Profile of metabolic and infectious stone-formers in a contemporary PCNL cohort

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Introduction: *To identify factors associated with stone composition in patients undergoing percutaneous nephrolithotomy (PCNL).*
Material and methods: *A retrospective analysis of patients who underwent PCNL at two academic institutions between 2002 and 2014. Stone composition, stone characteristics based on non-contrast computer tomography (NCCT), patient demographics, and the S.T.O.N.E nephrolithometry scores were compared. Stones were characterized as either infection or metabolic. Metabolic stones were classified as calcium phosphate-containing and all others.*
Results: *A total of 192 renal units underwent PCNL. Retrieved stones were found to be 75% (144) metabolic and 25% (48) infection by stone analysis. Of the metabolic stones, 51% (73) were phosphate-containing calculi. Overall, infection stones were found to have a significantly higher S.T.O.N.E nephrolithometry score than metabolic stones (9.2 versus 8.1, $p < 0.001$). Average Hounsfield units (HU) were significantly lower in infection stones (765 versus 899, $p < 0.05$). Sixty-three percent of patients with infection stones were female as compared to 46% of patients with metabolic stones. Patients with phosphate-containing stones in the metabolic group were significantly more likely to be female (56% versus 35%, $p < 0.01$), younger (mean 49 versus 60 years of age, $p < 0.02$), and have lower BMI's (30 versus 32, $p < 0.02$) compared with other metabolic stones.*
Conclusions: *Patient demographics including age, sex and BMI differ between patients with phosphate and non-phosphate containing metabolic stones. Higher S.T.O.N.E nephrolithometry scores were found in infection stones. These findings may serve as useful tools in the identification of stone compositions that are being seen more frequently in large and complicated stones undergoing PCNL.*

Key Words: calcium phosphate, nephrolithiasis, nephrostomy, lithotripsy, percutaneous, patient profile

Introduction

Urolithiasis is a common medical condition in the United States with an estimated prevalence of 11.7% by the age of 70.[1] In addition to the high prevalence and morbidity, at least 50% of individuals will experience a second stone episode within 10 years of the first.[2] Stones have a large socioeconomic impact and consume a large proportion of healthcare dollars, and large upper tract stones necessitating a percutaneous procedure to remove do have additional associated morbidity and cost.

Determining the composition of calculi in the preoperative setting has been a goal of several investigators. Researchers have studied the use of Hounsfield units (HU) on non-contrast CT (NCCT) to predict stone composition. Most studies have been able to predict pure uric acid stone composition from other stone types accurately. In vitro analysis has been able to differentiate uric acid, struvite and calcium oxalate compositions using absolute HU values.[3] In general, this technique is limited by several factors including mixed stone compositions as well as stone size.[4] Currently there are no available methods to reliably determine stone composition in the pre-treatment setting.

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The knowledge of stone composition in the pre-treatment setting has certain advantages. Uric acid stones for example can be approached medically with urinary alkalinization prior to or as an alternative to operative intervention. Endourologic treatment recommendations are also potentially influenced by known stone composition. Stone composition is related to its density and therefore its ability to be fragmented using shock wave lithotripsy (SWL).[5]

For large stone burdens requiring percutaneous nephrolithotomy (PCNL), stone fragility is less important due to the availability of tools efficient at fragmenting and removing all stone types. Stone type has, however, been shown to impact surgical outcomes in PCNL. Viprakasit et al found that patients with metabolic stones had lower complication rates while those with infection stones tended to require additional access and secondary treatment.[6] Infection stones also were found to have higher recurrence rates. These large stone burdens were traditionally thought to be infection stones,[7] but, more recently, large contemporary series have reported changes to a predominantly metabolic composition, particularly calcium phosphate.[6,8,9] Calcium phosphate stones, especially brushite, have been shown to develop in the presence of a distinctive crystal associated with nephropathy.[10,11] These stones often present with larger and bilateral stone burdens, are more likely to require surgical intervention and may be associated with lower stone-free rates after PCNL.[8,12,13]

Our aim was twofold: first, to determine patient and imaging factors that differed between infection and metabolic stones; and second, in the metabolic stone-formers, to detect differences between calcium phosphate-containing and other metabolic stone types and determine if pre-operative prediction of stone type was possible.

Materials and methods

We obtained Institutional Review Board approval to review a prospectively maintained kidney stone databases at two academic institutions. Patients who underwent PCNL between 2002 and 2014 at these two academic centers were reviewed and included in the study.

