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Demographics and Characterization of 10,282 Randall Plaque-Related Kidney Stones

A New Epidemic?

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Abstract: Renal stone incidence has progressively increased in industrialized countries, but the implication of Randall plaque in this epidemic remains unknown. Our objectives were to determine whether the prevalence of Randall plaque-related stones increased during the past decades after having analyzed 30,149 intact stones containing mainly calcium oxalate since 1989 (cross-sectional study), and to identify determinants associated with Randall plaque-related stones in patients (case–control study).

The proportion of Randall plaque-related stones was assessed over 3 time periods: 1989–1991, 1999–2001, and 2009–2011. Moreover, we analyzed clinical and biochemical parameters of 105 patients affected by calcium oxalate stones, with or without plaque.

Of 30,149 calcium oxalate stones, 10,282 harbored Randall plaque residues (34.1%). The prevalence of Randall plaque-related stones increased dramatically during the past years. In young women, 17% of calcium oxalate stones were associated with Randall plaque during the 1989–1991 period, but the proportion rose to 59% 20 years later ($P < 0.001$). Patients with plaques experienced their first stone-related event earlier in life as compared with those without plaque (median age 26 vs 34 years, $P = 0.02$), had increased ionized serum calcium levels ($P = 0.04$), and increased serum osteocalcin ($P = 0.001$) but similar 25-hydroxyvitamin D levels. The logistic regression analysis showed that age (odds ratio [OR] 0.96, confidence interval [CI] 0.926–0.994, $P = 0.02$), weight (OR 0.97, CI 0.934–0.997, $P = 0.03$), and osteocalcin serum levels (OR 1.12, CI 1.020–1.234, $P = 0.02$) were independently associated with Randall plaque. The prevalence of the Fok1 vitamin D receptor polymorphism was higher in patients with plaque (P = 0.047).

In conclusion, these findings point to an epidemic of Randall plaque-associated renal stones in young patients, and suggest a possible implication of altered vitamin D response.

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Abbreviations: CI = confidence interval, COD = calcium oxalate dihydrate, COM = calcium oxalate monohydrate, FTIR = Fourier transform infrared spectroscopy, OR = odds ratio, VDR = vitamin D receptor.

INTRODUCTION

There is strong evidence that renal stone incidence increased during the past decades in industrialized countries, now affecting >10% of the population and constituting a major public health challenge.1,2 Calcium oxalate stones are now identified as the main type of urinary calculi in western countries and account for at least 70% of all kidney stones. Longitudinal epidemiological studies performed in USA, Europe, or Japan evidenced that the progression in calcium oxalate and uric acid stones was responsible for the increase in the prevalence of urolithiasis.1,3–5 Calcium oxalate stone growth results from urine supersaturation due to low diuresis and intermittent biological disorders such as hypercalciuria, hyperoxaluria, and/or hypocitraturia. However, the starting point of calcium oxalate stones received little attention until recently.

Since Alexander Randall made the hypothesis that the origin of renal calculi was calcium phosphate plaque at the tip of renal papillae, relatively few studies were dedicated to the Randall plaque.6–10 A major contribution to this field was made by Evan et al11 who reported that Randall plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. The same group highlighted the relationship between calcium excretion and plaque formation.12 The recent increased interest for Randall plaque is likely to originate from the development of renoureteroscopy, which enables plaque visualization, and also from an increased incidence of stones due to heterogeneous nucleation processes from plaques.10 However, the implication of Randall plaque in kidney stone epidemic is not documented.
We conducted a study to assess the evolution of Randall plaque-related stone incidence during the last decades in France and characterize the specific clinical and biological profile of patients developing plaque-related stones to identify Randall plaque risk factors.

METHODS

Morphoconstitutional Analysis of Renal Stones

Morphologic examination and classification of renal stone surface and section were combined with Fourier transform infrared spectroscopy (FTIR) to classify renal stones and identify the different crystalline phases. Starting from a database of 71,000 urinary stones collected between 1989 and 2013, intact calcium oxalate stones (30,149, which passed spontaneously or removed intact) were selected for further analysis, whereas fragmented stones resulting from urological procedures were excluded because of the frequent loss of Randall plaque. The composition and structure of stones without Randall plaque were compared with those of stones developed at the surface of Randall plaques identified by the typical renal papilla imprint and plaque residues at stone surface. All the proportions of the main stone components were assessed, as well as the internal structure of the stone according to FTIR and morphoconstitutional stone classification. All stones have been analyzed by a single investigator (M.D.). The term “core” refers to the most internal part of the stone (developing on the Randall plaque when it is).

