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ARTICLE

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Lithiasis in cystic kidney disease and malformations of the urinary tract

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Abstract The prevalence of renal stones in renal cystic and malformative conditions exceeds the prevalence of renal stones in the general population, suggesting that the above-mentioned cystic and malformative disorders favor stone formation. Urinary stasis is generally assumed to play a major part in the pathogenesis of the nephrolithiasis associated with distorted renal anatomy due to a delayed washout of crystals and risk of urinary infections. However metabolic factors are also important in the pathogenesis of stones in these conditions. Indeed, metabolic abnormalities have been observed in the majority of stone-forming patients with conditions such as horseshoe kidney and ureteropelvic junction obstruction. Five different models of stone formation can be identified, depending on stone composition, risk of infection stones, and pathogenesis of renal cystic and malformative conditions. A proper metabolic evaluation should be conducted to diagnose specific, treatable metabolic disorders, thereby reducing the frequency of recurrent stone disease in these conditions as well.

Keywords Renal stone · Horseshoe kidney · Ureteropelvic junction obstruction · Autosomal dominant polycystic kidney disease · Medullary sponge kidney · Vesicoureteral reflux

Introduction

A number of articles have reported on the prevalence of renal stones in renal cystic and malformative conditions (Table 1). Generally speaking, these data are very heterogeneous, probably because most of these studies are retrospective and deal with very small case groups, and selection biases are likely since patients with stones are more likely to come under medical observation.

The frequency of renal stone disease in patients with autosomal dominant polycystic kidney disease (ADPKD) ranges from 8 to 36% in different studies [1]. Levine and Grantham [2] conducted a systematic study in 84 ADPKD patients using CT to determine the frequency of stones and cyst calcifications. Renal stones were found in 36% of patients. These subjects had suffered more frequently from flank pains (68 vs. 35%) and urinary tract infections (63 vs. 18%).

It is hard to say what the prevalence of renal stones may be in medullary sponge kidney (MSK), which generally comes to light because of stones. According to Ginalski et al. [3], the prevalence of MSK was 1% in subjects who underwent urography and were unaffected by nephrolithiasis. If MSK has a prevalence of 20% in renal stone formers [4], and the prevalence of nephrolithiasis in the general population is 10%, then we might expect 1% of the general population to have MSK without stones and 2% to have MSK with stones, i.e. a prevalence of 3% for MSK, and two in three cases would be stone formers. Thus, we can roughly estimate a $>70\%$ prevalence of nephrolithiasis in MSK patients.

The majority of patients with ureteropelvic junction obstruction (UPJO) do not form stones [5]. In fact, the risk of renal stones in this condition is low in absolute terms, since only 2.1% of 1,639 patients under 17 years of age reviewed over a 45-year period at the Mayo Clinic had a simultaneous renal stone [6], though that is 70 times the prevalence in an age-matched general population. This figure is similar to the one found by Rickwood and Reiner [7]. Moreover, nephrolithiasis was observed in 20% of 111 adults with UPJO reviewed between 1967 and 1983 at the same clinic [8].

The prevalence of renal stones in patients with vesicoureteral reflux (VUR) ranges from 4 to 19% [9]. Using intravenous pyelography, Kohler et al. [9] have shown that 18% of 115 adult patients, mostly females, with VUR have radiopaque stones. This is 45 times

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Table 1 Prevalence of lithiasis in cystic kidney diseases and malformations of the urinary tract

ADPKD	8–36%
MSK	>70%
UPJO	20%
HSK	21 to >60%
MC	Up to 70%
CD	9.5–50%
VUR	4–19%

higher than the prevalence observed in females with urinary tract infections screened using urography [10]. The prevalence of urinary stones in patients with megaureter has not been reported.

In a case series of 43 horseshoe kidney (HSK) patients, Evans and Resnick [11] have shown that 23% had a history of renal stones, which were bilateral in a third of them; according to said authors, who considered a number of reports, the prevalence of urolithiasis in HSK ranges from 21% to over 60%.

A Spanish group [12] found that 69% of 39 patients with megacalycosis had renal stones, struvite and whewellite being the most frequent compositions.

In calyceal diverticula, Liatsikos et al. [13] stated that stones occur in 9.5–50% of cases.

