

STONE FORMATION IS PROPORTIONAL TO PAPILLARY SURFACE COVERAGE BY RANDALL'S PLAQUE

SAMUEL C. KIM, FREDRIC L. COE, WILLIAM W. TINMOUTH, RAMSAY L. KUO,*
RYAN F. PATERSON, JOAN H. PARKS, LARRY C. MUNCH, ANDREW P. EVAN†
AND JAMES E. LINGEMAN‡§

From the Methodist Hospital Institute for Kidney Stone Disease (SCK, WWT, LCM, JEL) and Department of Anatomy and Cell Biology (APE), Indiana University School of Medicine (SCK, WWT, LCM, JEL), Indianapolis, Indiana, Division of Nephrology, Department of Medicine, Pritzker School of Medicine, University of Chicago (FLC, JHP), Chicago, Illinois, Department of Urology, Jefferson Medical College, Thomas Jefferson University (RLK), Philadelphia, Pennsylvania, and Division of Urology, Department of Surgery, University of British Columbia (RFP), Vancouver, British Columbia, Canada

ABSTRACT

Purpose: Randall's plaques are common in calcium oxalate (CaOx) stone formers (SF). Plaque coverage correlates directly with urine calcium excretion and inversely with urine volume. We hypothesize that plaque coverage should increase proportionally with increasing stone number. We measured plaque areas in idiopathic CaOx stone formers and nonstone formers (NSF), and identified significant relationships with quantified stone histories.

Materials and Methods: A total of 13 SFs and 4 control NSFs underwent nephroscopic papillary mapping with representative still images and MPEG (Moving Pictures Experts Group) movies used to identify plaque and papillary borders. Stone histories were obtained through patient interviews, and from medical records and radiographs. The relationship of plaque coverage to clinical stone events was assessed by general multivariate linear modeling. Log transformation normalized the distribution of percent plaque coverage and stone number.

Results: Plaque surface area in SFs differed significantly from that in NSFs ($p < 0.0001$). The duration of stone disease and the log transformed percent plaque coverage correlated significantly with the number of stones (0.677 and 0.620, $p = 0.003$ and 0.008 , respectively). On multivariate analysis and correcting for the duration of stone disease total percent plaque coverage correlated significantly with the number of stones ($R^2 = 0.496$, $p = 0.05$). Disease duration and plaque coverage did not correlate significantly ($p = 0.257$).

Conclusions: Percent plaque coverage directly correlates with the number of stones formed even when corrected for the duration of stone disease. However, plaque coverage does not correlate with the duration of stone disease. These results support the hypothesis that the pathogenesis of CaOx stones begins with Randall's plaques.

KEY WORDS: kidney, kidney calculi, calcium oxalate, calcium, kidney medulla

It has been conjectured that calcium oxalate (CaOx) renal stones form on the papillary plaques first described by Randall, which bear his name.¹ We have shown that plaque is always composed of apatite and it forms in the deep medullary interstitium.² Furthermore, the origin of plaque appears to be in the basement membranes of the thin limbs of the loops of Henle. We have also shown that the fraction of papillary surface covered by plaque is proportional to urine calcium and inversely proportional to urine volume and pH, and we proposed that plaque forms because water conservation in the thin limbs produces supersaturated luminal fluid with respect to calcium phosphate salts.^{3,4} Supersaturation with respect to calcium phosphate phases in thin limb fluid or papillary interstitium could promote apatite nucle-

ation in basement membranes. When extensive, plaque spreads through the deep inner medullary interstitium, involving suburothelial regions. Plaque that erodes through the urothelium presents a stable, anchored apatite surface on which it is postulated that CaOx can nucleate and grow to produce an attached stone.²

The observation that patients with larger papillary areas covered by plaque have an increased number of stones would be strong corroborating evidence for this sequence of events. In our recent series digital images were made during percutaneous nephrolithotomy (PNL) or following ex vivo examination of laparoscopic radical nephrectomy (LRN) specimens from which the fraction of papillary surface covered with Randall's plaque was determined in 13 CaOx stone formers (SFs) and 4 nonstone formers.^{2,5} From reviews of medical records and direct history taking the clinical stone histories of these stone forming patients were documented. Using these clinical and intraoperative data the relationship between papillary plaque coverage and the number of stones was examined.

METHODS

Patient characteristics. The 17 patients included in this study are part of a group of 19 well characterized patients described earlier who were studied during the course of PNL or LRN.²

Submitted for publication February 23, 2004.

Supported by National Institutes of Health Grant P01 DK56788 and a grant from the American Foundation for Urologic Disease.

* Financial interest and/or other relationship with Boston Scientific and Lumenis.

