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Current Computed Tomography Techniques Can Detect Duct of Bellini Plugging but not Randall's Plaques

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Abstract

Objectives—To assess the ability of noninvasive computed tomography (CT) scans to detect interstitial calcium phosphate deposits (Randall's plaques) and duct of Bellini plugs, which are possible stone precursor lesions.

Methods—At time of percutaneous nephrolithotomy (PCNL) for stone removal, all accessible individual papillae of 105 patients were endoscopically visualized and video recorded. Image processing software was used to estimate the percentage papillary surface occupied by plaque or plug in each pole (upper, mid, lower). The location of stones was also recorded. A radiologist blinded to the mapping results scored pre surgical (n=98) and post surgical (n=105) abdominal CT scans for the presence or absence of calcification by pole.

Results—Mean age of the cohort was 56 years [range 23–84]. Maximum papillary surface area of each area of the kidney occupied by plug correlated with CT calcifications on both pre and post procedure images by rank sum test. However, maximum plaque surface area did not correlate with radiographic findings (p range from 0.10–0.90 for each pole by rank sum test). Sensitivity and specificity of CT to detect plugs of at least 1% of the papillary surface area was 81% and 69%, respectively.

Conclusion—Calcifications seen on current generation clinical CT scans correspond to ductal plugging involving at least 1% of the papillary surface area. Current clinical CT scan technology appears inadequate for detecting Randall's plaques.

Keywords

urolithiasis; kidney; endoscopy; x-ray computed tomography; kidney calculi

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Introduction

Kidney stone disease is common, affecting nearly 12% of people in their lifetime, therefore causing significant morbidity and health care expense.^{1,2} New knowledge regarding pathogenic processes is needed to identify treatment targets. Minimally invasive techniques for stone treatment (ureteroscopy, percutaneous nephrolithotomy (PCNL)) facilitate visualization, documentation, and even biopsy of smaller stone precursor lesions. Thus, new paradigms are emerging. Evan and colleagues have characterized Randall's plaques as candidate precursor lesions for idiopathic calcium oxalate stone formation.⁴⁻⁷ Randall's plaques are discrete, flat layers of calcification which arise in the interstitium of the papillum, namely the basement membrane of the loops of Henle. Another distinct candidate precursor lesion is hydroxyapatite deposits in ducts of Bellini or inner medullary collecting ducts, referred to as plugs.⁸⁻¹³ Ductal plugs, sometimes referred to as yellow plaque, have been associated with calcium oxalate stones in patients with gastrointestinal malabsorption syndromes.⁸⁻¹⁰ Stone formers with brushite stone disease,¹¹ renal tubular acidosis,¹² and hyperparathyroidism¹³ can also harbor duct of Bellini plugs.

Currently, the only way to identify plaque and plug precursor lesions is by invasive endoscopy, usually performed at the time of an acute stone event. Thus, the ability to characterize the precursor lesions in large populations of patients for clinical care or research is limited. The goal of the current study was to determine if current computed tomography (CT) scanning methods tailored to stone imaging can detect Randall's plaque and/or plugs.

Materials and Methods

After institutional review board approval and informed consent, non-pregnant patients over the age of 18 years undergoing PCNL for urolithiasis were prospectively recruited from September 2009 thru February 2012. The cohort represents 105 consecutive PCNL patients at a tertiary care facility that consented for the study. The patients were evaluated for stone formation risk factors and previous stone events. If a recent CT exam was not available for operative planning, a dual energy computed tomography (DECT) was performed. On postoperative day one, a second scan was performed, DECT if possible, to detect residual fragments and assess the need for further surgery.

