Demographics and Characterization of 10,282 Randall Plaque-Related Kidney Stones: A New Epidemic?

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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 *Fok*I *f* 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.[1–3] 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.[1,4–7] 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.[8–10] A major contribution to this field was made by Evan et al[11] 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.

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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.[13,14] 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.[13–15] 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.[13–15] 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.[16] 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 m^2), genetic or enteric hyperoxaluria, and treatments interfering with calcium homeostasis: bisphosphonates and diuretics. 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[17] and Mossetti et al.[18] The forward primer for *Apa*I and *Taq*I polymorphism was 5′-AGCAGAGCAGAGTTCCAAGCAGA-3′. The reverse primer for *Apa*I and *Taq*I polymorphism was 5′-ATCTTGGCATAGAGCAGGTGGCT-3′. The forward primer for *Bsm*I polymorphism was 5′-CAACCAAGACTACAAGTACCGCGTCAGTGA-3′. The reverse primer for *Bsm*I polymorphism was 5′-AACCAGCGGAAGAGGTCAAGGG-3′. The forward primer for *Fok*I polymorphism was 5′-ACTGACTCTGGCTCTGACCGT-3′. The reverse primer for *Fok*I polymorphism was 5′-TGGGTTGGTGTAGGAGGCTGT-3′. Each polmerase chain reaction product was digested with the appropriate restriction endonuclease (FastDigest for *Bsm*I, *Apa*I, *Taq*I, and *Fok*I) as recommended by the manufacturer instruction (Thermo Scientific, Illkirch, France). The presence of *Bsm*I, *Apa*I, *Taq*I, and *Fok*I 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, or median (p25 and p75). Variables potentially associated with Randall plaque ($P < 0.10$) were entered in a multivariable logistic regression. These variables were age, 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 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