† Financial interest and/or other relationship with Boston Scientific.

‡ Correspondence: 1801 North Senate Blvd., Suite 220, Indianapolis, Indiana 46202 (telephone: 317-962-2485; FAX: 317-962-2893; e-mail: jlingeman@clarion.org).

§ Financial interest and/or other relationship with Boston Scientific, Lumenis, TherMatrix, Olympus, Storz, Midwest Mobile Lithotripsy, Progressive Thermotherapy and Midstate Mobile Lithotripsy.

Briefly, 15 patients were calcium oxalate stone formers who underwent PNL for treatment of a large stone burden and had papillary mapping and biopsies performed concurrently. The other 4 patients underwent LRN for renal cell carcinoma, and had mapping and biopsies performed after specimen extraction. One of the 15 patients did not have complete mapping and in 1 we could not accurately quantify prior stone events. Stone events were defined as newly diagnosed stones separated temporally and requiring medical and/or surgical treatment. Direct personal interviews, and reviews of medical records and prior radiographs were used to ascertain the number of stones formed up to the time of our intraoperative study. The duration of stone disease was calculated as the interval from the first stone to the time of the operative study in years. In patients without stones this value was set to 0.

Plaque mapping. All idiopathic CaOx SFs underwent PNL to remove the entire stone burden prior to mapping. The débridement process did not damage or alter papillary plaque sites. Subsequently video images recorded using a combination of rigid and flexible nephroscopy (Pentax Videosystems, Englewood, Colorado) were obtained of all accessible papillae. An identical video imaging process was used for all papillae of LRN specimens following the creation of a small pyelotomy *ex vivo* immediately after specimen removal. Each papilla was characterized intraoperatively using a protocol that we have described previously.⁵ Briefly, MPEG (Moving Picture Experts Group)-1 movies were constructed of each papilla, representative color, and black and white photos were made and a single observer (JEL) circumscribed areas of plaque deposition and the papillary boundaries therein. We defined plaque as areas on the papilla that were characterized by a focal white lesion, consistent with Randall's original description. Using Photoshop 7.0 (Adobe, San Jose, California) the fractional area of plaque coverage of each papilla was determined by dividing the number of pixels occupied by plaque by the pixel area occupied by the papilla. We then calculated the mean percent of papillary surface area covered by plaque (or plaque surface area) by adding the fractional coverage of each individual papilla and dividing by the total number of papillae.

Data analysis. Since the distribution of values for the mean percent papillary surface area covered by plaque was markedly skewed, we used log (10) transformation to obtain distributions that were more normal in character. Comparison of plaque surface area to stone number was then performed using stepwise general linear modeling and simple regression. We repeated this analysis using the log (10) transformed stone number, obtained by adding 1 to the number of stones in all subjects. Since the results of the 2 analyses were similar, we present only the first one. Using multivariate regression analysis a plaque time score ($1.788 + 1.386 \times \log 10$ mean plaque surface area + $0.082 \times$ time) was calculated. This score incorporates the duration of stone disease and plaque surface area with the partial coefficients derived from our general linear model.

RESULTS

Independent of each other, the duration of stone disease and log transformed mean plaque surface area had strong partial correlations with the number of stone events (0.677 and 0.620, $p = 0.003$ and 0.008 , respectively). After incorporating the duration of stone disease into the model as a dependent variable, log transformed percent plaque coverage retained its significant partial correlation (0.496, adjusted squared multiple $R = 0.459$, $p = 0.05$). When the duration of stone disease and log transformed percent plaque coverage were incorporated into the multivariate model, R^2 increased to 0.592 ($p = 0.002$, $F = 10.2$).

A direct plot of stone number against log 10 mean plaque surface area illustrates this correlation (fig. 1, *a*). The ellipse

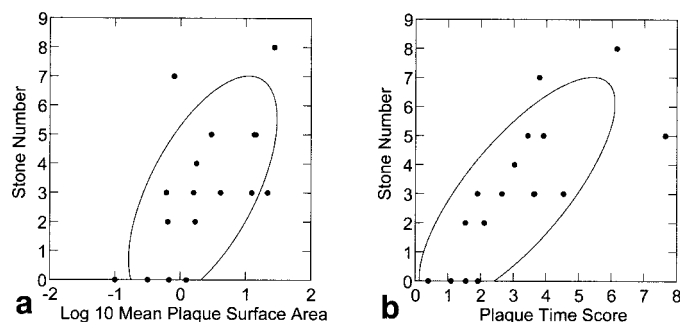


FIG. 1. *a*, number of stones vs log transformed mean plaque surface area. Nonparametric ellipse of containment includes 2 SD. *b*, number of stones vs multivariate regression equation from general linear model, including stone disease duration and plaque surface. Plaque time score $\times 1.788 + 1.386 \times \log 10$ mean plaque surface area + $0.082 \times$ time.

of containment, set at 1 SD unit, was strongly anisotropic and tilted upward and to the right. When the number of stones was plotted against plaque time score, the correlation was much stronger ($R^2 = 0.592$, fig. 1, *b*). Although it is a reasonable speculation that plaque coverage increases with the duration of stone disease, the correlation between these 2 variables was not significant ($p = 0.257$).

