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ORIGINAL PAPER

Dyslipidemia is associated with an increased risk of nephrolithiasis

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Abstract The pathophysiology of nephrolithiasis is multifactorial. Obesity, diabetes mellitus and hypertension are implicated in its formation. Dyslipidemia (DLD) recently has received attention as well. Congruent with a vascular etiology in stone formation, DLD theoretically would predispose patients to nephrolithiasis. We investigated a possible association of DLD with nephrolithiasis. A random cohort of 60,000 patients was established by collecting the first 5,000 patient charts per month in the year 2000. After excluding pediatric patients, a retrospective study was performed by reviewing age, sex, comorbidities, and last patient follow-up. Median lipid laboratory levels also were reviewed. Descriptive statistics were performed as well as Cox proportional-hazards regression analysis, and univariate and multivariate analyses. 52,184 (22,717 women/29,467 men) patient charts were reviewed. The average age was 31.0 ± 15.2 years. On univariate analysis, DLD was associated with nephrolithiasis with a hazard ratio (HR) of 2.2 [Confidence Interval (CI), 1.9–2.5; $p < 0.001$] and on multivariate analysis HR = 1.2 (1.0–1.5; $p = 0.033$). Low-density lipoprotein and triglycerides had no association with stone disease. Patients with high-density lipoprotein (HDL) values <45 for men and <60 for women had an HR of 1.4 (1.1–1.7, 95% CI, $p = 0.003$) on univariate analysis and on multivariate analysis; HR = 1.27 (1.03–1.56; $p = 0.024$) for nephrolithiasis. DLD was associated with an increased risk of stone disease though the only specific lipid panel associated with lower nephrolithiasis was HDL. Clinicians should consider obtaining lipid levels with the intent that treatment could potentially not only mitigate atherosclerotic disease but also decrease nephrolithiasis risk.

Keywords Urolithiasis · Dyslipidemia · High-density lipoprotein

The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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Introduction

The rate of nephrolithiasis is increasing in the United States. Over 5 % of the population at some point has had a symptomatic nephrolithiasis [1]. The average cost per stone event, per patient, is nearly $3,500. Each year 1 % of the working adult population will have a stone event [2]. The etiology of nephrolithiasis is multifactorial and recently metabolic diseases have been implicated as causative factors. Hypertension (HTN) and obesity are associated with stone disease and increasing evidence also shows diabetes mellitus to have an association [3–5]. Dyslipidemia (DLD) has also begun to receive attention and may have an association with stone disease. Inci et al. [6] in Turkey demonstrated that stone formers had elevated triglyceride

levels compared to control patients. In Japan, Itoh et al. [7] showed that a high cholesterol diet in animal studies could lead to increased renal calcium stone formation.

In this study, we sought to determine if a diagnosis of DLD was associated with a higher risk of nephrolithiasis. We also examined available patient lipid levels to determine if all specific aspects of DLD are associated with nephrolithiasis.

Patients and methods

A retrospective analysis was performed on a random cohort of patients from our institution, Naval Medical Center San Diego, USA which treats active duty military personnel, retirees, and their dependents. The random cohort was established by searching for the first 5,000 charts of outpatient encounters per month in the year 2000, ensuring no duplicates. Any outpatient encounter with any department, not necessarily urology, was used. Within a 12-month period, 60,000 independent charts were identified. All pediatric patients were excluded from analysis. The patients had their charts examined from January 1st, 2000 until January 1st, 2012.

Demographic data from patients were collected, namely age and sex. Patient charts were examined for the outcome variable, nephrolithiasis, by identifying ICD-9 codes 592.x (calculus of kidney and ureter) and 274.11 (uric acid nephrolithiasis). Charts were also searched for other predictor variables by identifying ICD-9 codes for DLD, HTN, obesity, diabetes mellitus (DM), peripheral vascular disease (PVD), congestive heart failure, coronary artery disease (CAD) and tobacco abuse. The observation period was established from January 1st, 2000 until the last follow-up date or date of stone diagnosis.

Lipid levels were collected from those patients who had the laboratory blood work performed at any time of the study period. Only the first available LDL, HDL and triglyceride level from each year in 2000 to 2010 was recorded. Consequently, some patients had several laboratory values recorded and some had a single value or no value recorded. For analytical purposes, the median values of the recorded LDL, HDL and triglyceride levels were used.