Drawing a broad conclusion, it seems fairly obvious that such rates exceed the prevalence of renal stones in the general population, suggesting that the above-mentioned cystic and malformative conditions favor stone formation. Urinary stasis is generally assumed to play a major part in the pathogenesis of the nephrolithiasis associated with conditions involving a distorted renal anatomy due to a delayed washout of crystal aggregates and conditions facilitating the onset of urinary infections. But this should not detract from the relevance of metabolic factors. Indeed, metabolic abnormalities have recently been suggested to have a role in the majority of stone-forming patients with conditions such as HSK and UPJO [6, 8, 14].

This article separately reviews these conditions to draw insight into the leading pathogenic factors of renal stone formation, since such an understanding may have practical implications for the treatment of stone disease in these patients.

Stones in patients with ADPKD

According to Torres et al. [15], stones in ADPKD are mainly constituted by calcium oxalate (CaOx) (47%) and/or uric acid (57%). Though the former is less prevalent than in non-ADPKD patients, what is really striking is the fact that around 50% of stones in ADPKD patients are made of uric acid.

The high prevalence of uric acid stones in ADPKD patients has recently been confirmed by Daudon et al. [16], far higher than the 5–10% frequency of these stones found in the general population of renal stone formers.

The relatively low prevalence of CaOx stones [15, 16], and specifically of whewellite and weddellite [16], in ADPKD patients suggests that hyperoxaluria and hypercalciuria have a less relevant role than in idiopathic calcium kidney stone disease. In fact, the prevalence of hypercalciuria is low in ADPKD patients with stones (only 11%) [15]. The figure worth noting in these patients is the greater prevalence of hypocitraturia (up to 67%) [15], which probably does not reflect a tubular acidification defect, since less than 10% of these patients had an abnormal ammonium chloride test, and only 10% of the stones were composed of calcium phosphate, which should be the most prevalent component in patients with renal acidification defects [17]. In addition, the pH in the morning urine of ADPKD patients with renal stones is lower—not higher, as we might expect if an acidification defect were to have a major role [1]. Hypocitraturia is also very common in ADPKD patients who do not form renal stones, however. Grampsas et al. [18] have shown that the prevalence of hypocitraturia is 60 and 49% in ADPKD patients with and without stones, respectively, while in control stone patients it is lower than 20% [15].

Hyperuricosuria is less frequent in ADPKD patients than the high frequency of uric acid stones would lead us to expect, i.e. it is 15 versus 38% in non-ADPKD stone formers [15]. On the other hand, when 163 ADPKD patients were compared with their non-ADPKD relatives, Kaehny et al. [19] found no differences in the prevalence of hyperuricemia or in serum uric acid level, uric acid clearance or fractional excretion. Data from Torres et al. [15] confirm this observation. The greater frequency of uric acid stones and low morning urine pH in ADPKD resemble the situation observed in gouty uric acid stone formers and may suffice to explain uric acid lithiasis. In gouty subjects, renal ammoniogenesis is defective and leads to low urine pH [20], and a defective ammonium excretion after ammonium chloride challenge has been observed in ADPKD patients too [21, 22].

Grampsas et al. [18] have also reported that ADPKD patients forming renal stones have a 30% lower urinary volume and lower urine magnesium levels. Both conditions facilitate urinary lithogenesis.

As mentioned previously, urinary stasis within the intrarenal calyceal system caused by direct compression from enlarging cysts has been accused of contributing to stone formation. Grampsas et al. [18] have indeed demonstrated that the total number of cysts and the predominant cyst's size are significantly greater in patients with ADPKD and stones than in patients with ADPKD without nephrolithiasis. Cysts are also larger and more numerous in kidneys revealing stones within their collecting system: this supports the view that as the anatomical disorder progresses, there is a more severe distortion of the collecting system and a greater likelihood of stone formation, presumably caused by urinary stasis. Urinary stasis would delay the washout of crystal aggregates and favor urinary infections. The frequency

of urinary infections is only marginally increased in ADPKD patients, however. Distortion of the renal medulla architecture due to the cysts may nevertheless have a profound effect on tubular function too, interfering with the normal transfer of ammonium to the final urine.

Judging from the findings reported by Torres et al. [15] and Grampsas et al. [18], a combination of anatomical and metabolic abnormalities caused by ADPKD seems to be responsible for the greater frequency of nephrolithiasis (and uric acid stones in particular) in this population.