For the CT exam, single- or dual-energy helical CT was performed using a dual-energy (DECT) scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). The kV and quality reference mAs for the two x-ray tubes were adjusted depending on the patient size. The low-energy setting of 80kV was used for patients with a lateral width of 35cm, and for patients with lateral width of 36-44 cm 100 kV was used. In both cases, high-energy data were acquired using 140 kV, with a tin filter placed in the 140 kV beam.^{14,15} For patients with a lateral width > 45 cm, a single energy CT was acquired since patient size would substantially degrade DECT image quality. Lateral width was measured with the patient lying supine on the CT table from the CT radiograph used to plan the start and end locations of the scan.¹⁶

Total radiation exposure for the DECT was set to be the same as for a single-energy scan of the same sized patient, with a nominal radiation output being 15 mGy. Processed data from the DECT was used to identify stone composition and to reconstruct images for further analysis.¹⁷ Both thin (1 mm) and thick (5 mm) images were reconstructed using a 300 mm field of view and a medium smooth reconstruction setting (B40). The reconstruction interval was 0.8 mm for the thin images and 2.5 mm for the thick images. Coronal images were also reconstructed using a 2 mm width at 1.8 mm spacing.

At time of PCNL, percutaneous access was obtained in either an upper or lower pole posterior renal calyx to maximize stone removal. In all patients, one fragment of the stone was sent for culture, another for clinical infrared spectrophotometry (IR) stone analysis, and the remaining for micro CT and directed IR stone analysis. After all stone material was removed, the internal papillary structures of the kidney were systematically evaluated using a flexible digital nephroscope (ACMI gyrus, DUR-D). The location of each papilla was determined using fluoroscopy after instillation of contrast through the nephroscope. Digital video data obtained at time of nephroscopy was recorded onto DVDs in MPEG-2 format. Each dataset was reviewed and edited to short video clips, using the fluoroscopic still imaging data as a reference to confirm papillary location. Surgical notes were used to corroborate the selection of video segments. Representative still images of each papilla were captured from the final footage. A single urologist (A.E.K) and a specially-trained image analyst reviewed all videos and images to determine the location and distribution of the papillae, plaque, and plugs. Using image processing software (Mayo Clinic Analyze, Rochester, MN), the area of the papillae, and individual plaques and plugs, if present, were outlined. Randall's plaque appeared as glossy white regions exposed on the papillary urothelium. Plugs appeared as yellowish, stone-like protrusions from the papillary surface. The percent surface area of plaque and plug was then calculated for each papilla.

All preoperative and postoperative CT images were reviewed by a single radiologist (T.J.V.) blinded to the endoscopic and clinical findings. The location and size of each calculus was determined. The radiologist separated the kidney into three regions: upper, middle, and lower. The presence (or absence) of parenchymal calcifications in each region of the kidney were also recorded. On pre-operative CT, all poles with confirmed stones were excluded. All distinct, highly-attenuating objects ≥ 1 mm were counted as urinary stones (the size limit of reliable detection using 1 mm cuts). Other attenuating objects with vague margins or distinct margins < 1 mm in the region of the caliceal tips were also counted (see Figure 1). The 5mm axial, 1mm axial and 2 mm coronal images were all reviewed for each study. Any patient thought to harbor a residual stone (> 1 mm calcification) returned to the operating room for a secondary PCNL procedure in an attempt to render the patient stone free.

Statistical Analysis

CT findings (reported separately for pre and post PCNL scans) were compared to PCNL percent plug and plaque area for each pole, and for the kidney as a whole. Both the mean and the maximum of the percent surface area of recorded plaque and plug on PCNL were compared using the rank-sum test to the presence or absence of attenuating objects detected by CT. Since the data for plug area included many zeros, data were summarized on a patient level for medians and percentage with readings above zero. Sensitivity and specificity were calculated to display the association of attenuating objects on CT (yes, no) with presence of plug ($>0\%$ and $>1\%$) seen on PCNL. Similar sensitivities and specificities were not calculated for plaque since they were not reliably detected by CT (see Results). All analyses used SAS v9.2 software (SAS Institute, Cary, NC).

