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The increased risk of urinary stone disease in betel quid chewers

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Abstract The chewing of betel quid is a common practice in many countries of the world, particularly in Southeast Asia. The quid consists of a preparation of areca nut, betel leaf and calcium hydroxide "lime" paste ("chuna"). For the first time, we present a study that links its use to urinary stone disease. Eight patients (seven male and one female) who presented to our Stone Unit with recurrent urinary stones were included in the study. All were from the Indian subcontinent and were found to regularly chew betel. The patients underwent metabolic screening including blood, random urine and 24-h urine tests, quantitative chemical analysis of their calculi (where possible) and each completed a 7-day Diet Diary on his/her free, home diet. The study demonstrated a high incidence of hypercalciuria, a tendency to pass an alkaline urine and low urinary citrate excretion among the patients. Together these urinary risk factors increase the probability of developing both calcium phosphate-containing and calcium oxalate-containing stones. In support of this hypothesis, the patients were found to form stones consisting mainly of calcium phosphate but mixed with calcium oxalate. It is concluded that the use of calcium hydroxide "chuna" in the betel quid is the major contributor to the cause of urinary stones in its users. Moreover, the development of urinary lithiasis in such patients may be a precursor to milk-alkali syndrome in those individuals whose chewing habit is more extensive than in the patients in this study and who do not seek to decrease their habit over the long term.

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Introduction

The practice of chewing betel quid has been common since ancient times and is still widespread among many communities in Southeast Asia. Over time, migrant populations have introduced the habit to Africa, Australia, North America and Europe, so that it now has several hundred million users worldwide. After caffeine, alcohol and nicotine, betel quid is said to contain the fourth most commonly used psychoactive substance in the world [1].

The preparation of this mixture varies greatly, not only with geographical distribution but also according to personal taste. The standard form involves three main ingredients. First, the fruit of the areca palm tree has its thick, fibrous covering removed to leave behind the seed, known as the areca nut. A leaf from the betel pepper tree is taken and daubed with a calcium hydroxide (lime) paste (called "chuna")—made from burning seashells or coral and adding water to the powder until the desired consistency is reached. The nut is carefully wrapped with the leaf so that the lime paste forms a layer between the two. Other "condiments" may be added to the mixture depending on the user's preference and may include tobacco, cloves, sesame seeds or catechu gum. The resulting ball-like configuration is tucked between the cheek and the sides of the teeth and is usually sucked rather than chewed for up to several hours before being spat out (giving rise to the characteristic bright orange-red stains on the ground familiar to those living in areas of high use).

The popularity of this habit is most likely due to the psychoactive nature of the ingredients: the areca nut contains arecoline and its hydrolysed derivative arecedaine which act as central nervous system stimulants [2, 3]; the betel leaf contains psychoactive phenols and the all-important lime activates enzymes which stimulate the alkaloids present in the nut and leaf so that the desired effect is reached within a shorter period of time [4]. The effects of betel-quid range from a general sense of

wellbeing and heightened alertness to excessive salivation, euphoria, inebriation and dizziness depending on the frequency with which it is taken [3].

Chewing betel quid has been associated with health problems in the past, most notably the links with oral [5] and oesophageal [6] cancers. For the first time, this study suggests that the habit may also place users at an increased risk of urinary stone disease due to the high calcium content of the 'lime' paste in the quid. There have also been a few instances of milk-alkali syndrome reported in patients who chew betel quid on multiple occasions per day [7, 8].

Patients and methods

Eight patients (seven male and one female, all of Bangladeshi origin) included in this study were recurrent stone formers who indulged in betel-quid chewing up to four times per day. The patients were evaluated using a scheme that has been previously described [9] and is outlined below.

