded from the study if they had i) urinary tract infection ii) any type of cancer iii) pyelonephritis iv) hypothyroidism or hyperthyroidism v) the unwillingness to participate.

All patients underwent the following procedures: history taking by questionnaire, physical examination, blood pressure (BP) measurement, fasting biochemical analysis (including measurement of levels of insulin, thyroid hormones, cortisol and total testosterone (for male patients only), spot urine analysis, 24–hour urine collection to measure urinary protein, sodium excretion, and creatinine clearance. During the anamnesis procedure, we recorded the socio–demographic and clinical characteristics including age, presence of diabetes, presence of hypertension, history of gout, history of NL, presence of coronary artery disease, medication, smoking status and alcohol intake. Interestingly, none of the patients reported any alcohol intake. Body mass index (BMI) was calculated as the ratio of weight in kilograms to height squared (in square meters). An information leaflet along with a urine container was given to all subjects and they also received a verbal explanation about how to collect a proper 24–hour urine sample. After excluding the first morning urine sample of the collection day, urine was collected over 24 h, which included the first urine sample of the next morning. During the sampling period, subjects were instructed to keep urine samples in a dark and cool place. At the end of the collection period, the urine containers were taken to the laboratory within 2–4 h. Seated clinical BP was measured manually, after 5 minutes of rest, with a mercury column sphygmomanometer and an appropriately sized cuff. Presence of hypertension was defined as systolic blood pressure $\geq$140 mmHg and diastolic BP $\geq$90 mmHg.

Patients were then referred to the radiology department for a renal ultrasound examination. The ultrasound examinations were performed blindly, randomly, and by various radiologists. It was previously demonstrated that USG examination is a sensitive method for detection of NL [14].

Laboratory analysis

The routine laboratory parameters were measured after 10–12 hours of fasting. If the patients were not fasting at the time of first admission, they were instructed to be fasting for 8–10 hours and then their laboratory parameters were measured on the next day after initial necessary laboratory analysis. The laboratory parameters including fasting blood glucose, blood urea nitrogen, creatinine, uric acid, sodium, potassium, calcium, phosphorus, hemoglobin, albumin, total cholesterol, low density lipoprotein cholesterol (LDL–cholesterol) high density lipoprotein cholesterol (HDL–cholesterol), triglycerides, thyroid stimulating hormone, free T3, free T4, were measured. The Hba1c and serum total testosterone levels were measured only in diabetic and male patients respectively. The levels of fasting glucose, urea, creatinine, uric acid, total cholesterol, LDL–cholesterol, HDL–cholesterol and triglycerides were determined by using commercially available assay kits with an autoanalyzer (Architect® c16000, Abbott Diagnostics, Abbott Park, Illinois, USA). Hemoglobin was measured by an automated blood analyzer (CELL–DYN 3700 cell counter Abbott Diagnostics Division, Abbott Laboratories, Illinois, USA). Serum sodium and potassium and urine sodium were measured by a direct potentiometric method using ion specific electrodes. 24–hour protein excretion was measured by Benzethonium Chloride Method by (Architect® c16000, Abbott Diagnostics, Abbott Park, Illinois, USA). Albumin was measured by the bromcresol purple method. TSH, FT3, FT4, insulin and cortisol levels were assayed by direct chemiluminescence method (Advia Centaur XP, Siemens, Dublin, Ireland).

Insulin resistance was calculated by the homeostasis model assessment (HOMA–INDEX), using the following formula: (HOMA–INDEX): [fasting plasma glucose (in millimoles per liter) × fasting serum insulin (in microunits per milliliter)]/22.5.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Evanston, Illinois, USA). Results were considered statistically significant if two–tailed P value was less than 0.05. Comparison of numerical variables among patients with and without NL was carried out by Mann–Whitney U test. Comparison of categorical variables between patients with and without NL was performed either by Chi–Square test or Fisher's exact test, as deemed appropriate. Logistic regression analysis was performed to analyze the independent factors related with the presence of NL.

