Nephrolithiasis in Israel: Epidemiological Characteristics of Return Patients in a Tertiary Care Center

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ABSTRACT: **Background:** The prevalence and etiology of nephrolithiasis vary, depending on geography, gender and ethnicity.

Objectives: To analyze the demographic data of return nephrolithiasis patients in a tertiary care center.

Methods: We retrospectively reviewed our prospective registry database of return patients seen at our outpatient clinic for nephrolithiasis. Data included gender, age at first visit, age at first stone event, body mass index (BMI), self-reported hypertension, diabetes mellitus (DM), and hyperlipidemia. All patients were seen at least twice and had undergone a metabolic workup.

Results: A total of 260 return patients were seen during the period 2010–2015. The male:female ratio was 3.1:1. Mean age at the first stone event was 44.1 years. Median time elapsed since the first stone event to medical evaluation was 5 years (interquartile range 1–12 years). Hypertension was reported by 33.1% of the patients, DM by 23.5% and hyperlipidemia by 30.4%. All three diseases were reported by 11.5% of patients. The metabolic abnormalities detected were hypocitraturia (60%), low urine volume (LUV) (60%), hypercalciuria (40.8%), hyperoxaluria (24.2%), hyperuricosuria (16.5%) and hyperuricemia (13.5%). Stone compositions from most to least frequent were calcium-oxalate (81%), calcium-phosphate (11.9%) and uric acid (7.1%). We also found that 24.6% were obese (BMI ≥ 30 kg/m2) and showed higher rates of hypertension, DM, hyperlipidemia, hyperuricemia and hyperuricosuria compared with non-obese patients. Significantly higher rates of obesity and LUV were detected in females compared with males. Patients over age 45 had lower rates of hyperuricemia compared with patients ≥ 45 years old ($P = 0.038$).

Conclusions: Factors related to nephrolithiasis can potentially differ among populations and countries. Our findings emphasize the significance of individualized national health programs to address local issues.

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KEY WORDS: nephrolithiasis, epidemiology, return patients

The estimated prevalence of nephrolithiasis varies around the world with reported rates ranging from 3.5% in South Korea [1] to 8.5% in the United States [2]. The traditionally stated male:female ratio of 3:1 can still be found in some countries [2,3], yet in other parts of the world it can reach to as high as 5:1 [4]. The global trend, though, is a reduction of the male-female gap and an overall increase in stone prevalence probably due to nutrition and lifestyle changes [2,5-8].

Metabolic syndrome or its components are known risk factors for kidney stone formation [2,9-12], although ethnicity [2,4] and family history [1,3,6,13] were also suggested. The relevant English-language medical literature from the past decade is quite sparse, focusing mainly on the prevalence of nepholithiasis in the general population. Moreover, most of the studies came from places where the general population is ethnically homogenous.

Israel is unique with regard to the epidemiology of nephrolithiasis: it is a melting pot of various populations, it is located in the Middle East yet its inhabitants tend to adopt a Western lifestyle, and due to its small size and the medical system being public in nature the accessibility to tertiary care centers is high. Thus, a cross-section of patients with renal stones is seen. In this study we aimed to explore the demographic and metabolic characteristics of nephrolithiasis patients repeatedly seen in a tertiary care center.

PATIENTS AND METHODS

Following approval obtained from our Institutional Review Board we established a prospective registry database of adult patients repeatedly seen at our tertiary care medical center for nephrolithiasis. The demographic variables recorded included the patient's age at the first visit, patient's age at discovery of the first stone, gender, body mass index (BMI), and self-reported co-morbidities (hypertension, diabetes mellitus, hyperlipidemia, smoking, among others). In accordance with the most recent American Urological Association guidelines for medical management of kidney stones [14], blood samples were drawn for the evaluation of serum urea, creatinine, calcium and uric acid level. One sample of 24 hour urine collection was obtained from each patient and consisted of total urine volume, pH, creatinine, sodium, potassium, calcium, uric acid, oxalate, and citrate. Stone composition was recorded whenever applicable.

The database was reviewed retrospectively. Low urine volume (LUV) was defined as < 2000 ml/day, high urine sodium level as > 200 mmol/day, hypercalciuria was set at > 200 mg/day, hyperuricosuria at > 750 mg/day, hyperoxaluria at > 45 mg/day, and hypocitraturia at < 600 mg/day (for both men and

women). Regarding serum levels, hypercalcemia was defined as > 10.4 mg/dl and hyperuricemia as > 7.4 mg/dl. All patients were seen at least twice the by the same doctor.