Evolution of Plaque-Related Stone Incidence Over the Past Decades

In order to assess the longitudinal changes in the proportions of stones initiated from a Randall plaque, we compared the incidence of Randall plaque in men and women over 3 equal periods of time: 1989–1991, 1999–2001, and 2009–2011. We considered the number and the percentage of stones, grown from plaques or not, among all the stones mainly composed of calcium oxalate (>85% of the stone according to FTIR) recorded in our database, and which passed spontaneously or were removed intact.

Clinical and Biological Data of Renal Stone Formers

More than 1000 renal stone formers were referred for metabolic investigation to our Physiology unit between 2000 and 2012 (Tenon Hospital, Paris). Patients provided a 24-hour urine collection under a free diet. They all were referred for an oral calcium load test, the results of which were similar in both groups (not shown). Serum and urine parameters were assessed as previously described. Because identification of Randall plaque may be underrecognized in fragmented stones, we selected only patients who had both complete biological data and also intact renal stones analyzed exclusively in the Cristal laboratory (Paris). In addition, we selected stones containing >85% calcium oxalate according to FTIR analysis. Exclusion criteria were primary hyperparathyroidism, renal tubular acidosis, renal failure (assessed by measured creatinine renal clearance lower than 60 mL/min/1.73 m²), genetic or enteric stasis, renal failure (assessed by measured creatinine renal clearance) or other metabolic investigation. Diagnosis was confirmed by measured iPTH >40 pmol/L, and there were no patients with a serum phosphorus concentration higher than 1.5 mmol/L. Overall, 105 patients met these criteria. To our knowledge, none of the 22 women included in the study have been diagnosed with osteoporosis or received hormone replacement therapy.

DNA Analysis

Buffy coats were collected from patients who provided informed written consent, according to French legislation, in the view of further genetic analyses. The cohort is registered (Commission nationale de l’informatique et des libertés Declaration Number 1709404v0). The regions containing single nucleotide polymorphisms of the vitamin D receptor (VDR) gene were amplified using the appropriate primer set, by methods adapted from Seo et al. and Mossetti et al. The forward primer for Apol and Tag1 polymorphism was 5’-AGCA-GACGAGATCCACGCA-3’. The reverse primer for Apol and Tag1 polymorphism was 5’-ATCTTGGCATAAGGC-AGGTTGGCT-3’. The forward primer for BsmI polymorphism was 5’-CAACAAAGACTCAAGTACCGGT-3’. The reverse primer for BsmI polymorphism was 5’-ACCAG-CGGAAAGGTCAAGG-3’. The forward primer for FokI polymorphism was 5’-AATGCTTTGATTCTTCA-3’. The reverse primer for FokI polymorphism was 5’-GGTGTAGGAGGCTGT-3’. Each polymerase chain reaction product was digested with the appropriate restriction endonuclease (FastDigest for BsmI, Apol, Tag1, and FokI) as recommended by the manufacturer instruction (Thermo Scientific, Illkirch, France). The presence of BsmI, Apol, Tag1, and FokI restriction enzyme sites was designated as lowercase b, a, t, and f, respectively, whereas absence was designated as uppercase B, A, T, and F, respectively.

Statistical Analyses

Chi-square test was used for stone composition and epidemiological data; Student t test was used to compare the mean proportion of calcium oxalate phases. Fisher exact test and Mann–Whitney U test were used to compare other categorical or quantitative variables, respectively (clinical, biological, and genetic determinants of Randall plaque). Reported values represent number (percentage), mean ± standard deviation, median (p25 and p75), median value or mean value, and median value or mean value, respectively. Potentially associated variables were assessed using the Chi-square test for categorical variables and the t test for quantitative variables. Variables potentially associated with Randall plaque (P < 0.10) were entered in a multivariable logistic regression. These variables were weight, ionized calcium, phosphate reabsorption rate, 25-hydroxyvitamin D, and osteocalcin. A P value <0.05 was considered significant. Statistics were performed independently by 2 authors using both number cruncher statistical system (NCSS) 6.0 (NCSS statistical software, Kaysville, UT, USA) and StatView 5.0 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Morphoconstitutional Analysis of Randall Plaque-Related Stones