Blood and random urine specimens were collected from the patients when they attended the Out-Patient Stone Clinic. The plasma samples were analysed for urea, creatinine, bicarbonate, sodium, potassium, albumin, calcium, magnesium, inorganic phosphate, alkaline phosphatase and urate. The random urine samples were analysed for pH, urea, creatinine, sodium, potassium, calcium, phosphate, oxalate and uric acid. A comprehensive medical history, including a complete stone history, was recorded at the Clinic as well as body mass index, occupation and various lifestyle features such as stress, exercise and travel to countries with a hot climate. A 7-day Diet Diary was completed by the patient in order to calculate the intakes of fluids, calcium, oxalate, total protein, purine, refined carbohydrate, sodium and potassium. Two 24-h urine samples were collected on consecutive days on the patients' free, home diets—the first into a bottle containing 20 ml 1.2 M HCl and the second into a plain container. The acidified sample was analysed for volume, creatinine, calcium, magnesium, oxalate and citrate. The plain sample was analysed for volume, creatinine, pH, protein, urate, sodium and potassium. The biochemical probability of forming stones (P_{SF}) was calculated from the 24-h urine data as previously described [9].

Wherever possible, the stones were analysed quantitatively by Fourier transform infra-red spectrometry (FTIR).

Results

The mean age of the patients, when seen in clinic, was 47.3 years (range 39–62) and their history of stones (i.e. the number of years since the first episode) ranged from 5 to 21 years (mean 11.4 years). During that period, the number of stone episodes ranged from 2 to 6 (mean 4.1) excluding one patient (H) who had passed too many stones to recollect (Table 1). This represented significant morbidity from urinary lithiasis amongst a reasonably young cohort of patients.

Table 2 shows that there were no gross abnormalities in blood biochemistry that might be responsible for an increased risk of stone formation. The random urine analysis data are shown in Table 3 and the 24-h urine data in Table 4.

Table 3 shows that all the patients had a reduced notional tubular maximum for the reabsorption of calcium (normal range: Tm_{Ca}/GFR = 2.0–2.2 mmol/l GF) and thus had a renal leak of calcium. There was a minor degree of renal impairment in four of the cases as defined by their creatinine clearances (C_{Cr}).

Table 4 shows that seven of the eight urinary calcium excretions were above the normal range, with a mean value of 8.12 mmol/l/day (range 5.70–13.3). In addition, all but one of the urinary citrate levels (an inhibitor of stone-formation) were below the normal range, mean 1.89 mmol/l/day (range 0.15–5.14). These two factors together resulted in an increased risk of calcium oxalate stones even although the urinary oxalate levels were in the normal range. Since most of the patients also passed alkaline urine (pH values in the upper half of the normal range, i.e. >6.0), the combination of the hypercalciuria, alkaline urine and hypocitraturia produced a high risk of forming calcium phosphate calculi. It is interesting to note that as stone-formers, these patients have presumably taken advice to increase their fluid intake (mean 3.08 l/day, range 1.99–5.16) but this was insufficient to cope with their adverse combination of hypercalciuria, hypocitraturia and alkaline urine.

Table 5 shows all the patients had a high biochemical risk of forming CaP-containing stones often with a

Table 1 The mean age of the patients and their history of stones

Patient	Sex	Age (years)	Betel quids chewed (no./day)	History of stones (years)	No. of stone episodes
A	M	55	3	8	2
B	M	62	3	7	6
C	M	42	3	8	5
D	M	39	4	8	4
E	M	39	4	13	4
F	F	43	3	5	4
G	M	46	2	21	4
H	M	52	3	21	Multiple
Mean ± SEM	–	47.3 ± 2.9	3.1 ± 0.2	11.4 ± 2.2	4.1 ± 0.5

The patient with multiple stone episodes was excluded from the statistics, as no figure is available

Table 2 Blood serum composition in patients chewing betel quid (in mmol/l, unless otherwise stated)