Data are presented as either number (%) or mean ± standard deviation (SD) unless otherwise specified. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, Version 17.0, Chicago, IL, USA). Student's *t*-test was used for analysis of continuous variables and the chi-square test was used for analysis of categorical variables. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

A total of 260 adult patients were seen at least twice by the same doctor between the years 2010 and 2015. Their demographics and clinical data are presented in Table 1. Calculated male:female ratio in this cohort was found to be 3.1:1.

Table 1. Demographic and clinical data

	Total	Males	Females	*P* value
N	260	196 (75.4)	64 (24.6)	
Age at 1st stone (yr)	44.1 ± 15.1	44 ± 14.8	44.4 ± 16.1	0.42
Age at 1st visit (yr)	53.4 ± 14.3	53.4 ± 14.1	53.3 ± 14.9	0.87
BMI (kg/m2)	28.4 ± 6	27.9 ± 5.1	29.9 ± 8.1	‹ 0.001
Hypertension	86 (33.1)	64 (32.6)	22 (34.4)	0.72
NIDDM	61 (23.5)	41 (20.9)	20 (31.2)	0.08
Hyperlipidemia	79 (30.4)	63 (32.1)	16 (25)	0.31
At least two disorders	69 (26.5)	49 (25)	20 (31.2)	0.33
All three disorders	30 (11.5)	24 (12.2)	6 (9.4)	0.53
Smoking	27 (10.4)	22 (11.2)	5 (7.8)	0.33
Urine volume (ml)	1888.6 ± 54.5	1978.2 ± 64.9	1617 ± 90.4	0.029
Urinary Na (mmol/24 hr)	185.6 ± 73.9	194.2 ± 6	160.8 ± 11	0.78
Urinary Ca (mg/24 hr)	217.7 ± 135	227.4 ± 10.2	188.7 ± 16.7	0.97
Urinary uric acid (mg/24 hr)	599.9 ± 234	640.3 ± 18.2	467.5 24.9	0.20
Urinary oxalate (mg/24 hr)	36.8 ± 17.7	39.1 ± 1.5	29.4 ± 1.8	0.046
Urinary citrate (mg/24 hr)	504.5 ± 350	504.3 ± 27.2	504.8 ± 49.6	0.60
Serum Ca (mg/dl)	9.4 ± 0.5	9.4 ± 0.5	9.5 ± 0.5	0.88
Serum uric acid (mg/dl)	6 ± 1.5	6.3 ± 1.4	5.3 ± 1.7	0.12
Low urine volume	156 (60)	110 (56.1)	46 (71.2)	0.016
Hypocitraturia	156 (60)	115 (58.7)	41 (64.1)	0.59
Hypercalciuria	106 (40.8)	83 (42.3)	23 (35.9)	0.78
Hyperoxaluria	63 (24.2)	52 (26.5)	11 (17.2)	0.22
Hyperuricosuria	43 (16.5)	38 (19.4)	5 (7.8)	0.048
Hyperuricemia	35 (13.5)	31 (15.8)	4 (6.2)	0.08
High urinary sodium	42 (16.2)	33 (16.8)	9 (14)	0.86

BMI = body mass index, NIDDM = non-insulin-dependent diabetes mellitus

Fifty-seven patients (21.9%) were first-time stone formers while 203 patients (78.1%) were repeat stone formers (i.e., history of at least two renal stone events) when presenting at our clinic. Figure 1 depicts patients' age at the first visit versus age at the first stone event. Median time elapsed since the first stone event to repeat follow-up and treatment was 5 years (interquartile range 1–12 years), and as demonstrated in Figure 1 was more prominent in older age groups.

Metabolic abnormalities for the entire cohort from most to least frequent were as follows: hypocitraturia (60%), LUV (60%), hypercalciuria (40.8%), hyperoxaluria (24.2%), hyperuricosuria (16.5%) and hyperuricemia (13.5%). Stone compositions from most to least frequent were calcium-oxalate (81%), calcium-phosphate (11.9%) and uric acid (7.1%).

Regarding gender-related differences [Table 1], females had higher BMI and higher prevalence of LUV compared with males. Higher levels of urine volume and urine oxalate were observed in males compared with females, and male patients demonstrated higher rates of hyperuricosuria than did female patients ($P = 0.048$). The remaining categories showed no gender-related differences.

Overall, 69 patients (24.6%) had a calculated BMI higher than 30 kg/m2. For further analysis, BMI was dichotomized as ≥ 30 kg/m2 or < 30 kg/m2 [Table 2]. Comparison of the two groups revealed that obese patients (BMI ≥ 30 kg/m2) were significantly older when first seen in our clinic but not at the first renal stone event. Moreover, this group had a higher prevalence of hypertension, diabetes mellitus (DM) and hyperlipidemia by self-report. Regarding metabolic abnormalities, obese patients had a higher prevalence of hyperuricemia and hyperuricosuria and a lower prevalence of hypocitraturia compared with non-obese patients.