Of 30,149 intact stones containing mainly calcium oxalate analyzed between 1989 and 2013, 10,282 stones harbored Randall plaque residues (34.1%). The predominant crystalline phase determined by FTIR was either calcium oxalate monohydrate (COM or whewellite) or calcium oxalate dihydrate (COD or weddellite); only 84 Randall plaque-related stones had a different composition (mainly uric acid associated with COM). The existence of Randall plaque was not influenced by sex because 23.8% of stones with plaque and 24.6% of stones without plaques originated from women. The morphoconstitutional analysis evidenced that Randall plaque-related stones were predominantly made of COM, and their core, in contact with the plaque, was a typical radial and concentric COM-type “Ia” structure.
FIGURE 1. Representative calcium oxalate stones from the database. (A) Typical COM (subtype la) stone with a Randall plaque (arrow) made of carbapatite. (B) Calcium oxalate stone composed of COM (dark area) around the Randall plaque (arrow) and secondary covered by COD crystals (light part on the left side). (C) Typical subtype la cross-section of a COM stone initiated from a Randall plaque. Note the crystallization of COM is organized from the light carbapatite deposit, which corresponds to the Randall plaque (arrow). (D) Calcium oxalate stone mainly composed of COD. The stone was initiated from a Randall plaque. Note the depressed surface that corresponds to the umbilication, that is, the imprint of the papilla. The white deposit is the part of the Randall plaque located at the surface of the papilla (arrow). Of interest, the first layers of calcium oxalate around the Randall plaque are made of COM (dark area). (E) Example of subtype la stone developed in free caliceal cavities (without Randall plaque). (F) Cross-section of the same stone exhibiting a well-organized and compact structure made of very thin concentric layers with radial organization. (G) Typical subtype Ila COD stone developed in free caliceal cavities (without Randall plaque). (H) Typical subtype Ila COD stone section characterized by a loose and poorly organized structure (without Randall plaque).
converging on the plaque (Figure 1, and supplementary Figures S1, and S2, http://links.lww.com/MD/A210).

An Epidemic of Randall Plaque-Related Stones

During the past 2 decades, the incidence of stones derived from plaques increased dramatically in France, especially in young men and women (Figure 2). We observed over the last 2 periods, a dramatic increase of Randall plaque-related stones in children and young adults (Figure 2). For instance, in female patients between 20 and 30 years, 17.2% of calcium oxalate stones were due to Randall plaque during the 1989–1991 period, but the proportion rose to 59.2% 20 years later ($P < 0.001$). In parallel, the male/female ratio decreased from 3.26 to 2.59 ($P < 0.001$) during these 2 decades.

Clinical and Biological Determinants of Randall Plaque

In order to identify clinical or biological parameters specifically associated with Randall plaque, we collected data from 105 patients who had both extensive metabolic evaluations in our physiology unit, and intact calcium oxalate stones analyzed in the Cristal laboratory, with or without Randall plaque residues at stone surface (42 and 63 patients, respectively, Table 1). In the latter group, no phosphate was detected in stone cores, ruling out the hypothesis of calcium oxalate stones released from the papilla with a plaque covered up by subsequent growth of calcium oxalate. Patients with Randall plaque were younger than those without plaque ($P = 0.005$, Table 1), and experienced their first stone-related event earlier in life (median age 26 vs 34 years, $P = 0.02$). Twenty four-hour urine collection under free diet did not reveal any difference in 24-hour urine volume, calcium excretion or salt and protein consumption because sodium and urea daily excretions were similar in both groups of patients. Ionized calcium serum levels and renal phosphate reabsorption rate were significantly higher in the Randall plaque group ($P = 0.04$ and $P = 0.03$, respectively). There was no significant difference in 25-hydroxyvitamin D status or parathyroid hormone levels, and 1,25-dihydroxyvitamin D serum levels were similar in both groups. By contrast, osteocalcin, a bone remodeling marker, was markedly increased in patients with plaques ($P = 0.001$) unlike bone alkaline phosphatase and urinary deoxypyridinoline.

