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ARTICLE

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The riddle of kidney stone disease: lessons from Africa

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Abstract Urolithiasis has not been extensively researched in the African continent due to a general lack of facilities and resources. Consideration of the few published papers indicates that there are some regions where the occurrence of stones is extremely rare. South Africa is unique in two respects. Firstly, it has both stone-prone and stone-free population groups and secondly, it is an African country in which a fair amount of research has been conducted in this field. These studies have shown that routine urine parameters cannot explain stone rarity, but that structural differences of inhibitory urinary proteins appear to be important. Similarly, the studies have demonstrated that common dietary components cannot necessarily be correlated with urine composition, particularly oxaluria, nor can they necessarily explain stone rarity, but that the role of oxalate-degrading bacteria has the potential to offer explanatory insights. By investigating the factors influencing stone rarity, those affecting stone formation have been concomitantly scrutinized. As a result, it is suggested that a paradigm shift from a focus on pathology to one on physiology is needed in urolithiasis research in general.

Keywords Calcium oxalate kidney stones · Stone rarity · Urinary proteins · Oxaluria · Oxalate-degrading bacteria

Introduction

There are over 40 countries in the continent of Africa. However, only about 200 urologists are registered members of the Pan African Urological Surgeons Association (PAUSA). In general, there is a lack of research facilities in the continent. As a consequence, urolithiasis has not been extensively investigated. Indeed, very few published papers in peer-reviewed journals are apparent. There are no epidemiological surveys or data on stone incidence. Consideration of the few papers that have been published on stone disease leads to the very general observation that urolithiasis in Africa can be broadly divided into three categories. Firstly, there are regions in which endemic paediatric bladder stones occur: Ethiopia [1], Cameroon [2], Niger [3], Algeria [4], Egypt [5]. Secondly, there are areas in which calcium oxalate upper urinary tract stones have been reported: South Africa [6], Tanzania [7], Northern Sudan [8–10]. Finally and perhaps most interestingly, there are regions in which the occurrence of stones has been found to be extremely rare: Nigeria [11–13], Southern Sudan [10], South Africa [6]. It is immediately obvious that South Africa appears in two categories. The uniqueness of urolithiasis in this country lies not with geographical differences as in Sudan, but with racial differences. It is well known that in South Africa, calcium oxalate urolithiasis occurs in the white population to the same extent as in other western countries, but that the incidence of stones in the black population group is extremely rare [6].

The endemic stones in Africa have been attributed to infection, hyperuricosuria (malnutrition) and poor diet. These are well-known aetiological factors. Regarding stone rarity, it has been suggested that in Southern Sudan, this could be attributed to the relatively low temperature, high relative humidity, low urinary calcium and high urinary volume [10]. Again, these factors seem reasonable. Interestingly, a paper published in 1981 alludes to ethnicity being a factor by drawing attention to the Afro-Arab population in the north and the "pure" African population in the South [10]. Stone rarity in Nigeria has been attributed to the low calcium content of the drinking water, the low consumption of dairy products and the labour intensive lifestyle [11]. While the latter is an accepted factor which is linked to low stone risk, the low calcium ingestion from water and dairy

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Table 1 Comparison of urine chemistries in black and white South African subjects

	Healthy black males ($n=75$)	Healthy white males ($n=202$)	P
Ca (mmol/24 h)	2.53	3.05	0.03
Ox (mmol/24 h)	0.22	0.17	0.01
Cit (mmol/24 h)	2.39	2.51	0.47
RS CaOx	2.35	2.53	0.55
Tiselius RI	216	152	0.01

RS relative supersaturation, *RI* risk index

products is recognised today as a risk factor rather than a protective one if it is coupled with a diet that is high in oxalate.

Despite the lack of convincing reasons for stone rarity in Nigeria and Southern Sudan, the near absence of this disease in certain regions is extremely intriguing. However, scientific conclusions cannot be drawn unless reliable, scientific data are available. Studies of stone disease in South Africa differ from most other countries in Africa in this regard.

Urine composition

An obvious factor in which to seek explanations for the stone rarity in South African blacks is in their urine chemistry. Table 1 shows some urinary parameters in both race groups. It is immediately apparent that some of the results are very surprising. Thus, although urinary calcium is lower in black subjects (and might contribute to a lower stone incidence in this group), urinary oxalate is higher. This is most unexpected since it would have been perfectly reasonable to have anticipated the converse. Furthermore, the observation that the calcium oxalate relative supersaturation in blacks is not different to that in whites is equally surprising. The higher Tiselius risk index in the black subjects adds further intrigue to the mystery. The lessons to be learned here are summarised in Table 2.

