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Paraplegia

Citrate Excretion in Spinal Cord Patients

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Summary

Low urinary citrate is a risk factor in calcium renal stone disease.

The aim of this work was to identify the factors responsible for the low excretion of citrate frequently observed in patients with spinal cord lesions.

Thirty male patients with spinal cord lesions were studied by blood and urine biochemistry.

The most important single factor related to urinary citrate was urinary potassium. The presence or absence of urinary stone disease and variations in urinary volume also contributed significantly to variations in citrate excretion.

Determination of plasma and urinary citrate, urinary sodium and bacteriological culture of urine permitted complete discrimination of the 7 stone formers from the other patients.

Key words: *Citrate; Paraplegia; Potassium; Urinary calculus.*

Low urinary citrate concentration is a risk factor in calcium renal stone disease. Citrate possesses the properties of forming soluble complexes with calcium and magnesium and also of inhibiting the formation, growth and aggregation of crystals of calcium phosphate and calcium oxalate (Fleisch, 1978). Low urinary citrate excretion is frequently observed in patients with calcium renal stone disease (Nicar *et al.*, 1983).

Spinal cord patients have an increased incidence of renal stone disease, which is nearly always associated with chronic urinary infection and thought to be infection-induced (Burr, 1981). Citrate excretion in a group of paraplegic patients was significantly below normal (Burr *et al.*, 1985) and it seemed important to establish the reason for this finding.

Patients and methods

Thirty male patients with spinal cord lesions who had been admitted to this Centre were studied. So that urinary composition should vary widely, early and late spinal

patients were included. The following information was obtained: level, completeness and duration of cord lesion, age of patient, urine bacteriology, posture, level of activity, occurrence of spasms, drugs administered, consistency of stools, ingestion of fruit juices and relevant medical history.

From each patient two 24 hour urine samples were collected into a receiver kept in ice. On both days a sample of venous blood was obtained with a minimum of venous stasis and with the patient fasting and supine.

Urinary pH was measured by electrode on completion of collection. Urinary and plasma citrate and urinary isocitrate, inorganic pyrophosphate, urate and oxalate were determined by enzymic methods, magnesium by fluorimetry and calcium, ammonium and inorganic orthophosphate by spectrophotometric methods (Welshman and McCambridge, 1973; Sutor and Percival, 1978; Sutor and Wilkie, 1978; Urica Color (Boehringer); Oxalate kit no. 590 (Sigma); Sinha and Trew; 1971; Gindler and King, 1972; Chaney and Marbach, 1962; Daley and Ertingshausen, 1972). Plasma and urine sodium, potassium and creatinine and plasma chloride, glucose and urea (Beckmann ASTRA), serum calcium, phosphate, albumin, total protein, bilirubin, aspartate aminotransferase and urate (Technicon SMA2), magnesium (calmagite method—Randox Chemicals), blood gases and acid-base parameters (Radiometer ABL2), full blood count (Coulter Counter S Plus 4 or STKR) and erythrocyte sedimentation rate (ESR) were also determined. Creatinine clearance was calculated for both days. Mean results for this and for plasma citrate and urinary constituents and the other measurements performed once were submitted to linear and multiple regression and discriminant analysis (Statistical Package for the Social Services, SPSS-X). All multiple correlations were adjusted for the number of degrees of freedom.

A separate urine sample obtained aseptically was examined by the bacteriologist. If a mixed growth of organisms was obtained on first culture, the culture was repeated and the organisms identified.

For the purpose of statistical analysis the following codings were adopted: level of cord lesion—spinal segments numbered consecutively from C1; complete: 1, incomplete: 2; spasms—present: 1; absent: 2; posture—out of bed for part of day: 1; bedfast: 2; stool consistency—hard to very soft: 1 to 4; history of stone disease—absent: 1; present: 2; organisms isolated from urine—absent: 1; present: 2; drugs (groups were assigned to a letter code)—prescribed: 1; not prescribed: 2; fruit juice (orange, grapefruit or pineapple juice, more than 100 ml per day)—not taken: 1, taken: 2.