The logistic regression analysis showed that age (odds ratio [OR] 0.96, confidence interval [CI] 0.926–0.994, $P = 0.02$), weight (OR 0.97, CI 0.934–0.997, $P = 0.03$), and osteocalcin serum levels (OR 1.12, CI 1.020–1.234, $P = 0.02$) were independently associated with Randall plaque.

Vitamin D Receptor Polymorphisms

A written consent for DNA collection was obtained in 69 among the 105 participants. We retrospectively analyzed VDR polymorphisms once biological determinants of Randall plaque have been assessed. All patients but 1 were white. Table 2 shows the prevalence of BsmI, ApaI, TaqI, and FokI VDR genotypes in patients with and without Randall plaque. The prevalence of FokI f allele was significantly higher in patients with Randall plaque ($P = 0.047$). No statistical difference was observed in the distribution of ApaI, BsmI, and TaqI polymorphisms between the 2 groups.

DISCUSSION

Our laboratory has been collecting stones sent for identification and classification from >200 hospitals in France. We thus accumulated material from >70,000 stones, of which >30,000 were intact calcium oxalate stones available for further analysis. Our data show that Randall plaque-related stones represented 34% of stones containing mainly calcium oxalate during the past decades; there is a dramatic and steady increase in the incidence of Randall plaque-related stones particularly in the younger population (<30 years) defining a new epidemic; osteocalcin serum levels are independently associated with Randall plaque. These data together with higher prevalence of the VDR F FokI allele suggest as a working hypothesis that the recent propensity to supplement children with vitamin D may be one of the factors responsible for the dramatic increase of Randall plaque-related stones in genetically predisposed subjects.

Over the past years, evidence has been accumulated that Randall plaque growth was related to increased calcium concentration in distal tubular fluid. This led to consider a 2-step
process: first, a calcium-dependent growth of the plaque within papilla interstitium, resulting in plaque outbreak through urothelium and, secondarily, calcium oxalate crystallization due to increased urine supersaturation. In the United States, endoscopic evidence of papillary Randall plaques was found in 74% to 99% patients having ureteroscopic or percutaneous stone removal.\(^\text{10,20}\) Our study shows that Randall plaque was a minor determinant of stone formation in France 20 years ago, but some recent changes resulted in an epidemic of Randall plaque-related stones, especially in young adults. Salt and protein intakes are well known as major dietary determinants of calcium urinary excretion.\(^\text{21}\) It was thus tempting to speculate that increased salt and protein consumption by children and young adults during the past 20 or 30 years may explain our observations. However, a decrease in meat consumption has been observed in children during the past decades in France.\(^\text{22}\) Moreover, salt intake increased gradually during the past century but decreased during the past years in France, after intensive public health interventions.\(^\text{23}\) In addition, we observed no difference in sodium and urea daily excretion between the 2 groups of patients. Thus, our data suggest that other recent dietary changes would explain the modifications of Randall plaque-related stone incidence. It seems unlikely that the change in prevalence of stones with Randall plaque could be attributed to the changes in nature of urological intervention over the past 20 years as we analyzed plaque prevalence among calcium oxalate stones only, and observed a similar increase of fragmented stones referred to our laboratory among various stone species, due to the development of renoureteroscopy (unpublished data).

Several lines of evidence argue for a potential role of vitamin D metabolites and VDR in stone formation.\(^\text{24–26}\) Recently, an increased biological response to 1,25-dihydroxyvitamin D has been reported in genetic hypercalciuric stone-forming rats.\(^\text{27}\) Breslau et al\(^\text{28}\) previously showed that hypercalciuria might be driven by an increased sensitivity to vitamin D in some patients