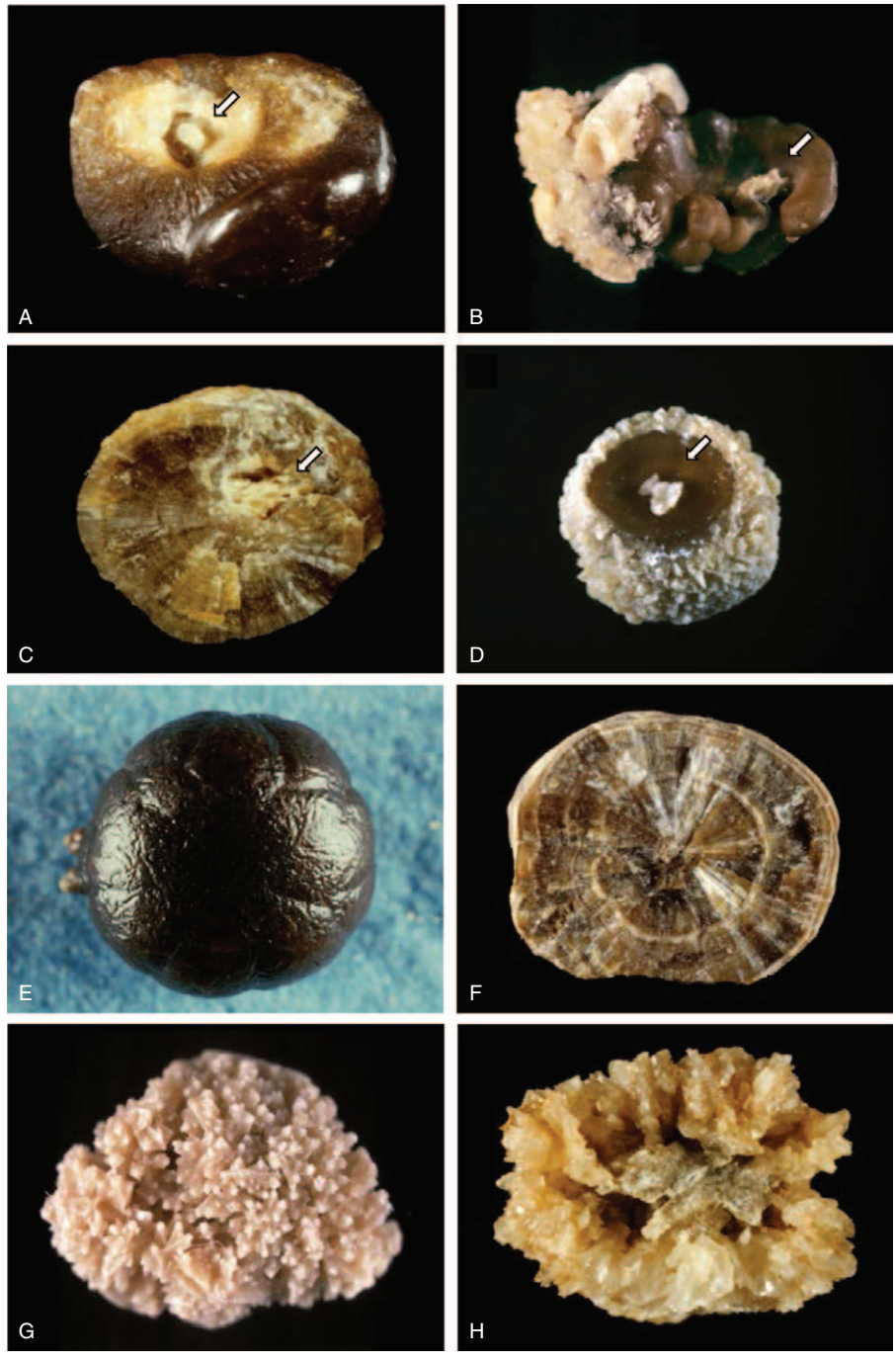

FIGURE 1. Representative calcium oxalate stones from the database. (A) Typical COM (subtype Ia) stone with a Randall plaque (arrow) made of carbapatite. (B) Calcium oxalate stone composed of COM (dark area) around the Randall plaque (arrow) and secondary covered by COD crystals (light part on the left side). (C) Typical subtype Ia 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 Ia 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 IIa COD stone developed in free caliceal cavities (without Randall plaque). (H) Typical subtype IIa COD stone section characterized by a loose and poorly organized structure (without Randall plaque).