Results

Endoscopic mapping was performed on 105 patients at the time of clinically-indicated PCNL. Of the 98 preoperative CT scans of sufficient quality for review, 55 were DECT, while 80 of the 105 postoperative scans were DECT. Mean patient age was 56 years (range 23-84) and 38(36%) were male. Predominant stone composition and mean stone size for each patient is listed in Table 1. Calcium oxalate was the most common stone encountered, followed by calcium phosphate. Access was obtained in the lower pole in 50 (47.4%) patients, and upper pole in 43 (41.2%) patients, mid upper or mid lower in 5 (4.4%) patients, and by multiple accesses in 7 (7.0%) patients. Residual fragments (1mm or greater) were

noted on the postoperative CT scan in 38 (36%) patients, who went on to a second procedure for completion of stone clearance.

The mean (SD) number of papillae mapped at time of the procedure was 4.6 (2.0). The overall median percentage surface area of papillae covered by plaque and plug for the entire cohort was 3.6 (range 0.5-44.5) and 0 (range 0-43.0), respectively. Radiographically, for the entire cohort non-stone attenuating objects were noted on 51(54%) preoperative CTs and on 42 (49%) postoperative CTs. There was no correlation on either the preoperative or postoperative CT scans of endoscopically-detected plaque (maximum papillary surface area) with non-stone attenuating objects detected by CT (Table 2). However, there was a significant association of endoscopically-visualized plug (maximum surface area) and non-stone attenuating objects detected by CT for all regions of the kidney on the postoperative scan, and the mid, lower, and total kidney on the preoperative scan (Table 2). Subsequent comparisons using mean surface area covered by plaque and plug produced similar results (not shown). There was no association between patient age and non-stone attenuating objects on the preoperative or postoperative CT scans.

Since plaque was not reliably detected by CT, sensitivity and specificity of CT was calculated only for plug detection (Table 3). Postoperative CT detected 28 of 40 patients with any plug (surface area percent > 0), while non-stone attenuating objects were not reported in 31 of 45 that also lacked endoscopic plug. Furthermore, postoperative CT detected 25 of 31 patients with significant plug (greater = 1% surface area) while non-stone attenuating objects were not reported in 30 of 47 without significant plug. Overall sensitivity (specificity) of post-procedure CT to detect any plug (surface area >0%) and significant plugging (surface area = 1%) was 70% (69%) and 81% (69%), respectively. The sensitivity and specificity of the preoperative scans were somewhat less (Table 3), perhaps due to interference from nearby large stones.

Comments

In our prospective evaluation of over one hundred patients we found that identification of renal stone precursor lesions is challenging, even using current state of the art CT imaging technology. Indeed, we could not correlate endoscopically-noted papillary plaque with non-stone attenuating objects on preoperative or postoperative CT scans. However, we could reliably correlate endoscopically-visualized Duct of Bellini plugs with non-stone attenuating objects on CT. The sensitivity and specificity of CT scan for plug detection improved when we restricted the analysis to detection of = 1% plug surface area of the papillum.

Evan and colleagues have provided evidence that the earliest lesions of stone formation among idiopathic calcium oxalate stone former are deposits of calcium phosphate that initiate in the basement membrane of the loop of Henle, termed Type 1 Randall's plaque.⁴ Growth and erosion of these deposits through the urothelium is thought to provide a nidus for calcium oxalate overgrowth and stone formation. Evan's group reported that the amount of plaque surface area in each papilla correlated with several stone risk factors including urine volume (inverse), urine pH (inverse), and urine calcium (direct).⁵ Furthermore, the mean plaque surface area correlated with the number of clinical stone events.⁶ However, the number of patients that can be practically mapped for plaque by endoscopic techniques is relatively small. Therefore, the ability to noninvasively document and quantitate Randall's plaques would greatly facilitate research regarding their natural history and pathogenesis. Furthermore, identification of such lesions prior to stone formation could provide a unique opportunity to avoid future stone events by preemptively altering the metabolic urinary environment of a patient. Unfortunately, our data demonstrates that the CT imaging

protocols routinely used for stone assessment, whether single- or dual-energy scanning, are not sensitive enough to identify such lesions.