| Parameter                           | No Plaque | Randall Plaque | P Value |
|-------------------------------------|-----------|----------------|---------|
| n                                   | 63        | 42             |         |
| Male patients, %                    | 50 (79)   | 33 (79)        | 1.00    |
| Age, y                              | 50.0 (40.5, 57.0) | 44 (28.2, 48.7) | 0.005 |
| Age at first stone, y               | 34.0 (25.0, 44.0) | 26.0 (20.2, 37.7) | 0.02    |
| Recurrence, %                       | 48 (76)   | 35 (83)        | 0.47    |
| White and North African, %          | 62 (98)   | 41 (98)        | 1.00    |
| Weight, kg                          | 77.0 (70.0, 88.0) | 72.0 (64.0, 79.0) | 0.01    |
| Height, cm                          | 173 (164, 178) | 175 (168, 180) | 0.27    |
| Blood                               |           |                |         |
| Creatinine, mg/dL                   | 0.88 (0.75, 1.01) | 0.90 (0.81, 0.97) | 0.97    |
| Cr clearance, mL/min                | 125 (103, 156) | 122 (103, 141) | 0.43    |
| Calcium, mg/dL                      | 9.04 (8.76, 9.20) | 9.08 (8.88, 9.52) | 0.12    |
| Calcium ionized, mg/dL              | 4.68 (4.56, 4.8) | 4.76 (4.64, 4.84) | 0.04    |
| Phosphorus, mg/dL                   | 2.82 (2.51, 3.03) | 2.76 (2.45, 3.13) | 0.69    |
| Phosphate reabsorption rate         | 0.89 (0.85, 0.91) | 0.91 (0.86, 0.93) | 0.03    |
| Magnesium, mg/dL                    | 2.07 (1.90, 2.19) | 2.02 (1.95, 2.14) | 0.86    |
| Uric acid, mg/dL                    | 5.91 (4.75, 6.82) | 5.80 (5.14, 6.86) | 0.66    |
| PTH, pg/mL [N=8–76]                 | 42 (33.7, 51.0) | 33 (27.0, 52.0) | 0.29    |
| 25(OH)D, ng/mL                      | 16.7 (11.3, 24.5) | 23.4 (15.2, 32.7) | 0.08    |
| 1,25(OH)2D, pg/mL                   | 57.8 (40.7, 82.5) | 62 (51.0, 78.4) | 0.38    |
| Osteocalcin, mg/mL                  | 12.5 (10.0, 14.4) | 15.0 (12.8, 19.2) | 0.001   |
| BAP, ng/mL                          | 12.0 (9.3, 14.9) | 13.2 (10.5, 14.9) | 0.37    |
| Urine                               |           |                |         |
| Volume, mL/d                        | 2040 (1522, 2575) | 1911 (1528, 2096) | 0.13    |
| Calcium, mg/d                        | 266 (171, 364) | 238 (163, 299) | 0.35    |
| Oxalate, mg/d                        | 29.7 (20.7, 35.2) | 28.8 (22.5, 36.0) | 0.84    |
| Citrate, mg/d                        | 409 (232, 614) | 526 (284, 695) | 0.32    |
| Urea, g/d                           | 11.79 (9.02, 14.17) | 11.76 (10.11, 14.06) | 0.60    |
| Creatinine, mg/d                     | 1630 (1111, 2076) | 1531 (1271, 2016) | 0.62    |
| Phosphate, mg/d                      | 861 (607, 1127) | 935 (777, 1046) | 0.16    |
| Uric acid, mg/d                      | 613 (497, 772) | 643 (494, 865) | 0.71    |
| Magnesium, mg/d                      | 100.0 (73.7, 132.4) | 116.8 (84.9, 142.1) | 0.10    |
| Sodium, g/d                          | 3.33 (2.39, 4.62) | 3.31 (2.35, 4.44) | 0.67    |
| deoxypyridinoline/Cr, nMol/mMol      | 4.12 (3.49, 5.60) | 4.45 (4.02, 5.77) | 0.34    |
| Ammonia, mg/d                        | 634 (498, 800) | 771 (519, 992) | 0.18    |
| Fasting pH                           | 5.86 (5.43, 6.40) | 6.04 (5.59, 6.51) | 0.32    |

Clinical and biological characteristics of calcium oxalate stone formers with intact stones submitted for analysis, with or without Randall plaque. Reported values represent number (percentage) or median (p25, p75). 1,25(OH)2D = 1,25-dihydroxyvitamin D, 25(OH)D = 25-hydroxyvitamin D, BAP = bone alkaline phosphatase, Cr = creatinine, n = number of observations, PTH = parathyroid hormone.
with normal 1,25-dihydroxyvitamin D serum levels. Large inter-
ventional studies aimed for bone protection by vitamin D and
calcium reported an increase in renal stone incidence in treated
patients. Many dairy products are now enriched with vitamin D,
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patients.29 Many dairy products are now enriched with vitamin D,
increases worldwide making urolithiasis a public health problem. We postulate that vitamin D intakes during childhood may promote Randall plaque formation, in genetically predisposed patients, possibly resulting in an increased risk of renal stones.

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