Urinary proteins

If indeed one of the lessons is that ''non-routine urinary factors'' may provide stone prophylaxis, an obvious group of components would be urinary proteins. Several of these have been universally identified as inhibitors of calcium oxalate crystallisation. These include urinary prothrombin fragment 1 (UPTF1), Tamm Horsfall glycoprotein (THG), albumin, osteopontin and bikunin. In general, these (and other) proteins are though to exert inhibitory action via one or more mechanisms, namely attenuation of crystallisation itself, crystal cell attachment and/or crystal degradation following endocytosis. In our studies on the black and white groups in South Africa we have focussed our attention on the five proteins mentioned previously. Our protocol is summarised in Table 3. In all cases, our objective has been to compare the urinary proteins derived from the two race groups. In our crystallisation experiments we tested the proteins in the parent urines from which they were derived and also switched the combinations in a cross-over design.

Two common results were found. Firstly, all of the proteins were found to be inhibitors of calcium oxalate aggregation, with the protein derived from the urine of black subjects being superior in this regard. Secondly, we observed a synergism between the protein and the urine in which it was tested, with the optimum combination being that of the black subjects.

Two of the proteins revealed structural differences between the groups. UPTF1 from black subjects has more Gla (gamma carboxyglutamic acid) and more sialic acid residues than that derived from white subjects. On the other hand THG from black subjects had a higher molecular weight, more cystein and glycine, and less alanine, valine, leucine and phenylalanine. The structural differences identified in these proteins may affect physicochemical properties and functionality, particularly inhibitory capacity. The lessons to be gleaned from these observations are summarised in Table 4.

Table 3 Urinary protein protocols

Protocol 1	Isolation, purification, verification
Protocol 2	[^{14}C]-oxalate deposition kinetics (real urine)
Protocol 3	CaOx crystal number–size–volume distributions (Coulter Counter)
Protocol 4	CaOx crystal formation kinetics (real urine) (Coulter Counter)
Protocol 5	CaOx crystal sedimentation kinetics
Protocol 6	Protein-coated CaOx crystal zeta potentials
Protocol 7	Protein structure characterisation

Table 4 Lessons from urinary proteins

Since urinary proteins appear to be important in modulating CaOx crystallisation, their other potential inhibitory mechanisms need to be investigated:
Crystal adhesion
Crystal degradation

Table 2 Lessons from urine chemistry

Lesson 1	Routine urine parameters cannot explain stone *rarity* in black subjects
Lesson 2	Perhaps too much importance is placed on these parameters for assessing stone *formation*
Lesson 3	Urinary oxalate, in isolation, is obviously not the all-important factor in stone rarity (and possibly in stone formation too)
Lesson 4	Perhaps other non-routine urinary factors provide prophylaxis in stone rarity

Table 5 Comparison of diets

	RDA	Healthy black males ($n=10$)	Healthy white males ($n=10$)	P
Ox (mg)	100–150	298 ± 69	128 ± 21	0.025
Ca (mg)	800–1200	663 ± 99	1,080 ± 106	0.011
Mg (mg)	350	326 ± 31	468 ± 40	0.013
Vitamin B6 (mg)	2.0	2.06 ± 0.41	3.06 ± 0.31	0.063
Total protein (g)	56–68	80 ± 9	120 ± 13	0.022
Animal protein (g)	38–46	45 ± 6	65 ± 7	0.037

Diet

Another obvious area in which to seek possible differences between white and black subjects in attempting to explain the difference in their incidence of urolithiasis is diet. Are there meaningful dietary differences between the two race groups and, if so, can these differences be correlated with urine chemistry? In a pilot study involving ten subjects from each group, the results were very surprising (Table 5).

Two types of comparison are warranted. Firstly, consideration of the data for the two groups relative to each other reveals that in black subjects dietary oxalate is higher while dietary calcium, magnesium and (to a less significant extent) vitamin B6 is lower than in white subjects. While these dietary differences are consistent with the relatively higher urinary oxalate observed in black subjects, it might have been reasonably expected that the strongly hyperoxalrogenic diet would culminate in urinary oxalate values which lie outside of the normal range. However, our data in Table 1 show that this is not the case. Of further interest are the lower total and animal protein intakes in black subjects which would predispose towards lower urinary oxalate in this group. Yet, as has just been pointed out, the converse is true. Thus it appears that dietary oxalate, calcium, magnesium and vitamin B6 might be more important in determining urinary oxalate than dietary protein. Secondly, it is of interest to compare the dietary intake of black subjects with the RDA values. (RDA is not available for oxalate. However, the value given in Table 5 [14] is an average oxalate intake.) Comparisons show that the oxalate intake in black subjects lies above the average range while intakes for calcium and magnesium lie below the range. Despite these factors, no relative hyperoxaluria occurs in this group! Moreover, the anomalies do not end there. In a study conducted in our laboratory we gave a high oxalate–low calcium diet to ten volunteer subjects from both race groups [15]. Once again the results were most surprising. While urinary oxalate increased in the white group as expected, no change in this parameter was observed in the black group. Although our dietary studies have thus far been limited to small groups ($n=10$), it is tentatively suggested that lessons can be learned from our results. These are presented in Table 6.