Descriptive statistics and Cox proportional-hazards with nephrolithiasis as a survival event were performed. All p values were two-sided and statistical significance was set at $p = 0.05$. All statistics were performed using Stata 12 (StataCorp, College Station, TX, USA).

Results

After excluding pediatric patients, 52,184 (22,717 women, 29,467 men) patients were identified. They had an average age of 31.0 ± 15.3 years with a median follow-up time of 41.4 months [14.6, 112.1 Inter-Quartile Ranges (IQR)]. Seven-hundred two (332 women, 370 men) patients were diagnosed with incident nephrolithiasis. The median age of those who formed a stone was 36.3 years (27.3, 47.3 IQR) and the median age of those who never had a stone diagnosis was 27.5 years (21.3, 38.7 IQR).

Univariate analysis demonstrated that all risk factors (PVD, DM, HTN, CAD, obesity, tobacco abuse, and DLD) were associated with incident nephrolithiasis except for gender. In multivariate analysis, HTN, DLD, tobacco abuse and obesity remained associated with nephrolithiasis while the other risk comorbidities did not have statistical significance (Table 1).

Lipid panel laboratory data were available for 12,607/52,184 (24.2 %) of the entire cohort and 6,136/7,743 (79.2 %) of subjects with DLD Subjects with nephrolithiasis had unfavorable median lipid values compared to subjects without nephrolithiasis (LDL 116 versus 114 mg/dL, p value =0.521, HDL 47 versus 50 mg/dL, p value =0.001, and triglycerides 121 versus 116, p value =0.505, respectively).

Univariate Cox proportional-hazards regression analysis showed no association between nephrolithiasis and the median LDL level, or with the median triglyceride level; HR = 0.999 (0.996–1.003, 95 % CI, $p = 0.639$) and HR = 1.0008 (0.9998–1.002, 95 % CI, $p = 0.119$), respectively. Median HDL level did have an association with nephrolithiasis HR = 0.98 (0.97–0.99, 95 % CI, $p < 0.001$). Because only HDL appeared statistically significant, a subanalysis by gender was performed. For men, it was 42 versus 45 mg/dL, p value =0.065 for stone formers versus non-stone formers. For women it was 53 versus 55 mg/dL, p value =0.210 for stone formers versus non-stone formers.

A second subanalysis was performed with an HDL cutoff level of 45 mg/dL for men and 60 mg/dL for women because of known accepted gender differences regarding HDL [8]. Univariate Cox proportional-hazards regression analysis demonstrated an increased risk of nephrolithiasis HR = 1.4 (1.1–1.7, 95 % CI, $p = 0.003$) for those below these cutoff values. The increased risk of nephrolithiasis was also seen in multivariate analysis HR = 1.3 (1.0–1.6, 95 % CI, $p = 0.003$). Table 2 shows results of the multivariate analysis using the gender-based cutoff levels for HDL.

Discussion

Our study demonstrates two significant findings. First, a diagnosis of DLD appears to confer an increased risk of nephrolithiasis. Second, of the lipid panel (LDL, HDL and Triglyceride), only HDL was associated with nephrolithiasis. Specifically, we determined that cut off values of

Table 1 Association of patient factors with stone disease

	Without nephrolithiasis	With nephrolithiasis	Hazard ratio (95 % CI)	*p* value	Hazard ratio (95 % CI)	*p* value
	Total without stones = 51,482	Total with stones = 702	Univariate analysis		Multivariate analysis	
Age >35	16,719/51,482 (32.5 %)	378/702 (53.8 %)	1.7 (1.4–1.9)	<0.001*	1.1 (0.9–1.3)	0.56
Men	29,727/51,482 (57.7 %)	370/702 (52.7 %)	0.9 (0.8–1.0)	=0.156	1.0 (0.9–1.2)	0.94
Peripheral vascular disease	1,820/51,482 (3.5 %)	71/702 (10.1 %)	1.7 (1.4–2.2)	<0.001*	1.2 (0.9–1.6)	0.13
Diabetes mellitus	2,529/51,482 (4.9 %)	122/702 (17.4 %)	2.2 (1.8–2.7)	<0.001*	1.1 (0.9–1.4)	0.45
Hypertension	6,893/51,482 (13.4 %)	320/702 (45.6 %)	2.7 (2.3–3.2)	<0.001*	2.0 (1.6–2.4)	<0.001*
Coronary artery disease	1,264/51,482 (2.5 %)	62/702 (8.8 %)	2.2 (1.7–2.9)	<0.001*	1.0 (0.8–1.4)	0.77
Obesity	3772/51,482 (7.3 %)	182/702 (25.9 %)	2.2 (1.9–2.7)	<0.001*	1.6 (1.3–1.9)	0.004*
Tobacco abuse	2,635/51,482 (5.1 %)	104 (3.8 %)	1.6 (1.3–2.0)	<0.001*	1.3 (1.0–1.6)	0.04*
Dyslipidemia	7,433/51,482 (14.4 %)	310/702 (44.2 %)	2.2 (1.9–2.5)	<0.001*	1.2 (1.0–1.5)	0.03*