RESULTS

Initially 153 patients were enrolled in the study. 3 patients with urinary tract infections, 2 patients with basal cell carcinoma and breast cancer, 1 patient with pyelonephritis, 3 patients with hypothyroidism, 1 patient with hyperthyroidism, and 7 patients unwilling to participate were excluded. The final patient population was composed of 136 patients. Among the 136 patients, 30 had NL. Among these patients, 2 had 4 or more urinary stones, 1 had 3 stones, 5 had 2 stones and the remaining patients had a solitary stone. The average diameter of the urinary stones was 10.4 mm. 14 patients had a stone in the left kidney, 10 patients in the right kidney, and 6 patients had stones in both kidneys. The localization of the stones was mostly in the lower anterior pole followed by the upper pole, calyxes, and ureter. The comparative demographic characteristics of patients with and without NL are shown in Table 1.

The comparative laboratory characteristics of patients with and without nephrolithiasis are shown in Table 2.

Subgroup analysis in diabetic and male patients

The current study included 58 diabetic patients. Among diabetic patients; patients with NL were older (65.3 ±8.1 years vs. 54.4 ±14.9, P:0.005), had higher uric acid (448.5 ±86.8 µmol/L *vs*. 342.6 ±85.7 µmol/L, P <0.0001) and insulin levels (15.61 ±4.47 µU/mL *vs*. 12.4 ±6.0 µU/mL, P:0.018) and lower HDL cholesterol (1.01 ±0.23 mmol/L *vs*. 1.22 ±0.18 mmol/L, P:0.001). However, the hba1c levels were similar in diabetic patients with and without NL (7.0% 4 ±0.67 *vs*. 7.1% 6 ±1.11, P:0.682).

Table 1. *Comparison of demographic and clinical parameters between patients with and without nephrolithiasis*

Parameter	Patients with Nephrolithiasis (N:30)	Patients without Nephrolithiasis (N:106)	P
Age (years) †	60.1 ±15.1	52.6 ±18.5	0.029*
Gender (male/female) (N:)	20/10	44/62	0.015**
Body Mass Index (kg/m^2) †	31.9 ±5.8	28.1 ±5.6	<0.0001*
Smoker/Non–smoker (N:)	11/19	18/86	0.023**
Presence of hypertension (yes/no) (N:)	20/10	62/44	0.419**
Presence of diabetes (yes/no) (N:)	20/10	38/68	0.003**
History of nephrolithiasis (yes/no) (N:)	8/22	11/95	0.035***
History of gut attack (yes/no) (N:)	6/24	8/98	0.081***
Presence of coronary artery disease	4/26	8/96	0.466***
Hematuria (yes/no) (N:)	10/20	26/80	0.335**
ACE inhibitor use (yes/no) (N:)	10/20	24/82	0.241**
Use of ca channel blocker (yes/no) (N:)	8/22	24782	0.646**
Use of beta adrenergic blocker (yes/no) (N:)	10/20	16/90	0.025**
Use of Alpha adrenergic blocker (yes/no) (N:)	0/30	8/98	0.199***
Use of Thiazide diuretics (yes/no) (N:)	4/26	14/92	0.986***
Use of Aldactone (yes/no) (N:)	2/28	2/98	0.228***
Use of angiotensin receptor blockers (yes/no) (N:)	6/24	16/90	0.576**
Clinical systolic blood pressure (mmHg) †	133.3 ±11.4	128.9 ±15.3	0.103*

† – Mean ±Standart Deviation, * – P value is based on Mann–Whitney U test, ** – P value is based on Chi–Square test, *** – P value is based on, Fisher's exact test

Table 2. *The comparative laboratory characteristics of patients with and without nephrolithiasis*

