ORIGINAL

# Hyperoxaluria in Arab Stone Formers

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## ABSTRACT

**Twenty four hour urine analyses were made on 50 normal men, 50 normal women, and 50 male Bahraini stone formers. Also serum analysis was done on the stone formers. Hyperoxaluria was the only abnormal biochemical finding.**

**Since the nationals drink tea without milk, an experiment was done to compare the availability of oxalate in tea with and without milk. No difference was found.**


Bahrain has a high incidence of urinary stones that seems to be increasing. At the Salmaniya Medical Centre there are 81 admissions for stones per 100,000 population, and in 1985 131 stones were passed per 100,000 male Bahraini per year. This indirectly compares with the highest British town [1] where 54 patients per 100,000 were diagnosed as having stone in one year (many of whom did not pass the stone).

In 1985 168 stones passed by Bahrainis were found to contain calcium in 96%, oxalate in 82%, phosphate in 55% and urate in 17%. The male : female ratio was 3:1 (Salmaniya Medical Centre records).


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Since similar studies on Gulf Arabs have not been published before, I examined the urine of a sample of the normal population for comparison, and then compared it with that of the stone formers and with figures given in Western literature.

On finding hyperoxaluria in our stone patients, I studied the dietary intake of oxalate. Since the nationals drink tea without milk (tea being a major dietary source of oxalate [2]. An experiment was performed to find the amount available in tea with and without milk (since the calcium in milk might form an insoluble percipitate with oxalate, and thus not be absorbed by the gut).

## METHODS

For normal controls I selected 50 men and 50 women in good health and of an even age distribution (approximately ten for each decade from 15–55 years), who had no history of stone disease, or metabolic illness, or chronic drug intake. They were either patients, or their relatives or hospital staff. Half the men were of technical or clerical occupation, and the remainder mostly labouring or farming occupations.

Twenty-four hour urine specimens were collected in 5% thymol preservative, and examined in Baker's centrifugal analyser for calcium, oxalate, uric acid and phosphate; calcium by a modified Aizarin reaction, and oxalate by Hodgkinson's method

(1972) in which oxalate is converted to glycolic acid. Creatinine was also measured, which helped to confirm the completeness of the urine collection. Men who passed less than 4.5 mmol of creatinine, and who had a low urine volume were rejected, and similarly women who passed less than 3 mmol. Collections took one year to complete so both hot and mild whether conditions were prevailing.

Fifty male patients who passed, or had calcium, oxalate or phosphate stones removed ($NH_4$ containing stones were excluded) were asked to give 24-hour urine samples, and serum for calcium and uric acid. Those in hospital had collections done within 24-hours of admission so as not to distort results. No patients were in a state of renal colic or other distress. Serum samples were taken randomly as regard to fasting for calcium, uric acid and phosphate. It was decided to study men only as we found that their excreted substances are in a higher range than those of women.

In order to study the availability of oxalate in tea, three samples of tea (Lipton's) were prepared at different concentrations – weak, medium and strong. 10 ml of each were measured for oxalate concentration, and to another 10 ml of each was added 5 ml of Nido reconstituted milk. Those containing milk were then boiled and filtered to remove the solids, and the filtrate measured for oxalate concentration. A correction for dilution was made.

Fifty Bahrainis and fifty Asians were questioned about their daily tea consumption.

## RESULTS

Table 1 shows the ages of volunteers. I found a general correlation of calcium rising with age but with the limited number there was no statistical significance. The ages of the stone formers are not given, but they were all young to older adult with no extremes of age. (Each year we do have patients under 10 years of age passing idiopathic calcium stones, and some as low as 3 years).

**TABLE 1**

**Age Distribution of Healthy Volunteers**

| *Age in years* | *Men* | *Women* |
|---|---|---|
| 15-24 | 12 | 15 |
| 25-34 | 18 | 13 |
| 35-44 | 4 | 12 |
| 45-54 | 8 | 6 |
| 55 + | 8 | 4 |

Table 2 is the results from the healthy controls. The means are similar to those quoted for the U.K. [4], shown in Table 5. The 95% range (2 standard deviations on a Gausian curve) is that usually quoted for reference values, but the U.K. reference values correspond to our 90% range of normals. All the results show that men excrete more solute than women ($p<0.05$) which is due to the difference in lean body mass.