Stones in patients with medullary sponge kidney

Carbapatite and brushite are especially well represented in the stones of patients with MSK, while struvite is almost absent (found in only 2.5% of stones), so the risk of infection stones is modest in MSK, despite the intrapapillary urine stasis. According to Daudon et al. [16], the stones' composition and morphology suggest the existence of frequent distal tubule acidification defects. It is well known, in fact, that type 1 renal tubular acidosis and hypocitraturia are frequently seen in these patients (in up to 40 and 77%, respectively). Hypercalciuria is also common in this category of patients (up to 88% of cases).

We have recently suggested [23] that the abnormal ectasic aspect of papillary ducts in MSK is the morphological counterpart of a more generalized dysembryogenic process responsible for the coexistence of a number of renal tubular dysfunctions. In this light, stone formation in MSK seems to be a process driven more by the concurrence of multiple metabolic risk factors than by the abnormal papillary architecture.

Stones in patients with ureteropelvic junction obstruction

The composition of the renal stones in patients with UPJO is much the same as in control stone formers [15], suggesting that hypercalciuria and hyperoxaluria have an important part to play. Infections should also have a role, however, suggested by the slightly higher incidence of stones containing some struvite [15]. Recent studies have confirmed that metabolic abnormalities are very common in UPJO patients with stones. In a prospective study performed in 1995–1999 on 48 UPJO patients, 21 of them with renal stones, Matin and Streem [24] found that 67% (vs. 38% in the control UPJO group with no stones) had some urinary abnormalities potentially responsible for lithogenesis. This finding is similar to the 76% reported by Husmann et al. [6] after a retrospective observation spanning 42 years: in non-struvite stone patients with UPJO, they found hypercalciuria in 55% of patients, hyperuricosuria in 12% and hypocitraturia in 14%. The frequent occurrence of metabolic abnormalities has been confirmed by other authors in various countries [25], though the prevailing metabolic defect in Turkish children was different from that of American reports [6, 8], since hypocitraturia seemed to be the most common risk factor (in Turkey), probably reflecting unique population characteristics for the etiology of stone formation [25].

The high prevalence of metabolic abnormalities in UPJO patients with renal stones is not very different from the one observed in idiopathic renal stone formers. Whether this high prevalence of metabolic urinary abnormalities is primary or secondary to the obstructive uropathy is not known, though the former seems more plausible for the following reasons:

- The prevalence of metabolic abnormalities was lower in patients with UPJO without stones, despite similar degrees of obstruction.
- If an obstructive lesion is responsible for the excess metabolic dysfunction, we would expect to see acidification and concentration defects, but very few of these patients have renal tubular acidosis [6], and they have no increase in diuresis [8].
- Bilateral stones were observed in 24–53% of patients with unilateral UPJO [6, 8, 24], and in 60% of patients, stones recurred in the contralateral, unobstructed kidney [6].
- Correcting UPJO does not prevent the recurrence of stones (in 55% of patients) [6].

As mentioned previously, an obstructed urine flow was considered the main condition leading to lithogenesis in UPJO too, due to the impaired drainage of crystals and infections favored by urinary stasis. Pooling patients from a number of reports [6, 8, 24–26], 24% of the 130 patients with unilateral UPJO and concurrent ipsilateral stones also had contralateral stones, clearly demonstrating that the additional risk relating to the stricture amounts to a 76% difference. However, although the stricture seems to have such a relevant role, given the relatively small number of UPJO patients suffering from stones [6, 8], it is fairly obvious that the stricture per se is not enough to cause renal stones. So there would have to be a pathogenic role for metabolic disturbances. This impression is supported by a number of observations. For instance, although the risk of recurrence is quite high for UPJO patients with both struvite and non-struvite renal stones, in the case of non-struvite stones, the said risk is associated with metabolic abnormalities. In fact, while the vast majority of children with recurrent non-struvite stones have a metabolic abnormality, this is true of only 17% of cases with recurrent struvite stones [8]. Moreover, although bilateral stones have been observed in both conditions (but the limited number of struvite stone patients makes it impossible to establish any valid statistics), contralateral stones were only just observed in non-struvite stone patients [6]. Finally, active interventional treatment of the underlying disorders reduces the likelihood of recurrent nephrolithiasis, as shown in adult patients with UPJO [8].