Figure 2 shows an increase in papillary plaque coverage in 3 CaOx SFs with an increase in the duration of stone disease and stone events compared to a control. Figure 2, *a* shows a papilla from a CaOx SF who has had only 1 stone event and a short duration of stone disease of 0.17 years. The average percent surface area of the papilla covered by plaque in this patient was small (1.69%). Figure 2, *b* shows a papilla from a CaOx SF who has had 2 stone events and a moderate length of stone disease of 15 years. The average percent surface area of papilla covered by plaque in this patient was 12.42%. Figure 2, *c* shows a papilla from a CaOx SF who has had 7 stone events and 30 years of kidney stone disease. An extensive amount of plaque (27.41%) was observed in this patient. The average percent surface area of the papilla covered by plaque in the control was 0.67%. This patient had no history of stone disease.

DISCUSSION

The intent of our inquiry was to answer the question of whether a simple count of stones formed by a patient correlates positively with the fraction of renal papillae covered by plaque. The answer is unambiguously yes. Since the number of stones formed strongly depends on the duration of stone disease, as noted, it is crucial to correct for duration. We accomplished this using standard multivariate general modeling. When corrected for duration, plaque coverage has a significant and independent correlation with the number of stones.

There were 4 patients in the group who were not stone formers. As others have noted, individuals without stones are not free of plaque. Rather, they have less plaque, as is obvious from the distribution of their 4 points along the zero stone line in figure 1 compared to values in the stone forming patients. Their stone count of zero fits well with the regression model, strengthening the idea that plaque surface promotes stones. In their absence the remaining 13 stone forming cases were too few to provide a significant regression for plaque surface, although the dependence of stones on disease duration remained significant, as expected.

Randall was the first to suggest that a calcified area beneath the urothelium "can lose its epithelial covering and from then on be bathed in caliceal urine, becoming the nidus upon which a different urinary salt crystallizes."⁶ His original studies showed plaque in 19.6% of 1,154 examined pairs

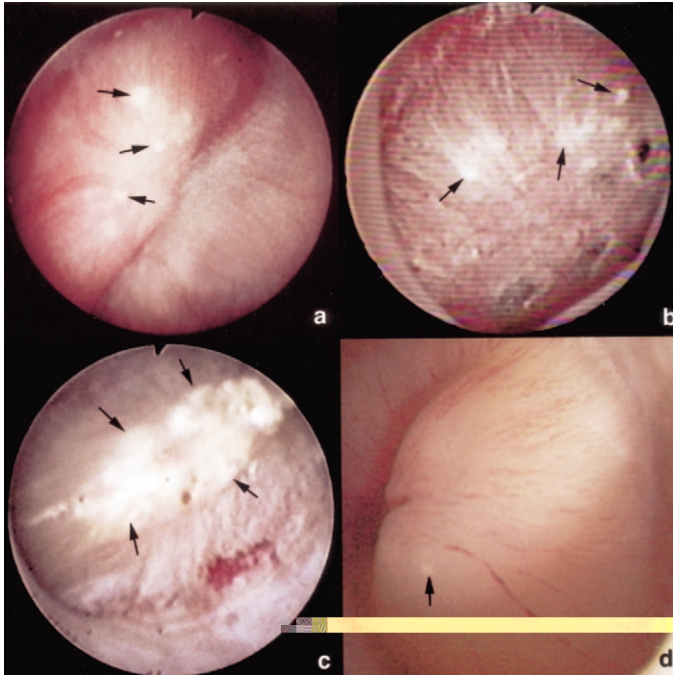


FIG. 2. *a* to *c*, increasing amounts of surface plaque (arrows) on papilla of 3 CaOx SFs as duration of stone disease and number of stone events increased. *d*, minimal surface plaque of papilla in 1 control.