Finally, the study group was analyzed according to age group (e.g., < 45 years or ≥ 45 years) [Table 3]. Patients younger than 45 had a significantly lower prevalence of self-reported hypertension, DM, hyperlipidemia or a combination of the latter three diseases compared with older patients. Nevertheless, the two groups did not differ in terms of metabolic abnormalities with the exception of hyperuricemia, which was found to be more frequent in the older age group.

Figure 1. Age at first visit versus age at first stone event

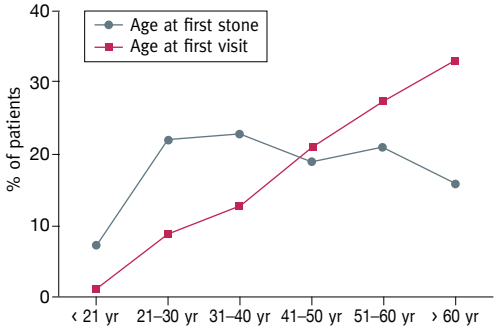

Table 2. Demographic and clinical data in accordance with BMI

	BMI < 30 kg/m^2	BMI ≥ 30 kg/m^2	*P* value
N (213)	144 (75.4)	69 (24.6)	
Age at 1st stone	44.4 ± 15.7	46.6 ± 14.3	0.19
Age at 1st visit	52.6 ± 15.4	55.4 ± 11.6	0.004
Hypertension	37 (25.7)	35 (50.7)	< 0.001
NIDDM	28 (19.4)	24 (34.8)	0.007
Hyperlipidemia	40 (27.8)	29 (42)	0.017
At least two disorders	32 (22.2)	28 (40.6)	0.005
All three disorders	11 (7.6)	15 (21.7)	0.003
Smoking	14 (9.7)	9 (13)	0.34
Urine volume	1764.6 ± 68.5	2059.9 ± 94.1	0.69
Urinary Na (mmol/24 hr)	177.4 ± 7.3	207.2 ± 9.5	0.72
Urinary Ca (mg/24 hr)	204.9 ± 10.2	245.4 ± 21.7	0.001
Urinary uric acid (mg/24 hr)	551.6 ± 17.6	694.3 ± 36	0.028
Urinary oxalate (mg/24 hr)	35.6 ± 1.8	40.5 ± 2.3	0.93
Urinary citrate (mg/24 hr)	489.4 ± 32.8	549.6 ± 46.1	0.58
Serum Ca (mg/dl)	9.4 ± 0.5	9.4 ± 0.6	0.27
Serum uric acid (mg/dl)	5.8 ± 1.4	6.4 ± 1.6	0.30
Low urine volume	94 (65.3)	34 (49.3)	0.059
Hypocitraturia	93 (64.6)	34 (49.3)	0.031
Hypercalciuria	53 (36.8)	33 (47.8)	0.12
Hyperoxaluria	30 (20.8)	21 (30.4)	0.11
Hyperuricosuria	16 (11.1)	18 (26)	0.004
Hyperuricemia	13 (9)	17 (24.6)	0.002
High urinary Na	18 (12.5)	15 (21.7)	0.09

BMI = body mass index, NIDDM = non-insulin-dependent diabetes mellitus

Table 3. Demographic and clinical data in accordance with age

	Age < 45 years	Age ≥ 45 years	*P* value
N (260)	133	127	
BMI ≥ 30 kg/m^2	31 (23.3)	38 (29.9)	0.55
Hypertension	24 (18)	62 (48.8)	< 0.001
NIDDM	19 (14.3)	42 (33)	< 0.001
Hyperlipidemia	28 (21.1)	51 (40.2)	0.001
At least two disorders	21 (15.8)	48 (37.8)	< 0.001
All three disorders	7 (5.3)	23 (18.1)	0.001
Smoking	15 (11.2)	12 (9.4)	0.80
Urine volume	1834.1 ± 77.6	1945.2 ± 76.5	0.95
Urinary Na (mmol/24 hr)	192.7 ± 8	178.9 ± 7.2	0.42
Urinary Ca (mg/24 hr)	225.6 ± 13	209.4 ± 11.7	0.64
Urinary uric acid (mg/24 hr)	611.8 ± 23.1	587.8 ± 21.9	0.65
Urinary oxalate (mg/24 hr)	35.6 ± 1.5	38.3 ± 2.1	0.031
Urinary citrate (mg/24 hr)	479.1 ± 27.3	531.7 ± 39.7	0.008
Serum Ca (mg/dl)	9.5 ± 0.4	9.3 ± 0.6	0.21
Serum uric acid (mg/dl)	5.9 ± 1.5	6.1 ± 1.5	0.76
Low urine volume	80 (60.1)	76 (59.8)	0.38
Hypocitraturia	83 (62.4)	73 (57.5)	0.64
Hypercalciuria	2 (1.5)	1 (0.8)	0.64
Hyperoxaluria	33 (24.8)	30 (23.6)	0.95
Hyperuricosuria	24 (18)	19 (15)	0.70
Hyperuricemia	13 (9.8)	22 (17.3)	0.038
High urinary Na	25 (18.8)	17 (13.4)	0.41