Patient characteristics reviewed were gender, age, body mass index (BMI) and presence of a preoperative urinary tract infection (UTI).

Stone analysis

Stone fragments collected during surgery were sent to the Mayo Clinic commercial laboratory for stone analysis. Stone compositions were sub-classified into infection or metabolic. Infection stones were defined as having any component of struvite or carbonate apatite as defined by the American Urological Association (AUA).[5] Metabolic stones were classified by the largest component greater than or equal to 50%. Metabolic stones were separated into two groups: calcium phosphate (apatite or brushite) containing and all others (calcium oxalate monohydrate, calcium oxalate dihydrate or uric acid). Patient characteristics as well as the NCCT were then reviewed for each of the two groups.

S.T.O.N.E. nephrolithometry score

A single reviewer evaluated all preoperative CT images and a S.T.O.N.E. nephrolithometry score for each patient was calculated. According to Okhunov et al, the scoring system is used to classify stones based on pre-procedure NCCT which has been shown to predict treatment success and the risk of perioperative complications following PCNL. The five components of the score are: S = stone size, T = tract length, O = obstruction, N = number of involved calyces, E = essence or stone density measured by HU.[14]

Surgical interventions

All PCNL procedures were performed by two fellowship-trained endourologists. Our technique for PCNL has been previously reported.[15]

Follow up imaging

All patients underwent postoperative NCCT imaging and stone free status was defined as fragments less than or equal to 2 mm.

Statistical analysis

Significance was determined using Fisher's exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables.

Results

A total of 192 renal units were treated with PCNL between 2002 and 2014. Females made up 50% (96) of the treated cohort. Of the 192, 75% (144) were metabolic and 25% (48) were infectious. Seventy-three (51%) of the metabolic stones were phosphate-containing calculi. Patient demographics and the differences seen in metabolic and infection stone groups are shown in Table 1. UTI data were available for 70 patients, and of these, 55% of the infectious and 22% of the metabolic had positive urine cultures prior to surgery which did not differ significantly.

The overall S.T.O.N.E. nephrolithometry score differed significantly between the two groups with

TABLE 1. **Differences in metabolic and infection stones**

	Metabolic	Infection
No. patients (%)	144 (75%)	48 (25%)
Mean patient age (yrs)	54	55
No. female (%)	66 (46%)	30 (63%)
Mean kg/m^2 BMI	31	30
Mean OR time (sample size)	2.2 hrs (38)	2.3 hrs (11)
Stone-free status (%)	99 (69%)	27 (56%)
UTI preoperatively (sample size)	22% (50)	55% (20)
S.T.O.N.E. score	8.1	9.2

Differences in stone characteristics and patient demographics between metabolic and infection stones. UTI data is available for 70 patients. The difference in S.T.O.N.E. score is significant ($p < 0.001$). The difference is driven by stone volume (larger in infection stones), essence or HU (more dense in metabolic stones), and number of calyces involved (more calyces in infection stones).

infection stones having an average score of 9.2 (± 1.9) and metabolic stones a score of 8.1 (± 1.7), ($p < 0.001$). The components of the score accounting for the difference were stone volume, number of calyces involved and stone density. Stone density (measured in HU) differed significantly between the groups with metabolic stones being denser on average, 899 versus 765, Table 1. Average maximum single-shot area was 1234 mm^2 and 544 mm^2 for the infection and metabolic groups ($p < 0.001$) respectively. Mean number of calyces involved were 2.6 for the infection cohort and 2.2 for the metabolic cohort ($p = 0.02$). The presence of hydronephrosis and the average tract length did not differ between the groups.

TABLE 2. **Characteristics of metabolic stone-formers**

	Phosphate	Non-phosphate	p value*
Sample size	73 # (%)	71 # (%)	
Female	41 (56%)	25 (35%)	0.01
Urinary tract infection	6 (21%)	5 (23%)	1.00
Hydronephrosis	31 (46%)	27 (40%)	0.60
Stone-free	52 (71%)	47 (66%)	0.59
	Mean (SD)	**Mean (SD)**	
Age (yrs)	49 (16)	60 (13)	< 0.001
Body mass index	30 (9)	32 (8)	0.02
OR time (hrs)	2.2 (0.5)	2.1 (0.8)	0.20
Stone volume	512 (674)	578 (642)	0.14
Hounsfield units	1019 (379)	776 (363)	< 0.001
Tract length (cm)	10.4 (3.3)	11.8 (3.3)	0.008
Calyces	2.1 (0.9)	2.3 (0.9)	0.20
S.T.O.N.E. score	8.0 (1.6)	8.1 (1.7)	0.79