Parameter †	Patients with nephrolithiasis (N:30)	Patients without nephrolithiasis (N:106)	P*
Serum glucose (mmol/L)	6.44 ±1.74	6.07 ±2.53	0.055
Blood urea nitrogen (mmol/L)	8.96 ±4.25	9.03 ±5.28	0.717
Creatinine (µmol/L)	129.1 ±67.2	125.5 ±69.8	0.719
Hemoglobin (g/L)	131.4 ±9.4	127.7 ±16.8	0.249
Sodium (mmol/L)	138.9 ±4.3	139.4 ±3.5	0.505
Potassium (mmol/L)	4.78 ±0.63	4.59 ±0.63	0.153
Albumin (g/L)	43.3 ±3.5	43.4 ±4.6	0.823
Total cholesterol (mmol/L)	5.14 ±1.01	4.91 ±1.15	0.111
LDL–C (mmol/L)	3.06 ±0.98	3.05 ±1.0	0.604
HDL–C (mmol/L)	1.09 ±0.27	1.14 ±0.23	0.370
Triglyceride (mmol/L)	1.88 ±1.15	1.67 ±0.78	0.025
Uric acid (µmol/L)	450.9 ±195.1	342.6 ±90.4	<0.0001
Thyroid stimulating hormone (mU/L)	2.29 ±1.28	2.47 ±1.91	0.842
FT3 (pg/ml)	3.32 ±0.54	3.15 ±0.56	0.252
FT4 (ng/dl)	1.29 ±0.18	1.26 ±0.17	0.431
Calcium (mmol/L)	2.33 ±0.17	2.31 ±0.18	0.805
Phosphorus (mmol/L)	1.33 ±0.24	1.23 ±0.21	0.09
Intact parathyroid hormone (pg/ml)	75.5 ±48.2	83.1 ±53.2	0.456
Creatinine clearance (ml/min)/1.73 m2	65.8 ±27.4	67.1 ±32.8	0.992
24–hour urinary protein excretion (mg/day)	328.1 ±259.8	419.7 ±948.6	0.208
24–hour urinary Na excretion (mEq/day)	173.2 ±87.6	149.6 ±58.5	0.249
Cortisol (nmol/L)	520.3 ±137.8	488.4 ±156.0	0.372
Insulin (µU/mL)	13.93 ±5.61	10.3 ±5.61	0.001
HOMA–Index	3.85 ±1.37	2.89 ±2.34	<0.0001
Urinary Ph	6.14 ±0.61	6.17 ±0.78	0.939

†: Mean ±Standart Deviation, *: P value is based on Mann–Whitney U test

Male patients with NL had higher diastolic BP (82.4 ±5.4 mmHg *vs*.76.6 ±10.9 mmHg, P:0.016), higher uric acid (488.3 ±214.1 µmol/L *vs*. 380.7 ±82.7 µmol/L P:0.037), higher phosphorus (1.36 ±0.26 mmol/L *vs*. 1.18 ±0.20 mmol/L P:0.020), higher insulin (15.86 ±4.66 µU/mL *vs*. 10.8 ±5.9 µU/mL P:0.002), higher HOMA–index (3.99 ±1.51 *vs*. 2.93 ±2.08 P:0.013), higher cortisol levels (533.5 ±120.9 nmol/L *vs*. 522.4 ±134.9 nmol/L P:0.032). However, serum total testosterone levels were not different among patients (534.7 ±275.1 ng/ml *vs*. 484.4 ±168.6 ng/ml P:0.436). Additionally, male patients with NL had a higher percentage of history of NL (31.3% *vs*. 9.1%, P:0.027) and higher percentage of diabetes (80% *vs*. 36.4%, P:0.001). The results of univariate and multivariate logistic regression analysis of independent factors related with the presence of NL is shown in Table 3.

Since insulin was the only hormone independently related with NL, we performed specific analysis regarding insulin percentiles and presence of NL. The 25th, 50th, and 75th percentile concentrations of insulin were 6.35, 10.06 and 14.6 µU/mL respectively. The presence of NL when going from 25th to 75th percentile were 2/34 (5.88%), 14/68 (20.59%) and 14/34 (41.18 %) respectively (P:0.002). Post–hoc analysis revealed that 25th and 50th percentile were not different (P:0.054). However, there was a difference between the 50th and 75th percentiles (P:0.028) and 25th and 75th percentiles (P:0.001) (Figure 1). Lastly, we performed logistic regression analysis of statistically different parameters, but only in male patients with and without NL. The independent parameters included history of NL, presence of diabetes, diastolic BP, uric acid, phosphorus, insulin, HBa1c, HOMA–index and cortisol. The results of multivariate logis-

tic regression analysis in male patients are shown in Table 4.