**TABLE 2**

**24 Hours Urinary Excretion of Calcium, Phosphorus, Uric Acid and Oxalate in Normal Bahrainis (mmol/dl)**

| | *Calcium* | | *Oxalate* | | *Uric Acid* | | *Phosphate* | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *95% Range* | *Mean* | *95% Range* | *Mean* | *95% Range* | *Mean* | *95% Range* |
| Men | 3.9 | 1.4 – 7.5 | 0.27 | 0.12 – 0.45 | 3.7 | 1.0 – 6.5 | 20.6 | 6.0 – 31.0 |
| Women | 2.7 | 0.8 – 6.5 | 0.24 | 0.10 – 0.43 | 2.9 | 1.0 – 5.0 | 15.3 | 6.0 – 25.0 |

**TABLE 3**

**24 Hours Urinary Excretion of Calcium, Oxalate, Uric Acid and Phosphate in Bahraini Stone Formers (mmol/dl)**

| | *Calcium* | | *Oxalate* | | *Uric Acid* | | *Phosphate* | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *95% Range* | *Mean* | *95% Range* | *Mean* | *95% Range* | *Mean* | *95% Range* |
| Bahraini stone formers | 4.0 | 1.4 – 7.5 | 0.39 | 0.18 – 0.65 | 3.2 | 0.6 – 6.0 | 19.5 | 7.0 – 32.0 |
| UK[4] | – | 2.5 – 7.5 | – | 0.2 – 0.4 | – | 3.5 – 4.2 | – | 0 – 32.0 |

**TABLE 4**

**Random Serum Levels of Calcium and Uric Acid and Phosphate in UK and Bahraini Stone Formers (mmol/dI)**

| | *Calcium* | | *Uric Acid* | | *Phosphate* | |
|---|---|---|---|---|---|---|
| | *Mean* | *95% Range* | *Mean* | *95% Range* | *Mean* | *95% Range* |
| Bahraini Stone formers | 2.3 | 2.1 – 2.6 | 0.34 | 0.23 – 0.46 | 0.17 | 0.1 – 0.26 |
| UK[4] | 2.3 | 2.1 – 2.6 | 0.34 | 0.21 – 0.47 | 0.17 | 0.1 – 0.26 |

**TABLE 5**

**Summary of Results of Urine Excretion and Serum Values in Normal and Stone Forming Bahrainis**

| | | *Normal* | *Stone former* |
|---|---|---|---|
| Urine | Calcium | Normal | Normal |
| | Oxalate | Normal | High |
| | Uric Acid | Normal | Normal |
| | Phosphate | Normal | Normal |
| | pH | Acid | – |
| Serum | Calcium | Normal | Normal |
| | Oxalate | Normal | Normal |

Table 3 shows that oxalate is the one product that stone formers excrete significantly more than the normals and the UK normals ($p<0.01$). Note that hypercalcuria is not a feature in stone formers.

Table 4 shows the serum of stone formers to be similar to UK normals, and that hypercalcaemia is not a feature.

Table 5 summarises the findings in stone formers and Bahraini controls.

The urinary pH of the controls was 6.6 in men (range 6.2 – 7.0) and 6.5 in women (range 5.5 – 7.0). The pH in stone formers was not recorded, but since we had no pure uric acid stones and ammonia containing stones were excluded, extremes of pH were not expected to be a contributory factor.

The mean volume of urine per 24 hours from normal Bahrainis was 1,206 ml in men (range 450-2,500) and 1,270 ml in women (range 440-2,900). The mean volume passed by stone formers was 1,900 ml (Range 600-3,000).

**TABLE 6**

**Concentration of Oxalate (μg / dl) in Tea with and without Milk in 3 Samples of Tea**

| | *Weak* | *Medium* | *Stronge* |
|---|---|---|---|
| With milk | 45 | 65 | 74 |
| Without milk | 51 | 67 | 69 |

Table 6 shows the result of the tea experiment. No significant difference was found whether milk was present or not. The 50 Bahrainis questioned consume daily on average 3.1 (range 0-5) full sized cups of tea. Of this 1.3 (range 0-3) is with milk, and 1.8 (range 0-5) is without. The 50 Asians consume a daily mean of 3.5 cups (range 1-5). Of this 3.4 (range 1-5) is with milk, and 0.1 is without (range 0-1).

## DISCUSSION

Calcium stone disease is now recognised to have a multifactorial aetiology rather than a single metabolic abnormality. For a person to have an increased risk of stone development he/she may be hypersensitive to normal stimuli or normosensitive to stimuli that are increased or prolonged.