Patients are sub-categorized according to the presence of the listed factor. Percentages of patients with and without stones are listed. Univariate and multivariate analyses are performed with Cox proportional-hazards regression analysis. Statistical significance is annotated with an asterisk. Note that dyslipidemia is associated with an increased risk of nephrolithiasis on univariate and multivariate

Table 2 Association of patient factors with stone disease after substituting a diagnosis of dyslipidemia with decreased HDL level (multivariate analysis)

	Hazard ratio (95 % CI)	*p* value
Sex (male:female)	1.4 (1.2–1.7)	0.001*
Age >35	0.8 (0.7–1.0)	0.084
Peripheral vascular disease	1.2 (0.9–1.5)	0.3
Diabetes mellitus	1.0 (0.8–1.3)	0.74
Hypertension	1.4 (1.2–1.3)	<0.001*
Coronary artery disease	1.0 (0.8–1.4)	0.97
Obesity	1.4 (1.2–1.7)	0.001*
Tobacco abuse	1.1 (0.8–1.4)	0.6
HDL (<45 for men, <60 for women)	1.3 (1.0–1.6)	0.02*

Patient conditions and comorbidities are analyzed with multivariate analysis. Pay particular attention to decreased levels of HDL showing a 30 % increased risk. Multivariate Cox proportional-hazards regression analysis was performed to obtain HR and *p* values. Dyslipidemia is not shown because of excessive collinearity with HDL. Factors with statistical significance are marked with an asterisk

<45 mg/dL for men and <60 mg/dL for women increased the risk of nephrolithiasis by 30 %.

The finding that DLD is associated with nephrolithiasis, specifically uric acid stones, has been reported previously [6, 9]. Unfortunately, causality of DLD leading to nephrolithiasis has not been established. It is plausible that our and others' findings are simply a phenomenon of association with known risk factors of nephrolithiasis. However, if causality truly exists then an explanation is in need.

The relationship between metabolic syndrome (DLD, HTN, obesity, impaired glucose tolerance) and nephrolithiasis might provide a partial explanation as DLD is a criterion for metabolic syndrome diagnosis [8, 10, 11]. One of the putative explanations for metabolic syndrome driven nephrolithiasis rests in insulin resistance and subsequent defective renal ammoniogenesis which is insulin mediated at proximal tubule. Systemic acidosis ensues which can then lead to bone demineralization-mediated hypercalciuria as well as renal citrate reabsorption and subsequent hypocitraturia [12]. Hypocitraturia becomes a risk factor for calcium based stones, while the urinary acidification becomes a risk factor for uric acid stones due to the low solubility of urate with a low urinary pH [13].

Torricelli et al. [9] demonstrated a relationship between DLD and 24-h urinary parameter abnormalities. The study involved comparing urine profiles of stone formers with DLD versus stone formers without DLD. They noted patients with low levels of HDL tended to be younger and did have increased levels of sodium. They offered several theories to explain this relationship: remodeling of LDL with insulin resistance and elevated HDL anti-inflammatory mitigation of insulin resistance [14, 15]. The authors acknowledged that they cannot fully explain the exact pathophysiology that connects stone disease with DLD and indicate that further study is necessary.

Stoller et al's vascular theory offers the connection between DLD and nephrolithiasis. The descending vasa recta make a hairpin turn in the medulla; a hostile, hypoxic and hyperosmolar environment. At this turn, there is a transition from a laminar to turbulent flow that potentiates a vascular injury. The buildup of plaque could lead to calcifications and subsequently erode into ducts of Bellini (frequently bathed in supersaturated urine), further enhancing the potential for stone growth [16].