Patient	Urea	Creat (μmol/l)	HCO_3	Na	K	Alb (g/l)	Ca	Corr. Ca	Mg	P	Alk Phos (IU/l)	Uric acid (μmol/l)
A	5.8	97	29	135	4.1	43	2.38	2.35	0.75	1.06	47	307
B	8.0	90	33	142	4.6	44	2.46	2.41	0.84	1.23	75	257
C	4.1	101	30	141	3.9	47	2.46	2.36	0.91	1.11	67	250
D	4.2	83	25	143	3.8	46	2.46	2.38	0.82	0.92	84	296
E	3.4	72	31	141	4.5	47	2.44	2.34	0.78	1.10	81	381
F	5.3	89	29	141	4.7	44	2.32	2.27	0.75	1.17	77	298
G	5.9	93	28	143	4.7	44	2.45	2.40	0.86	1.03	50	383
H	5.2	116	26	142	4.9	45	2.60	2.53	0.88	1.02	82	352
Normal range	2.5–6.7	70–115	24–30	135–145	3.5–5.0	35–50	2.15–2.60	2.12–2.55	0.75–1.00	0.8–1.45	30–120	210–480
Mean ± SEM	5.2 ± 0.5	93 ± 5	29 ± 1	141 ± 1	4.4 ± 0.2	45 ± 1	2.45 ± 0.03	2.38 ± 0.03	0.82 ± 0.02	1.08 ± 0.03	70 ± 5	315 ± 18

All normal ranges listed refer to the reference ranges used within the local NHS Hospital Trusts

Table 3 Biochemical composition of random "spot" urine samples from patients chewing betel quid

Patient	pH	Urea (mmol/l)	Creat (mmol/l)	Ca (mmol/l)	P (mmol/l)	Na (mmol/l)	K (mmol/l)	Ox (mmol/l)	Uric acid (mmol/l)	Tm_{Ca}/GFR (mmol/GF)	C_{Cr} (ml/min)
A	6.50	224.0	7.95	4.45	11.0	142	46	0.11	2.04	1.83	130
B	6.00	121.1	2.53	1.62	7.6	65	25	0.07	0.56	1.87	78
C	5.60	207.9	9.47	5.24	12.0	106	54	0.26	1.85	1.83	69
D	5.50	154.5	6.12	2.62	10.3	94	14	0.28	1.29	1.97	95
E	6.90	74.1	2.39	2.72	3.1	46	13	0.06	0.68	1.71	119
F	5.50	129.9	3.91	3.48	9.8	114	26	0.09	1.52	1.66	65
G	5.00	407.0	12.59	5.49	27.1	105	64	0.21	3.55	1.96	108
H	6.90	56.8	1.51	0.92	2.7	38	8	0.07	0.52	1.92	55
Mean ± SEM	5.99 ± 0.25	171.9 ± 39.4	5.81 ± 1.39	3.32 ± 0.59	10.5 ± 2.7	89 ± 13	31 ± 7	0.14 ± 0.03	1.50 ± 0.36	1.84 ± 0.04	90 ± 10

Random urine samples were collected as 'one-off' samples in the outpatient clinic and did not form part of the 24-h screening tests
Tm_{Ca}/GFR = notional tubular maximum reabsorption of calcium expressed in mmol/l glomerular filtrate
C_{Cr} = creatinine clearance expressed in ml/min

concomitant high risk of forming CaOx-containing stones. None of the patients demonstrated any risk of forming uric acid-containing stones mainly because of their tendency to pass an alkaline urine.

As shown in Table 6, it was not possible to perform analyses on all patients' stones. This was because some patients passed stones without retrieving them and others were referred from centres that were unable to provide us with the stone analysis. The stones were also analysed for uric acid, cystine, xanthine, 2,8-dihydroxyadenine, magnesium ammonium phosphate and silica but none was present. All stones assessed consisted of a mixture of calcium oxalate and calcium phosphate with the latter predominating in most stones.

Analysis of the patients' diets (Table 7) showed that the calcium intake was generally much higher than in the average population, [mean 25.2 mmol/day (range 17.1–35.1)]. These values include the calcium present in the

Table 4 Twenty-four hour urine values—composite of acid and plain collections (mmol/day) from patients chewing betel quid