Our findings of normocalcuria and hyperoxaluria in idiopathic stone disease is in contrast to hypercalcuria and mild hyperoxaluria that is found in most of the Western literature. Our results are supported by the normal values found in the controls, and the same finding in stone formers in Saudia Arabia by W G Robertson (1987 Personal Communication). Possibly a genetic difference is present in Arabs. On the other hand, approximately three quarters of our 24-hours urine collections were done in hospitals which can apparently give falsely low calcium values. It was found that urine calcium took 3 months to rise to normal levels following a stone event and that falsely low values of urine calcium by 40% can be obtained in hospital [5].

Regarding calcium in the blood, I noted from our ten patients with the highest urinary calcium that they had serum calciums in the middle of the normal range. This suggests that calcium is not an important factor. Incidentally, in the past five years we have had only two cases of hyperparathroyoid stones at the Salmaniya Medical Centre.

Concerning the cause of hyperoxaluria, it is known that 90% or more of the urinary oxalate comes from endogenous sources, such as ascorbic acid and glycine, and only 10% from the diet [6]. From our tea experiment, the drinking of tea without milk does not apparently increase its absorption. The diet of Bahrainis does not contain an excess of oxalate compared to a Western one, except that many people eat sunflower and melon seeds, and occasionally nuts which are rich in oxalae.

The dietary intake of oxalate is therefore probably not important, as the relationship between intake and excretion is a flat one unless in excess of 2 mmol/day [7]. Serum glycolate estimation distinguishes a metabolic cause of hyperoxaluria (raised) from a dietary one (normal).

The diet is implicated, however, with regard to animal protein. A marked rise of oxalate excretion occurs if protein consumption is above the level of 25 grams per day, and there is a similar steep relationship with calcium and uric acid [7]. This was confirmed by a study which found that 2,500 vegetarians had 50% of the expected incidence of stone disease [8]. Apart from protein, refined carbohydrates cause a rise in calcium excretion [9]. In Bahrain there is a reasonable intake of fibre, but the increased refined carbohydrate of recent years may well be contributing to the hyperoxaluria.

From the 1985 Stone Register I noted a sharp difference between Bahrainis and Asian immigrants in the incidence of stone. 129,060 Bahraini males passed 169 stones (131 per 100,000) whereas 69,710 Asians passed 37 stones (53 per 100,000) [10]. This gives a ratio of 2.5:1 which is highly significant. The main dietary difference between the two groups is that Bahrainis are more affluent and eat more animal protein. Otherwise the diet is comparable, as Bahrain has been heavily influenced by the Indo-Pakistan subcontinent for millenia. The Asian immigrants form most of the manual labour force, and therefore are exposed to the heat even more than the Bahrainis. This fact highlights the influence of difference in diet.

Regarding the climate, the volumes of urine collected from controls were similar to those in colder climates. A number passed as little as 500 mls which indicates uroconcentration, and they may have occurred in hot weather. Those from patients were not representative of normal conditions, so cannot be relied upon. However, I noted that admissions to the Urology Ward for stone was a mean of 9 per month during the 8 summer months compared to 4.5 per month in the 4 winter months (statistical significance $p<0.01$). During Ramadan when Muslims fast completely for 15 hours of daylight, ureteric colic seems more common than in other months (no figures available). However, in our experience stones do not spare the working in an air-conditioned environment; in fact it seems that more patients with stones work inside than work outside.

Uricosuria has been found to be a factor in calcium stone formation in up to 32% of cases [11, 12] and in 8% of cases the only metabolic derangement [13]. Our finding of normal urine is surprising as I found uric acid in 17% of 168 Bahraini stones, although no pure uric acid stones (I also found 96% to contain calcium, 82% oxalate, and 55% phosphate). Theories of epitaxial growth and binding of inhibitors by uric acid have been supported by experimental work [14, 15], but recently Goldwasser [16, 17] was unable to demonstrate either of these effects of uric acid. Uric acid seems to be unimportant in Bahrainis, but perhaps episodic rises of uric acid occur after large meat meals, which are common.

## CONCLUSION

**Idiopathic calcium stone disease is common in Bahrain, and is probably mainly due to the hot climate. Our finding of hyperoxaluria as the only biochemical abnormality in stone formers suggests that a high animal protein diet is an important and preventable cause, along with a refined carbohydrate intake. Increased oxalate intake may also be a factor in some patients.**

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