Patient characteristics and other imaging and operating room values stratified between phosphate and non-phosphate containing stones in the metabolic cohort only.
*Fisher's exact test for categorical variables; Wilcoxon rank-sum test for continuous variables

Stone free status did not differ significantly between the groups following PCNL (65% infection stone vsersus 64% metabolic stones) when evaluated post-procedure by NCCT.

When comparing phosphate to non-phosphate containing stones in the metabolic cohort, females were significantly more likely to have phosphate-containing stones (56% versus 35%, $p < 0.01$). Patients with phosphate stones were also more likely to be younger (mean 49 versus 60 years of age, $p < 0.02$) and have a lower BMI (30 versus 32, $p = 0.02$) as well as have a shorter tract length (10.4 cm versus 11.8 cm, $p = 0.008$). The only stone related factor that differed was the average HU with the phosphate group having denser stones (1019 versus 776, $p < 0.001$). There were no significant differences in stone volume, number of calyces involved or the S.T.O.N.E. nephrolithometry score. Stone-free status did not significantly differ, Table 2.

Discussion

Staghorn calculi are increasingly becoming a metabolic and not an infectious process. This trend is supported in other large contemporary series undergoing PCNL.[6,8,9] Our series of 192 renal units undergoing PCNL showed a 75% metabolic stone type and 25% infection stone type supporting the national trend. Our data adds to the growing literature characterizing the contemporary patient undergoing PCNL.

When comparing the differences between metabolic and infection stone types in this study, the S.T.O.N.E. nephrolithometry score was found to have a statistically significant difference with infection stones having a mean score of 9.2 versus 8.1 ($p < 0.001$) for metabolic stones. This may serve as a useful tool to help differentiate infection from metabolic stones in the preoperative setting and assist in patient counseling prior to PCNL.

The majority of metabolic stones in our cohort were found to be at least partially composed of calcium phosphate which is consistent with other series that report changes in urinary stone composition in the last 30 years. Parks et al studied 1,201 patients and noted a three-fold increase in calcium phosphate stone incidence between 1970 to 2003.[8] Mandel et al reviewed 33,198 stones samples between 1989 and 2003 using the national Veterans Administration Crystal Identification Center and showed an increased incidence of metabolic stones and decrease in infection stones.[9] The authors also noted that successive stone recurrences had increasing calcium phosphate composition. More recently, Viprakasit and colleagues completed a retrospective analysis on stone composition among patients who underwent PCNL for staghorn calculi between 2005 and 2010. Stone analysis revealed that a large proportion of complete staghorn calculi were composed of metabolic stones and calcium phosphate was the most common stone composition.[6]

Of the 75% metabolic stone rate in our series, 51% were phosphate containing calculi. When looking at the patient demographics of phosphate stone formers, we noted a statistically significant difference in sex (more likely female), age (more likely less than 60 years of age) and BMI (more likely less than 32). While descriptive in nature, these findings contribute to the data that is emerging on phosphate stone-formers.

Certain limitations of the study must be recognized. Although the kidney stone databases at two different academic institutions were prospectively maintained, our study was completed retrospectively which may introduce sampling bias. Additionally, the stone fragments collected did not undergo stone culture which limited our ability to confirm the categorization made by stone analysis. The S.T.O.N.E. score differences seen in stone types categorizes and helps direct the clinician but is not predictive of infection stones.

While we were able to define a patient profile that is associated with phosphate containing metabolic stones, we are unable to predict with accuracy the stone composition based on these associations alone. Further research is needed into the etiology as well as therapeutic targets to treat and/or prevent calcium phosphate stone formation. Our findings reinforce the need for a close follow up strategy in this patient population due to the other associated negative effects of this stone type. Based on our findings, we strongly advocate for a metabolic workup in the continued management of these patients.

Conclusions

This study identifies stone properties based on NCCT and patient demographics that differ between patients with infection and metabolic stones. We also identified a patient profile that is associated with calcium phosphate-containing metabolic stones. This information may help guide counseling, treatment, and follow up strategies for patients undergoing PCNL. ☐

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