DISCUSSION

The present study aimed to analyze the relationship between presence of NL and various hormones such as insulin, cortisol, free T3, free T4, intact PTH and total testosterone (in males only) in a comprehensive way. As a result, some interesting findings emerged such as: i) only insulin levels but not levels of cortisol, free T3, free T4, and intact PTH were related with the presence of NL, ii) in male patients none of the hormones, including total testosterone, were related with the presence of NL.

Another interesting finding of this study was that insulin levels, but not insulin resistance, were related with the presence of NL. This finding was in contrast with the previous findings which suggested that insulin resistance was a risk factor [15, 16]. This difference may be due to the diversity of measuring insulin resistance. Indeed, in one study it was demonstrated that there was no difference in HOMA–INDEX between stone formers and not. However, in the same study, the number of metabolic syndrome traits, which is a clinical measure of insulin resistance, was significantly associated with the risk. The authors speculated that cyclic biological variation in insulin levels and the lack of validity of HOMA–INDEX above fasting blood glucose levels of 140 mg/dL may be potential explanations [1]. The mechanisms through which insulin influences the presence of NL include: increased calcium excretion [2, 17], increased retention and decreased clearance of sodium which may also contribute to the decreased urine pH [18], and decreased urinary citrate excretion [19].

We did not demonstrate any relationship between cortisol levels and presence of NL. However, previously it was reported that glucocorticoids may increase the risk of kidney stones [10]. Glucocorticoid–dependent nephrolithiasis (GDNL) may result as a consequence of hypercalciuria, hyperuricosuria, and hypercystinuria, which are common features of patients with Cushing's syndrome [20, 21, 22] and are clearly associated with kidney stones formation [23]. However, GDNL probably has a multifactorial pathogenesis, because several other factors related with glucocorticoid excess such as obesity, hypertension, insulin resistance may contribute to kidney stones formation [10].

Faggiano et al. have shown that in patients with Cushing's disease, an increased prevalence of NL was

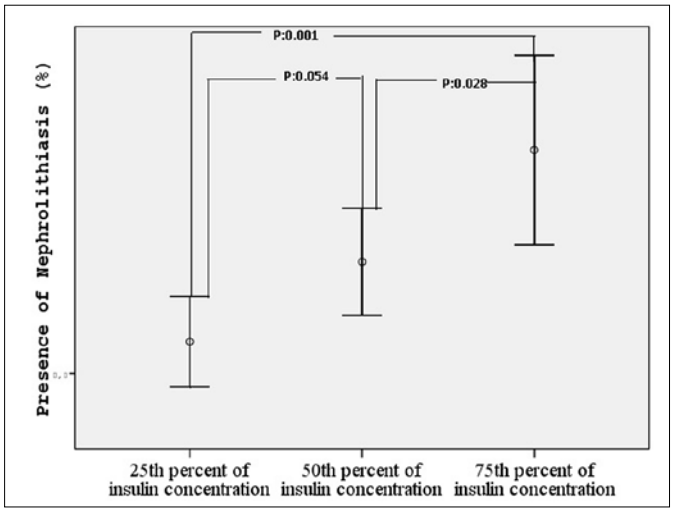

Figure 1. *Comparison of presence of nephrolithiasis among insulin percentiles.*

Table 3. *Univariate and Multivariate Logistic regression of independent factors related with the presence of NL*