Stones in patients with horseshoe kidneys

Though urinary obstruction and infection have generally been considered the primary etiologic factor behind stone formation in HSK, because of the anomalous shape of the renal pelvis and the course of the ureters in relation to the renal isthmus, and the frequent coexistence of UPJO, the composition of the stones in patients with HSK differs very little from the one observed in the general population of stone formers. Weddellite and whewellite are common, suggesting a role for hypercalciuria and hyperoxaluria, as in primary renal stone formers [16]. In a small case group of patients, Raj et al. [14] recently found urinary metabolic abnormalities quite frequent in stone formers with HSK, much the same as in control stone formers (though the prevalence of hypercalciuria was probably overestimated because they considered a lower cut-off value). These authors confirmed that most stones are composed of calcium oxalate and phosphate. Evans and Resnick [11] also found that seven out of a series of ten HSK patients with stones had at least one metabolic abnormality.

Thus, as in patients with most of the previously discussed renal anatomical anomalies, so too in HSK it appears that urinary stasis is not the sole cause of stone formation, and the reported high frequency of urinary tract infections in HSK—up to 41% of cases [27, 28]—certainly seems to play a minor part in the lithogenesis associated with these malformative conditions.

Stones in patients with vesicoureteral reflux

In the study by Kohler et al. [9], most VUR patients with stones (67%) had no history of stone-related symptoms. Renal stones were most frequently or nearly always ipsilateral to the VUR, located in clubbed calyces and concomitant to reflux nephropathy. This confirms the previous report by Torres et al. [29] that radiopaque stones were seen in 18% of adult VUR patients and almost exclusively in scarred kidneys. These observations suggest that urinary stasis and infection are probably major factors in stone formation in VUR. In fact, as many as 33% of stones contain some struvite (and 9% are composed mainly of struvite), and 43% mainly consist of carbapatite [16]. In terms of stone composition and the role of infection, this situation is reminiscent of the one observed in stone patients with mega-ureter (see below).

It is worth noting the comment from Daudon et al. [16] that although the prevalence of CaOx crystalline species is lower in VUR patients than in control stone formers, the weddellite/whewellite ratio is higher than 1, unlike urolithiasis in general and in all other malformative conditions of the urinary tract. The prevalence of brushite is also significantly greater than in control stone formers. Since weddellite and brushite are both calcium-dependent crystalline species, these observations suggest that hypercalciuria is involved in the pathogenesis of renal stones in VUR, or in a subgroup of these patients at least. In a study conducted in the Canary Isles, 58.6% of 46 children with VUR had hypercalciuria, a far higher prevalence than in healthy control children (3.8%) [30]. It is not clear from this paper whether the 7/27 cases of lithiasis were ipsilateral to the VUR, but if this is the case, as suggested by previous observations [9, 29], one may well question the role of hypercalciuria in the pathogenesis of renal stones in this condition, because we would expect to find bilateral stones (unless hypercalciuria is due to a renal leakage of calcium ipsilateral to the VUR). Hypercalciuria was likewise very common in the parents, of children both with VUR and with hypercalciuria, and of the normocalciuric children with VUR. The high prevalence of hypercalciuria and renal stones among the parents of children with VUR points to a genetic defect responsible for the hypercalciuria. The study did not investigate whether VUR was familial in these cases, but it is common knowledge that VUR is an inheritable, dominant condition. The study suggests that urolithiasis in patients with VUR may be partly due to a metabolic component [30].

Stones in patients with mega-ureter

Mega-ureter (MU) is a rather peculiar malformation in terms of renal stones, since it differs from those described previously (with the notable exception of VUR) in one fundamental respect, and that is a very high predisposition to infection-related stones. More than 50% of stones are made of carbapatite (47%) and struvite (6% consist mainly of struvite; 33% contain some struvite) [12]. A dilated and atonic ureter is known to facilitate the onset of infection due to bacterial migration from the bladder.

Though no studies have specifically addressed the metabolic risk factors for stones in MU, the role of metabolic conditions seems much less important than in other urinary tract malformations, given the low prevalence of weddellite and whewellite stones [16].