of cadaveric kidneys.⁷ Electron microscopic studies support his original observations with 1 group suggesting that 63 of 87 so-called papillary stones had an accompanying plaque.⁸ The recent findings of Low and Stoller in endoscopic mapping studies reinforce the relationship between plaque and calcium based nephrolithiasis.⁹ Of 57 patients undergoing ureteroscopic or percutaneous stone removal 74% had evidence of Randall's plaque. Calcium oxalate and calcium phosphate stone formers were more than 3 times as likely to have plaque as cystine and infection stone formers but unfortunately with the technology available at the time obtaining images that would permit rigorous statistical analysis was impossible. These observations are substantiated by recent studies demonstrating a direct correlation between plaque surface area with increased urine calcium and decreased urine volume.⁴ Although the sequence of observations supports the pathogenesis of stone from plaque, the plaque-stone hypothesis has problematic elements. The difficulty in demonstrating the relationship between visibly attached stone and Randall's plaque may be related to poor visualization of collecting system anatomy, a lack of sophisticated tools to permit quantifiable image analysis of intrarenal findings and difficulty localizing attached stones with underlying Randall's plaque.

To our knowledge we present the first numerical observations of plaque coverage and stone number with sufficient detail to test the plaque-stone hypothesis. Our positive results support the contention that plaque engenders CaOx stones. The finding that the duration of stone disease is reflected in clinical stone history shows that our patient population was appropriate for this analysis. Although this current study links the papillary plaque surface area retrospectively to the number of clinical stone events, future stud-

ies must examine the ability of plaque surface coverage to predict future stone events.

CONCLUSIONS

Using digital endoscopic imaging, image analysis software and general linear modeling, the amount of papillary plaque coverage was noted to be directly related to the number of stone events in calcium stone formers. A statistical correlation of plaque with clinical stone events is an important finding that furthers the assumption of Randall that papillary plaque is the progenitor of urinary calculous formation.^{1,6,7}

REFERENCES

1. Randall, A.: The origin and growth of renal calculi. *Ann Surg*, **105**: 1009, 1937
2. Evan, A. P., Lingeman, J. E., Coe, F. L., Parks, J. H., Bledsoe, S. B., Shao, Y. et al: Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest*, **111**: 607, 2003
3. Asplin, J. R., Mandel, N. S. and Coe, F. L.: Evidence of calcium phosphate supersaturation in the loop of Henle. *Am J Physiol*, **270**: F604, 1996
4. Kuo, R. L., Lingeman, J. E., Evan, A. P., Paterson, R. F., Parks, J. H., Bledsoe, S. B. et al: Urine calcium and volume predict coverage of renal papilla by Randall's plaque. *Kidney Int*, **64**: 2150, 2003
5. Kuo, R. L., Lingeman, J. E., Evan, A. P., Paterson, R. F., Bledsoe, S. B., Kim, S. C. et al: Endoscopic renal papillary biopsies: a tissue retrieval technique for histological studies in patients with nephrolithiasis. *J Urol*, **170**: 2186, 2003
6. Randall, A.: The etiology of primary renal calculus. *Int Abst Surg*, **71**: 209, 1940
7. Randall, A.: Papillary pathology as a precursor of primary renal calculus. *J Urol*, **44**: 540, 1940
8. Cifuentes Delatte, L., Miñón-Cifuentes, J. L. R. and Medina, J. A.: Papillary stones: calcified renal tubules in Randall's plaques. *J Urol*, **133**: 490, 1985
9. Low, R. K. and Stoller, M. L.: Endoscopic mapping of renal papillae for Randall's plaques in patients with urinary stone disease. *J Urol*, **158**: 2062, 1997

EDITORIAL COMMENT

The authors continue their evaluation of the importance of Randall's plaques and calcium oxalate stone formation. In their previous investigations they determined that papillary plaque coverage correlates directly with urinary calcium excretion and adversely with urine volume, suggesting that plaques may form due to water conservation and supersaturated luminal fluid within the loops of Henle. In the current study they evaluated the importance of plaque surface area in calcium oxalate stone formers and nonstone formers, suggesting that the percent of plaque coverage correlates directly with the number of stones formed. The authors suggest that these results support their hypothesis on one of the initiating events in calcium oxalate stone formation. I agree that future studies must examine the possibility of using Randall's plaque surface area to predict the propensity for stone formation. Unfortunately there are no radiographic imaging studies sensitive enough to assess plaque formation since the current practice of using direct endoscopic imaging to determine the extent of plaque surface area is not feasible. If more sensitive radiographic imaging were correlated with direct endoscopic observation, a less invasive means of plaque determination would allow the study of a large number of patients in prospective fashion, further clarifying the role of Randall's plaques and calcium oxalate nephrolithiasis.

Glenn M. Preminger
Comprehensive Kidney Stone Center
Duke University Medical Center
Durham, North Carolina