	Odds ratio (Exp(B)	95.0% CI for EXP(B)	P
Univariate Analysis			
History of NL	3.144	1.129–8.695	0.028
Being male	2.816	1.201–6.622	0.017
Presence of Diabetes	3.584	1.519–8.403	0.004
Age	1.025	1.005–1.051	0.048
Smoking	2.762	1.124–6.802	0.027
Body Mass Index	1.116	1.040–1.199	0.002
Diastolic blood pressure	1.071	1.023–1.121	0.003
HOMA–INDEX	1.192	1.005–1.414	0.044
Uric acid	1.533	1.187–1.979	0.001
Phosphorus	2.059	1.061–3.997	0.033
Insulin	1.115	1.037–1.199	0.003
Use of Beta blocker	2.808	1.113–7.092	0.029
Multivariate Analysis			
History of NL	3.597	0.888–14.492	0.073
Being Male	2.028	0.529–7.751	0.302
Presence of Diabetes	2.016	0.452–9.056	0.358
Age	1.028	0.990–1.067	0.145
Smoking	1.445	0.276–7.575	0.663
Body Mass Index	1.166	1.067–1.275	0.001
Diastolic Blood Pressure	1.013	0.949–1.082	0.689
HOMA–INDEX	1.025	0.741–1.419	0.880
Uric acid	1.382	1.047–1.825	0.022
Phosphorus	2.573	1.071–6.181	0.035
Insulin	1.128	1.029–1.236	0.01
Use of Beta blocker	4.587	1.340–8.963	0.015

present [10]. In the current study, we did not demonstrate any relationship between cortisol levels and NL. The lack of association may be explained in several ways. Firstly, the pathophysiologic cause of increased NL may not be due to effects of cortisol itself but due to other factors such as increased urinary excretion of calcium, phosphorus, potassium, uric acid, cystine, oxalate, and decreased urinary excretion of citrate [10]. Unfortunately, we did not measure these parameters. Secondly, hypercortisolism may exert its effect indirectly such as through the increased prevalence of obesity, arterial hypertension, diabetes mellitus, and increased blood glucose, all of which are risk factors for NL. Lastly, it is possible that single measurements of basal cortisol levels may be inadequate in showing circadian cortisol levels. It would be better to collect 24–hour urinary cortisol levels which may reflect circadian cortisol levels better. It is stated that the prevalence of NL is higher in men compared to women. This may be due to the protective effect of estrogen on NL [24]. Alternatively, testosterone may increase the risk of NL. Indeed, many studies have demonstrated that testosterone was associated with the presence of NL [4, 5, 6].

Thus by the light of these findings, we investigated whether testosterone levels were associated with the presence of NL in men. However, we did not demonstrate any independent relationship between testosterone levels and NL. The lack of findings may be due to the low number of patients and the measuring of total testosterone instead of free testosterone. We believe that more studies are needed regarding this issue.

In the current study, we found that BMI has been associated with the presence of NL. Previously, a dose–response relationship between body mass index (BMI) and the risk of kidney stones was also reported [25]. Potential mechanisms include higher net endogenous acid production [26], impaired ammonia production, [27] and lower urine pH [28].

In the present study, we found that the presence of diabetes mellitus is associated with NL in males. This finding is in support with the previous studies showing that diabetes is significantly associated with an increased risk of kidney stones [16, 29, 30].

One may consider that the prevalence of NL in the current study is high. This may be due to the characteristics of patients accepted to this study. Patients with hematuria, low back pain, costovertebral pain, and those who were referred from other clinics, compromise the patients' population in the current study.

Our study has some limitations that deserve mentioning. Firstly, the cross–sectional design precludes drawing inferences about causation. Secondly, we did not determinate dietary recall by a food questionnaire. Thirdly, we did not evaluate urinary citrate and potassium excretion. Lastly, we did not specifically determine the type of stones.

Table 4. *Multivariate Logistic regression of independent factors related with the presence of NL in Male patients*

	Odds ratio (Exp(B)	95.0% CI for EXP(B)	P
History Of NL	5.813	1.128–11.303	0.035
Presence of Diabetes	6.849	1.117–11.363	0.038
Diastolic blood pressure	1.034	0.956–1.118	0.401
Uric acid	1.582	1.134–2.208	0.007
HOMA–INDEX	1.367	0.717–2.610	0.341
Insulin	1.013	0.675–1.046	0.120
Cortisol	1.002	0.995–1.006	0.876

CONCLUSIONS

In conclusion, only insulin levels but not levels of other hormones were associated with the presence of NL in a group of patients with suspicion of NL. More studies are needed, to highlight the mechanisms regarding NL and hormone levels.

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