BMI = body mass index, NIDDM = non-insulin-dependent diabetes mellitus

DISCUSSION

Male predominance in nephrolithiasis continues to be the rule in general, although the male:female ratio varies around the world. Correspondingly, it is reported to be as low as 1.3:1 in North America [5] or as high as 5:1 in Saudi Arabia [4], placing European and Asian countries between those two extremes with a rough estimated ratio of 2.4–3:1 [1,3,7,13]. Our calculated ratio of 3.1:1 is higher than in Europe, yet not as high as in our neighboring country Saudi Arabia, a fact that reflects the mutual influence of geography and ethnicity on these numbers. Nonetheless, the mean age at the first stone event in Israel (44.1 years) is identical to that found in Iceland [13] and does not concur with the shift trend observed in Japan towards older age at the first stone event [7].

Gender differences may be expected when it comes to 24 hour urine composition given the different muscle and fat proportion in both sexes. In an analysis of 2800 patients Walker et al. [13] found significantly higher levels of oxalate, uric acid and calcium in 24 hour urine collection obtained from males compared with females and lower though non-significant levels of citrate. Our analysis failed to detect any difference in urinary components between the genders.

Metabolic syndrome is clinically defined by a clustering of abdominal obesity, dyslipidemia, hypertension and elevated fasting plasma glucose levels [12]. Previous studies identified metabolic syndrome or its components as an independent risk factor for kidney stone formation [9,11,12,15-17]. Correspondingly, in our study higher rates of hypertension, DM and hyperlipidemia were reported by obese patients compared with non-obese, probably as part of an entire metabolic syndrome.

Trinchieri and co-workers [6] investigated changes in prevalence of symptomatic upper urinary tract stones over a 12 year period in a small village near Milan. They found an overall increase in stone prevalence, particularly in males, which they attributed to increased animal protein consumption and lifestyle modifications. The present study reinforces this theory as

significantly higher rates of hyperuricemia and hyperuricosuria were found in obese compared with non-obese patients.

Interestingly, in our study, obese patients tended to seek medical attention later than the non-obese, a fact that may reflect both patients' low compliance and the reluctance of their caregivers to take responsibility for them [18].

Calcium salts in general and calcium oxalate in particular was found by previous studies to be the leading component of upper urinary tract stones [4,7,13] and Israel is no exception [19]. Our findings are in line with the most recent study from our country [19] as well as others.

Another point that warrants mentioning is the relatively long lag since the first stone event to periodic follow-up examinations by a tertiary care center urologist. Many of our patients, before attending our clinic, were previously seen by community urologists who seemed to overlook the importance of a full metabolic workup followed by appropriate medical and dietary treatment in stone patients. Unfortunately, this resulted in further stone events that could have been easily prevented had these urologists been better informed on the subject.

Friedlander et al. [20] retrospectively examined the relationship between age and 24 hour urine composition in 1115 patients. The patients were divided into four age groups: < 45 years, 45–54.9 years, 55–64.9 years, and ≥ 65 years. Similar to our findings, higher rates of hypertension and DM in the older ages were demonstrated. Yet, the difference between the groups in 24 hour urine composition was not apparent in our study compared with the other study, and with the exception of hyperuricemia there were no differences between the groups with regard to metabolic abnormalities.

Although this study has shed light on the nephrolithiasis population in Israel there are a few weak points that should be mentioned. The first is the relatively small study group. Second, given the lack of a national nephrolithiasis registry database we could neither compare the study population to the general population nor make conclusions about incidence and prevalence as did previous studies [1-3,6-7]. Another weak point is the fact that all reported co-morbidities in our study population were self-reported. Finally, due to a wide variability in group ethnicity, we were unable to analyze this category as we did with age, gender and BMI. Nonetheless, the take home message of the present study is that nephrolithiasis is a multifactorial disease that is subject to change as a function of geography, ethnicity and lifestyle.

CONCLUSIONS

Nephrolithiasis in Israel is a fifth-decade disease with an apparent high male:female ratio compared with the Western world. Analyzing nephrolithiasis patients according to age, gender and BMI reveals various differences and points that warrant attention such as a remarkable lag from the first stone event to medical consultation, particularly in the older age groups. This study emphasizes the significance of individualized national health programs to address local issues.

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