Patient	Urine vol. (l)	Creat	pH	Ca	Mg	P	Ox	Cit	Uric acid	Na	K	Protein (g)
A	2.87	18.1	6.60	7.60	6.00	31.0	0.37	5.14	4.65	155	52	0.10
B	2.26	10.1	6.40	6.65	3.57	29.7	0.35	2.34	3.42	236	51	0.09
C	1.41	10.0	6.50	6.53	3.30	20.0	0.30	2.00	2.70	120	65	0.18
D	2.22	11.4	6.30	10.3	3.20	12.0	0.45	0.84	2.20	136	27	0.11
E	4.68	12.3	6.60	13.3	6.80	22.4	0.31	0.63	2.59	172	38	0.11
F	3.25	8.3	6.50	6.70	4.68	18.1	0.33	2.04	2.48	215	54	0.12
G	1.51	14.4	5.90	8.19	4.80	23.5	0.23	2.01	3.76	143	38	0.09
H	3.72	9.2	6.80	5.70	4.00	18.0	0.39	0.15	2.06	167	41	0.25
Normal range	1.4–3.5	8–18	5.0–7.4	2.0–6.0	3.0–6.0	15–40	0.25–0.45	2.5–4.5	2.0–3.5	100–250	14–120	< 0.15
Mean ± SEM	2.74 ± 0.40	11.7 ± 1.1	6.45 ± 0.09	8.12 ± 0.89	4.54 ± 0.46	21.8 ± 2.2	0.34 ± 0.02	1.89 ± 0.54	2.98 ± 0.31	168 ± 14	46 ± 4	0.13 ± 0.20

Table 5 Biochemical risk of stones—P_{SF} values in composite 24-h urine samples from patients chewing betel quid

Patient	"Pure" uric acid	"Mixed" UA/CaOx	"Pure" calcium oxalate	"Mixed" CaOx/CaP	"Pure" calcium phosphate
A	0	0	0.06	0.18	0.54
B	0	0	0.22	0.40	0.75
C	0	0	0.62	0.82	0.86
D	0	0	0.74	0.85	0.96
E	0	0	0.13	0.34	0.94
F	0	0	0.06	0.15	0.77
G	0	0	0.65	0.56	0.69
H	0	0	0.09	0.31	0.91
Normal range	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5
Mean ± SEM	0	0	0.32 ± 0.10	0.45 ± 0.09	0.80 ± 0.05

P_{SF} Probability of stone-forming

Table 6 Stone composition in patients chewing betel quid

Patient	Stone weight (mg)	Calcium oxalate (w/w)(%)	Calcium phosphate (w/w)(%)
A	37	35	65
B	–	–	–
C	44	71	28
D	4,295	69	31
E	–	–	–
F	105	12	88
G	69	45	55
H	46	19	81
Mean ± SEM	766 ± 706	42 ± 10	58 ± 10

"lime" paste used in the betel quid and it appears to be this that is considerably increasing the calcium intake—each quid raises the urinary calcium by approximately 2 mmol/day. This additional calcium appears to be the cause of the hypercalciuria observed in these patients. The only other slightly abnormal intake was in oxalate, probably because some patients added sesame seeds (which have a high oxalate content) to their betel quid. All the patients were of Bangladeshi origin whose characteristic diets normally put them at a low risk of forming stones. For example, their purine intake is not increased as it is in many idiopathic stone-formers in the West, since Bangladeshis do not usually consume high quantities of meat, fish and poultry produce. Similarly, their refined carbohydrate intake is also not high. Low consumption of these two dietary constituents reduces the risk of stone formation as a high intake of sugar increases the intestinal uptake of calcium and a high intake of animal protein causes the kidney to leak calcium. Moreover, the only male Bangladeshi stone-formers in our database, containing 2,165 stone-formers, were found to be ones consuming betel quid, as it is otherwise uncommon for Bangladeshis to form stones. As discussed earlier, the fluid intake of the patients is good but is insufficient to cope with their adverse combination of urinary risk factors.