Table 6 Lessons from diet

Lesson 1	Common dietary (and urinary) factors cannot necessarily explain stone rarity (or stone formation)
Lesson 2	Hyper and hypo components in the diet cannot necessarily be correlated with urine composition
Lesson 3	Lack of correlation must be accounted for by alternative mechanisms

Gastrointestinal oxalate-degrading bacteria

Following the discussion in the previous paragraph, the question which arises regarding the dietary and urinary data in black subjects is "where is the oxalate?" As is well known, oxalate degrading anaerobic bacteria colonise the human intestine. Indeed a direct correlation has been identified between hyperoxaluria/stone disease and the absence of a particular bacterium *Oxalobacter formigenes*. We investigated oxalate-degrading bacteria in groups of black ($n=10$) and white ($n=10$) subjects by analysing faecal samples. Microbiological protocols involving bacterial culture media were used. The results are shown in Figs. 1 and 2. These show that black subjects have greater numbers of oxalate degrading bacteria than their white counterparts and that the oxalate utilisation capacity of these bacteria is greater in the former group. The lessons to be learned here are shown in Table 7.

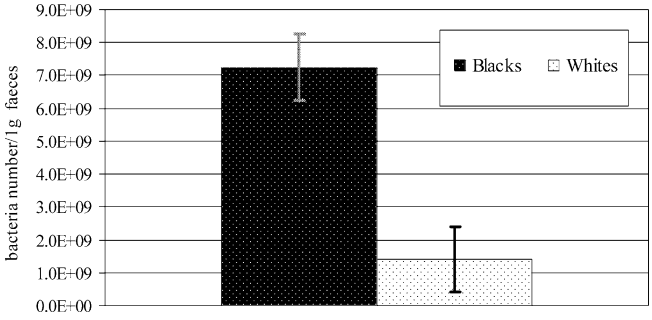

Fig. 1 Mean of total count of oxalate-degrading bacteria isolated per 1 g (wet weight) of faeces

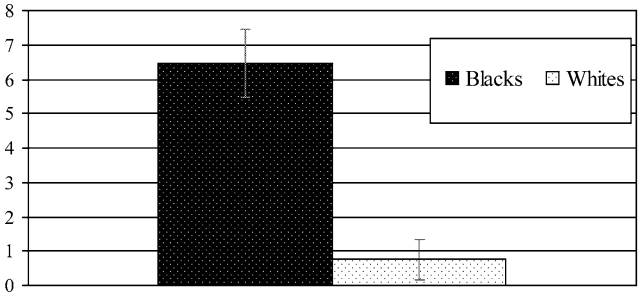

Fig. 2 Percentage oxalate utilisation per bacterial growth over 5 days

Table 7 Lessons from oxalate-degrading bacteria

Lesson 1	Apparent inconsistencies between dietary oxalate and oxaluria can be explained by oxalate-degrading gastrointestinal bacteria
Lesson 2	ODB are important for controlling oxaluria and may be a significant factor contributing towards stone rarity

Discussion

In terms of the global pathogenesis of urolithiasis, several lessons can be learned from Africa. Studies of a population group in which stones are rare have enabled us to get a ''reverse angle'' perspective on urolithiasis and to investigate whether lithogenic factors are absent and/or whether modulatory factors are present in this protected group. Ironically, this has allowed us to evaluate the importance of these factors in stone *pathogenesis* rather than in stone protection. Does this teach us lessons on how to proceed? Yes! Perhaps a few paradigm shifts are needed. Instead of asking ''*what causes stone formation*?'', we should rather ask ''*what prevents stone formation*?''. Instead of investigating *pathology* in stone formers, we should rather investigate *physiology* in normal healthy subjects. Instead of attempting to identify *lithogenic* agents, we should rather try to identify *anti-lithogenic* ones. Perhaps by adopting a change in mindset, new insights into stone disease might emerge.

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