Although Randall's plaques can cover a significant percentage of the papillary surface area, they are thin structures, which undoubtedly contribute to their difficult detection by CT. Current CT systems have a spatial resolution between 0.125mm -0.25mm in phantom models using the highest resolution techniques.¹⁹⁻²⁰ Review of the coronal reconstructions from modern CT scanners (e.g. multi-detector row systems) can also increase the visibility and diagnostic confidence for detecting urinary calcifications less than 5mm.¹⁸ However, a number of challenges remain for visualizing submillimeter high attenuation structures, including variations in acquisition techniques, scanner capabilities, and patient size. For example, in order to obtain the best spatial resolution, sub-mm scan modes must be used, as was done in this study. Image noise must be minimized at the same time as image sharpness is maximized, and these conflicting goals require use of very sharp reconstruction algorithms and edge-preserving noise reduction algorithms. These steps are not routinely available on clinical systems, and hence were not used in this study. Finally, ionizing radiation exposure for stone imaging protocols was kept as low as possible, in order to minimize any potential risk. It is possible that specialized scan protocols using higher doses, small reconstruction fields of view, sharper reconstruction algorithms, and noise reduction algorithms may have the sensitivity to detect Randall's plaques. At this time, however, it appears that the size and attenuation of Randall's plaques falls below what current clinical CT techniques can detect, whereas the larger size and greater attenuation of duct of Bellini plugging can be detected in a number of patients.

Current evidence indicates that Randall's plaque is not responsible for all stone disease formation, and that plugs can play an important role in stone formation for certain patients. Intraductal hydroxyapatite plugs appear to predominate among patients that form stones after gastric bypass procedures,^{8,10} brushite stone formers,¹¹ and stone formers with hyperparathyroidism¹³ or renal tubular acidosis.¹² Our study demonstrates that such plugs can be detected with reasonable sensitivity and specificity by current CT technology. Plugs are round and compact, which translates to an overall increased density, making them more attenuating and hence more visible by CT. The clinical relevance of detecting plugs by CT scan is potentially significant. CT detection of plugs could alert practitioners of a risk for stone disease before actual stone formation occurs, allowing for early metabolic evaluation and alteration of identifiable urinary risk factors, specifically in patients who have a strong family history of stone disease or when plugs are incidentally noted.

Currently, the role of CT scanning for stone risk prediction remains to be determined. However, many of the stone patient groups with plugs, the precursor lesion that CT detects, have clinically significant diseases that might benefit from preventative treatment strategies. For example, patients status post bowel resection or gastric bypass are at high risk for the formation of stones that are thought to start as ductal plugs.⁹ Therefore, among gastric bypass patients faint, non-stone attenuating calyceal calcifications visualized on CT should be assumed to be Duct of Bellini plugs rather than Randall's plaque. In such individuals aggressive dietary modifications including low fat, low oxalate, and calcium enrichment could be instituted early in an attempt to prevent future stone events or loss of renal function. Among patients with brushite stone disease, ductal plugging has been associated with parenchymal scarring¹¹. Therefore identification of such lesions noninvasively could alert physicians to the possibility of ongoing renal injury. Furthermore, identification of patients with early plug lesions could facilitate studies that are needed to determine the most effective treatment strategy in this challenging patient group.

This study has potential limitations. It was not possible to match the exact papilla identified at time of endoscopy with an exact calyx noted on CT scan, and therefore only areas of the kidney could be compared. Furthermore, we chose to evaluate both preoperative and postoperative CT scans because they both have potential limitations. Preoperative CT scans did not allow evaluation of calyces harboring stone disease. Conversely, postoperative CT scans allowed limited visualization of certain regions of the collecting systems and papilla due to artifact from nephrostomy tubes and air in the collecting system. Further, it was not certain that attenuating structures noted on postoperative CT scan were not residual stone fragments. To address the latter concern and minimize this potential confounder, we only counted non-round calcifications on CT that were that were located in the papillary tip area and less than 2 mm in size, and all possible retained stone fragments were confirmed or excluded by a secondary PCNL procedure. Ultimately, the data demonstrate that timing of the scan had little influence on the detection of either plaque or plug.