Discussion

The areca nut and betel leaf are well documented for their links with oral [5] and oesophageal carcinoma [6], but this is the first time that betel-quid has been linked with urinary stone disease. Others, however, have reported metabolic derangements secondary to the habit that are consistent with our findings. These include a case report of hypercalcaemia and metabolic alkalosis attributed to betel nut usage [7] and a further two cases sufficiently severe to be described as having milk-alkali syndrome [8] (characterised by the triad of hypercalcaemia, metabolic alkalosis and renal insufficiency). It should be noted that although the betel leaf or areca nut, (often colloquially referred to together as "betel nut"), are cited as causing these problems, it is in fact the cal-

Table 7 Average daily dietary composition in the patients chewing betel quid

Patient	Fluid intake (l)	Calcium (mmol)	Oxalate (mmol)	Total protein (g)	Purine (mg)	Refined CHO (g)	Na (mmol)	K (mmol)
A	2.89	26.3	2.52	97.1	250	74.0	167	72
B	2.37	19.4	1.27	78.6	193	113.5	249	68
C	2.07	24.2	1.17	58.2	157	114.7	134	70
D	2.65	28.9	2.97	54.4	124	98.4	137	54
E	5.16	35.1	2.39	86.8	144	54.6	201	67
F	3.51	30.6	1.88	69.3	172	60.4	229	58
G	1.99	17.1	0.93	66.0	206	54.9	105	55
H	3.96	19.8	2.34	62.7	148	71.6	170	44
Normal range	1.4–3.5	16–20	1.2–1.8	60–80	140–180	70–120	100–200	40–100
Mean ± SEM	3.08 ± 0.38	25.2 ± 2.2	1.93 ± 0.26	71.6 ± 5.2	174 ± 14.4	80 ± 9	182 ± 15	61 ± 3.5

cium hydroxide ''slaked lime'' paste (''chuna'') used in the mixture that is most likely responsible for the high intake of calcium and the subsequent metabolic problems.

We calculate that a patient consuming up to four betel-quids per day could increase their daily calcium intake by between 500 and 800 mg. This represents a considerable calcium intake in excess of daily need. About 20% of this additional calcium will be available for intestinal absorption and renal excretion [10]. The patients in whom a diagnosis of milk-alkali syndrome was made [7, 8], were reported as consuming from 15 to 40 betel-quids per day over a period of at least 30 years—a considerably higher intake over a much longer period of time than shown in our cohort (2–4 betel-quids/day). These particular patients demonstrated metabolic derangements of sufficient magnitude to render them systemically unwell, unlike our patients who presented with symptomatic urinary stone disease but were otherwise in good health. Similarly, metastatic calcification is a feature of true milk-alkali syndrome [11] but our patients did not demonstrate this—the radiological appearances and distribution of their stone disease was unremarkable.

It is interesting to note that hypocitraturia is most commonly a result of a poor dietary intake of potassium [12]. The dietary and urinary levels of potassium are each in the lower halves of their respective normal Western ranges and this may be contributing to the high incidence of hypocitraturia in our patients. Thus, the hypocitraturia may be due to diet rather than to the chewing of betel per se. In the more exaggerated case of betel chewing reported by Lin et al. [7], metabolic alkalosis and hypokalaemia were noted and the hypocitraturia attributed to the consequent low urinary potassium excretion. It may be argued that a state of alkalosis should increase rather than decrease citrate excretion and although these patients are consuming additional alkali [$Ca(OH)_2$], it is only a weak base and consequently may not have been sufficient to stimulate citrate excretion by the kidney. Also, we are so far unaware of any long-term kidney damage that may result from betel quid chewing and this may affect the renal handling of citrate.

An alkaline urinary pH usually stimulates the tubular reabsorption of calcium, but in these patients, it would appear that the opposite has occurred. Further studies are therefore needed to determine the reasons why betel chewers have a decreased ability to excrete citrate and reabsorb calcium. As well as this, it would be interesting to obtain 24 h urine samples from patients after a few weeks of not chewing betel quid in order to reassess them after the effect of the betel leaves had been cleared from their systems. Unfortunately, it has not been possible for us to collect this data as the habit appears to be addictive and users are not keen to abstain from chewing for medical research purposes.

In conclusion, this study suggests for the first time that the calcium hydroxide ''lime'' paste contained in betel quid is a major contributor to the formation of calcium-containing urinary stones in those who chew it, even at a relatively low rate of usage. Moreover, the development of urinary lithiasis in such patients may be a precursor to milk-alkali syndrome in those who chew betel more frequently than the group of patients reported in this study. This work also illustrates the value of recording a comprehensive medical and social history, particularly in patients whose ethnic traditions may affect their health.

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