A vascular etiology would not fully explain differences in urinary parameters. Upon further investigation, perhaps 24-h measurements should not be considered infallible. Curhan et al. [17] in 2001 demonstrated that 24-h urine excretions of normal control patients versus stone-forming patients reveal that urine parameters could not accurately predict which patients are more likely to form a stone.

A surprising finding in this study is that LDL and triglyceride levels had no association with nephrolithiasis, but low levels of HDL increased the nephrolithiasis risk. This is contrary to the study performed by Inci et al. [6], which showed that elevated triglyceride levels were associated with stone disease. All three lipid profiles (LDL, triglyceride and HDL) were found to be associated with abnormal 24-h urinary stone risk factors by Torricelli et al. [9], but why we did not see the clinical manifestation of nephrolithiasis with all lipid panel profiles is unclear.

Even though the difference in HDL values is only 3–5 mg/dL between stone formers and non-stone formers, it is statistically significant. We were reassured by the results obtained by Kang et al. [18] from South Korea. They showed that increased HDL was protective. The difference between stone formers and non-stone formers was only 3.4 mg/dLsc.

Is it possible that although all lipid profiles possess lithogenic predisposition, HDL confers the greatest predictor of nephrolithiasis? Although statin medications pharmacologically lower LDL levels, they also increase HDL through unclear mechanisms [19]. And in fact, statins have been demonstrated to decrease the risk of nephrolithiasis [20]. Age divided into two categories above and below 35 years trended towards significance in multivariate analysis. Rendina et al. [21] from Italy reported on age as a factor associated with stone disease, but they also reported that the average age of nephrolithiasis has been increasing from 35.7 to 42.9 and the initial diagnosis age had also increased from 25.1 to 30.6. Our results may have been due to oversimplification by having only two age categories for analysis, or it may be due to the fact that older patients generally have more comorbidities associated with stone disease. If the etiology of nephrolithiasis is multi-factorial, then the increasing age of diagnosis and increasing rates of diagnosis may seem to run hand-in-hand with increasing rates of metabolic syndrome in the adult population. Because the purpose of this study was not to investigate age, we did not pursue this analysis further.

As with any retrospective study, our study has limitations. Comorbidities were categorically defined with ICD-9 codes regardless of how well controlled or severe the disease process was.

We were able to obtain laboratory values, but not information on medication use, body mass index (BMI), or stone and urinalysis parameters. Stone data and 24-h urinalysis data are stored as text files at our institution and thus not abstractable for this dataset. Height and weight values were recorded separately from the variables used in this analysis and, therefore, we were unable to abstract BMI data for this analysis.

We know which patients carried a diagnosis of obesity, but we do not know what the determining factors were to make that diagnosis. More information on BMI would provide more insight.

Other information on patients with DLD is also unavailable in our database. We do not know what medications the patients were taking. This would be difficult to analyze because we would be required to consider when the patients started or changed their medication if any changes were made during the observation period.

No data prior to 2000 were available on our patient cohort including patients who may have had a stone episode prior to the observation period. Also, lipid levels understandably were not available for all patients. Surprisingly, 1 in 5 of patients with DLD did not have lipid levels which limits our interpretation of the data.

The traditional extensive-nephrolithiasis work-up entails collecting two 24-h urine collections, a basic metabolic panel, complete blood count, and a urine culture [22]. Stone disease is likely linked to bone damage, cardiovascular damage, chronic kidney disease, and hypertension [23]. Comorbidities such as obesity and hypertension have shown an association with stone disease and a heart-healthy diet, such as the DASH diet, has shown a reduction in stone disease [21, 24]. We should no longer focus solely on urinary parameter abnormalities as the source of stone disease in our patients.

The relationship between DLD and nephrolithiasis is intriguing but admittedly it is unclear whether this is simply an associated finding or truly a causal relationship. Future prospective studies should be considered to examine the relationship. Given the emerging relationship of metabolic syndrome and nephrolithiasis, it seems reasonable to obtain lipid panels with the metabolic stone evaluation.

Conclusion

Dyslipidemia is associated with an increased risk of stone disease. Even though LDL and triglyceride levels did not appear to correlate with an increased risk of stone disease, HDL levels <45 for men and <60 for women increased the risk of stone disease. Clinicians should consider obtaining lipid levels with the intent that treatment could potentially not only mitigate atherosclerotic disease but also decrease nephrolithiasis risk.

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Conflict of interest The authors declare that they have no conflicts of interest.

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