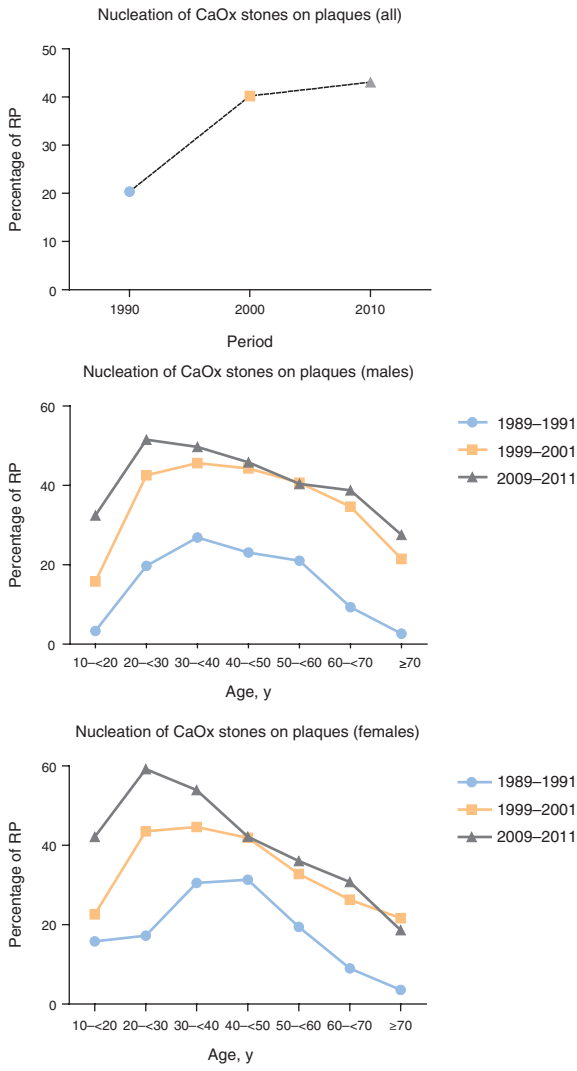

FIGURE 2. Epidemic of Randall plaque-related stones in men and women over 3 periods. The analysis of 1780 intact calcium oxalate stones during the 1989–1991 period (period I), 4310 during the 1999–2001 period (period II), and 3830 during the 2009–2011 period (period III) revealed a dramatic increase in the proportion of Randall plaque-related stones (period II and period III vs period I: $P < 0.001$ in men and women). CaOx = calcium oxalate, RP = 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 *Bsm*I, *Apa*I, *Taq*I, and *Fok*I *VDR* genotypes in patients with and without Randall plaque. The prevalence of *Fok*I *f* allele was significantly higher in patients with Randall plaque ($P = 0.047$). No statistical difference was observed in the distribution of *Apa*I, *Bsm*I, and *Taq*I 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 Fok*I 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.[19] This led to consider a 2-step

TABLE 1. Clinical and Biological Characteristics of Renal Stone Formers

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, ng/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.

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.[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.[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.[22] Moreover, salt intake increased gradually during the past century but decreased during the past years in France, after intensive public health interventions.[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.[24–26] Recently, an increased biological response to 1,25-dihydroxyvitamin D has been reported in genetic hypercalciuric stone-forming rats.[27] Breslau et al[28] previously showed that hypercalciuria might be driven by an increased sensitivity to vitamin D in some patients

TABLE 2. Prevalence of *Fok*I, *Apa*I, *Bsm*I, and *Taq*I *VDR* Polymorphisms

	No Plaque	Randall Plaque	*P* Value
*Fok*I			
FF (%)	21 (56.8)	12 (37.5)	
Ff (%)	13 (35.1)	13 (40.6)	
ff (%)	3 (8.1)	7 (21.9)	
Allelic prevalence (F/f)	74.3/25.7	57.8/42.2	0.047
*Apa*I			
AA (%)	11 (29.7)	9 (28.1)	
Aa (%)	18 (48.6)	13 (40.6)	
aa (%)	8 (21.6)	10 (31.3)	
Allelic prevalence (A/a)	54.1/45.9	48.4/51.6	0.61
*Bsm*I			
BB (%)	5 (13.5)	6 (18.7)	
Bb (%)	17 (45.9)	10 (31.3)	
bb (%)	15 (40.6)	16 (50.0)	
Allelic prevalence (B/b)	36.5/63.5	34.4/65.6	0.86
*Taq*I			
TT (%)	18 (48.6)	16 (50.0)	
Tt (%)	15 (40.6)	9 (28.1)	
tt (%)	4 (10.8)	7 (21.9)	
Allelic prevalence (T/t)	68.9/31.1	64.1/35.9	0.59

Prevalence of *VDR* polymorphisms in calcium oxalate stone formers with intact stones submitted for analysis, with or without Randall plaque. VDR = vitamin D receptor.

with normal 1,25-dihydroxyvitamin D serum levels. Large interventional studies aimed for bone protection by vitamin D and calcium reported an increase in renal stone incidence in treated patients.[29] Many dairy products are now enriched with vitamin D, and children receive frequent supplementation. Of notice, vitamin D intakes in USA have probably been higher than in Europe during the past decades, due to dietary enrichment, especially infant nutrient supplementation.[30]

By using data from a fully phenotyped population, we found significantly increased ionized calcium and osteocalcin serum levels, and modestly increased phosphate reabsorption rate in the Randall plaque group. These results are highly suggestive of an increased response to vitamin D in these patients as levels of 1,25-dihydroxyvitamin D, the active form of vitamin D, were similar in both groups. Of notice, 39 patients had high 1,25-dihydroxyvitamin D serum levels (>67 pg/mL), a common setting in renal stone formers, whereas few patients had elevated levels of 25-hydroxyvitamin D.