Stones in patients with calyceal diverticula and megacalycosis

The calyceal diverticulum (CD) is a non-excreting, transitional-cell-lined cavity in the renal parenchyma that communicates with the calyceal fornix via a diverticular neck. In a group of 14 patients with CD, Hsu and Streem [31] found that 50% had urinary excretion metabolic abnormalities, and 64% also had a history of other stones distant from the involved CD. Raj et al. [14] confirmed this observation in 13 patients with stones in a CD, demonstrating hypercalciuria in 62%, hypocitraturia in 31%, hyperoxaluria in 23% and hyperuricosuria in 54% of patients. These findings would suggest that metabolic abnormalities are at least as important as urinary stasis in

Table 2 Different paradigms of urolithiasis in cystic kidney diseases and malformations of the urinary tract

	Stone composition	Risk of infection stones	Role of calcium stone metabolic abnormalities	Bilateral stones
ADPKD	Uric acid, CaOx	Low	Low	Yes
MSK	CaP	Low	High	Yes
UPJO, HSK	CaOx, CaP	Modest	Yes	Yes
MC, CD	CaOx, CaP	Modest	No	Generally not
VUR, MU	Struvite	High	Possible	Generally not

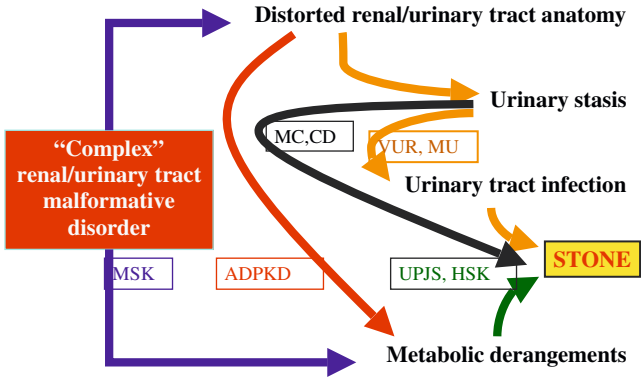

Fig. 1 Pathogenesis of renal stones in cystic kidney diseases and malformations of the urinary tract

the lithogenesis in CD. On the other hand, Liatsikos et al. [13] found a low frequency of metabolic abnormalities in 25 patients with CD stones. Though the discrepancy between the three studies may be due to a selection bias, given the limited number of patients investigated, the Liatsikos et al. [13] data are very informative, clearly demonstrating that stone formation in this condition may be due mainly to urine stasis.

Megacalycosis (MC) is a clinical entity characterized by dilation of all renal calyces, but not of the renal pelvis or ureter, in the absence of obstructive factors. No studies have investigated the prevalence of metabolic abnormalities prompting lithogenesis in patients with MC.

Stones forming in the abnormal calyceal apparatus or CD are mainly composed of whewellite, but they also contain carbapatite, which is probably due to an infectious component, despite struvite being only marginally increased [16]—findings substantially confirmed by other authors [12], who also found a concomitant urinary tract infection in 40% of cases, *Escherichia coli*, Proteus and Pseudomonas being the most frequent pathogens. The very low prevalence of weddellite stones is remarkable. Daudon et al. [16] suggest that this may be due to the secondary in situ conversion of weddellite crystals into whewellite as a result of the longstanding persistence of the stone in the pelvis or in the diverticulum.

Conclusions

Reported data point to a pathogenesis of stone disease in patients with cystic and malformative kidney and urinary tract conditions involving more than just urinary obstruction, stasis and infection. Five different models can be identified, depending on stone composition, risk of infection stones and pathogenesis (Table 2, Fig. 1).

The similar pattern of stone composition and metabolic urine abnormality profile seen in UPJO and HSK vis-à-vis the general kidney stone-forming population suggests a similar metabolic risk. In other words, stone formers with these malformative conditions are not a special group at greater metabolic risk, they belong to the general stone-forming population. This must be recognized in the diagnostic workup on these patients. But the far higher prevalence of renal stones than in the population at large and the higher prevalence of stones ipsilateral to the malformation support the conviction that stasis has a relevant pathogenic role in their lithogenesis. A proper metabolic evaluation should be conducted to diagnose specific, treatable metabolic disorders, thereby reducing the frequency of recurrent stone disease after correcting the obstruction.

Conversely, patients with ADPKD or MSK most probably carry a special, quite different, higher metabolic risk than renal stone formers generally. These two conditions are true parenchymal disorders, not just urinary tract malformations, and stone formation is probably triggered mainly by metabolic risk factors in both conditions.

In MC and CD, but even more in VUR and MU, the risk of infection-related stones is high and the role of metabolic disturbances probably negligible, while the anatomical condition is the main culprit responsible for stone formation (also by facilitating urinary infections), so treatment should address both infections and the malformation.

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