Conclusions

The ability of state of the art CT scanners to detect small attenuating structures is improving. Our study demonstrates that duct of Bellini plugging can be detected non-invasively with a high sensitivity and specificity when as little as one percent papillary surface area is involved. However, current CT technology cannot reliably detect any amount of papillary Randall's plaque. CT techniques with decreased image noise, increased spatial resolution, and improved material differentiation capabilities may provide a means to non-invasively assess the presence of Randall's plaque.

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Figure 1. Example of a non-stone attenuation in a lower pole calyx (yellow arrow) confirmed by endoscopic evaluation, identified on a postoperative CT scan
The nephrostomy tube is noted in the upper pole calyx extending into the renal pelvis (orange arrow).

Table 1

Stone composition, number and size as well as type of imaging.

	Total (N=105)
Major stone composition	
Brushite	7 (6.7%)
Hydroxyapatite	22 (21.2%)
Calcium oxalate	62 (59.6%)
Struvite	9 (8.7%)
Uric acid	4 (3.8%)
Matrix	1 (0.8%)
Missing	1
Preoperative CT scan	
Yes	105 (100%)
Postoperative CT scan	
Yes	101 (96.2%)
No or missing	4 (3.8%)
Number of CT scans	
Two	101 (96.2%)
Only one or missing	4 (3.8%)
Stone number at preoperative CT scan	
N	104
Mean (SD)	5.5 (5.9)
Median	3.5
Q1, Q3	2.0, 8.0
Range	(0.0-35.0)
Stone size(mm) at preoperative CT scan	
N	82
Mean (SD)	10.8 (7.0)
Median	10.0
Q1, Q3	5.0, 15.0
Range	(2.0-38.0)

Table 2

Comparison of maximum surface area covered by plaque and plug with attenuating objects seen on preoperative and postoperative CT scans.

PCNL		Pre CT Calcification			Post CT Calcification		
Factor	Location	Yes	No	p-value	Yes	No	p-value
Max SA plug, %	UP	36	44		26	33	
	Median %>0	0.00 28%	0.00 23%	0.4120	0.00 46%	0.00 15%	0.0094
	MP	24	35		18	32	
	Median %>0	0.00 42%	0.00 14%	0.0057	0.90 61%	0.00 13%	0.0001
	LP	26	45		29	35	
	Median %>0	0.00 42%	0.00 22%	0.0419	0.70 55%	0.00 23%	0.0019
	Kidney	51	44		42	43	
	Median %>0	0.68 51%	0.00 34%	0.0111	1.55 67%	0.00 28%	<0.0001
Max SA plaque, %	UP	36	44		26	33	
	median	2.7	2.5	0.71	2.91	2.19	0.73
	MP	24	35		18	32	
	Median	3.0	2.5	0.35	2.71	2.66	0.92
	LP	26	45		29	35	
	Median	2.9	1.9	0.42	3.08	1.91	0.13
	Kidney	51	44		42	43	
	median	4.54	2.92	0.11	4.63	2.69	0.12

Data presented by kidney location and entire kidney. UP: upper pole; MP middle pole; LP: lower pole.

PCNL = percutaneous nephrolithotomy

SA = surface area

CT = computed tomography

Table 3

Sensitivity and specificity of preoperative and postoperative CT scans for detecting maximum surface area (Max SA) plug.

Max SA plug %	Pre CT Calcification	Pre CT No calcification	Total	Plug defined as	Sensitivity	Specificity
0	25	29	54	>0%	63%	53%
0.1 to 0.9	3	5	8			
1.0 +	23	10	33	>1%	70%	55%
Total	51	44	95			
Max SA plug %	Post CT Calcification	Post CT No calcification	Total		Sensitivity	Specificity
0	14	31	45	>0%	70%	69%
0.1 to 0.9	3	6	9			
1.0 +	25	6	31	>1%	81%	69%
Total	42	43	85			