The most interesting finding was the observation that the bone remodeling marker, osteocalcin, unlike bone alkaline phosphatase, was independently associated with Randall plaque. The osteocalcin gene has a classical VDR response element in promoter region, and is considered as a hallmark feature of VDR activation.[31,32] Taken together, our results suggest that patients prone to develop plaques have an increased biological response to 1,25-dihydroxyvitamin D implying VDR. In turn, VDR activation increases calcium absorption by intestinal epithelial cells and eventually calcium renal excretion.[26,28] In addition, VDR activation in osteoclasts has been shown recently to promote bone resorption, increasing thereby calciuria.[27,33]

A few *VDR* polymorphisms (mainly *Apa*I and *Taq*I) have been related to an increased risk of urolithiasis, but the results may vary according to populations.[17,18,34] Interestingly, we observed a relatively high prevalence of *Bsm*I *b*, *Apa*I *a*, and *Taq*I *T VDR* polymorphisms (*baT* haplotype) in both groups, similar to the distribution observed in 62 European renal stone formers affected by fasting idiopathic hypercalciuria.[35] We identified the *Fok*I *f* allelic polymorphism as significantly overrepresented in the Randall plaque group. This polymorphism has been related to increased osteocalcin circulating levels.[36] However, no significant relationship could be identified between *f* allele and osteocalcin in our small series: osteocalcin median serum levels were 12.9 (10.3, 16.0) ng/mL and 13.7 (12.1, 18.2) ng/mL in *FF* homozygous patients and *f* allele carriers, respectively. It seems likely that other unidentified *VDR* polymorphisms or VDR coactivators may promote sensitivity to vitamin D and control serum osteocalcin levels in patients with Randall plaque.

At last, the timescale of stone formation should be considered. It has been shown that calcium phosphate crystallization begins in basement membranes of thin loops of Henle and then spreads toward the tip of the papilla.[11] Surface expression of Randall plaque would precede stone formation. Indeed, Randall plaques have been observed in patients in the absence of renal stones.[15] In addition, the concentric and radial structure of type Ia calcium oxalate stone evidences that stone grows from the Randall plaque (Figure 1C). However, the delay required for Randall plaque formation is unknown. The striking point of our epidemiologic data is the younger age of the population that develops calcium oxalate stones from Randall plaques, with the age peak of such stones ranging now between 20 and 30 years. This suggests the plaque is developed before 20 years of age and probably in children and teenagers. Since recent reports failed to evidence a beneficial effect of vitamin D supplementation on disease occurrence, our results raise concerns about the systematic use of vitamin D in children.[37,38]

Our study has several limitations. First, it was not designed to assess past vitamin D intakes of patients. Although there was a nonsignificant trend toward higher 25-hydroxyvitamin D serum levels in patients affected by Randall plaque, these levels were in the normal range and reflect only recent vitamin D intake and production in adulthood, not the exposure to vitamin D during infancy. We hope that the correlation we observed between biological activity markers of vitamin D and Randall plaque may lead to large epidemiological studies in children. Second, 71000 stones have been referred from >200 hospitals during decades, giving us an opportunity to draw a representative view of urolithiasis in Western Europe. Since calcium oxalate stone incidence grows in France and North America, it seems likely that Randall plaque may explain for a part the overall increase of calcium oxalate stone frequency observed during the past decades. However, the design of our study provides data about stone proportions but not stone incidence. At last, as stated above, *VDR* polymorphisms have been assessed in small groups, and *Fok*I *f* polymorphism is unable to explain alone patient phenotype, particularly osteocalcin levels. Moreover, unlike *Taq*I and *Apa*I, *Fok*I polymorphism has not been related to increased risk of urolithiasis.[39] Further, genetic studies are needed in larger populations of various ethnicities to confirm these preliminary results and identify other polymorphisms that would explain sensitivity to vitamin D.

In conclusion, our large-scale study draws attention on important aspects of Randall plaque-related stones. On the basis of the analysis of 30,149 intact stones, we observed a high proportion of calcium oxalate stones grown on Randall plaque. We describe an epidemic of Randall plaque-related stones, especially in young adults, whereas renal stone prevalence

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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