Results

Figures 1 to 3 give the distribution and duration of spinal cord lesions and age at time of study. Sixteen patients had been admitted for rehabilitation following the onset of the cord lesion, 6 had been admitted for the treatment of pressure sores, one for the investigation of recurrent urinary tract infections, one for cystoscopy, one each for fractured femur, lower back pain and spinal deformity. One patient was in renal failure associated with an aortic aneurism and another patient was in renal failure associated with stone disease.

Eleven patients were free of urinary infection. Organisms identified were in the

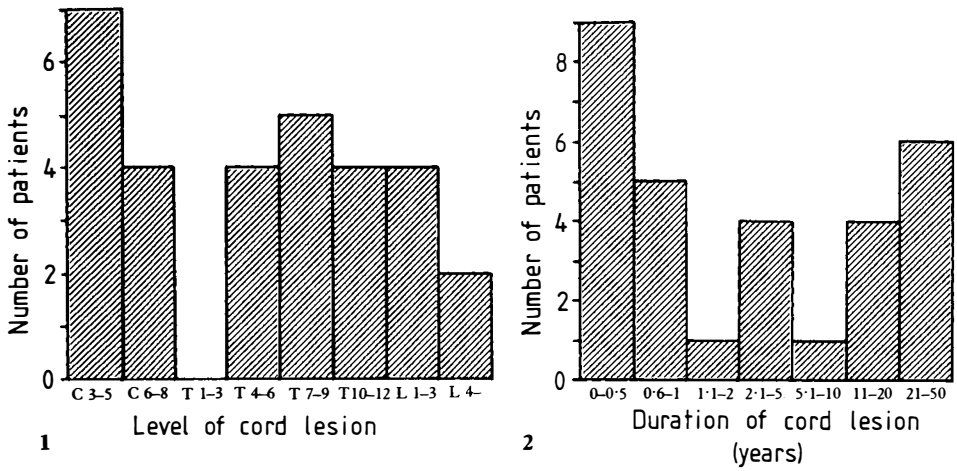

Figure 1 Distribution of spinal cord lesions among the patients studied.
Figure 2 Duration of spinal cord lesion.

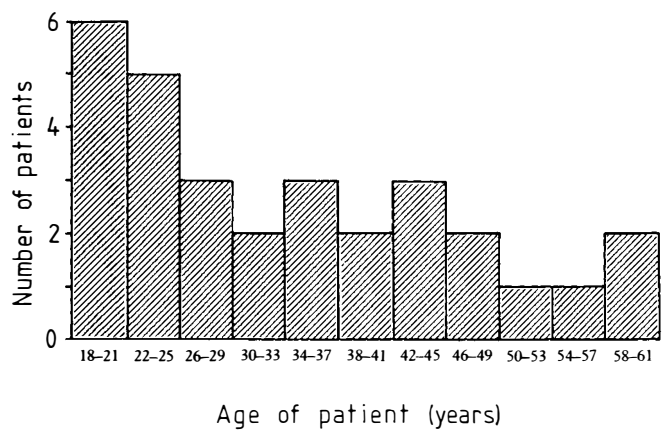

Figure 3 Age distribution of the patients studied.

following groups: *Acinobacter, Citrobacter, Enterobacter, Escherichia, Klebsiella, Proteus, Pseudomonas, Serratia, Staphylococcus,* and *Streptococcus.*

Six patients had a history of renal stone, 1 had had recent rapid growth of a large bladder stone. These stone forming patients were grouped together.

Ten patients were subject to spasms, 13 were bedfast, 21 had neurologically complete cord transection. 27 were traumatic in origin, the remainder being neurologically stable non-traumatic cases.

Three patients were receiving no drugs at all. Eight were receiving aperients, 7 antibiotics, 5 anticoagulants, 2 diuretics and 1 each an antidepressant, an antiepileptic and hexamine hippurate. Analgesics, antihypertensives, non-steroidal anti-inflammatory agents and spasmolytics were also being prescribed. One patient was receiving desmopressin, gonadotropin, hydrocortisone and thyroxine.

Table I Results of analysis of urine samples. Two 24 hour collections from each of 30 male patients with spinal cord lesions

		Mean	Standard deviation	Range	Lower limit of normal	Number of values below
Volume	(l/24 hours)	3·02	1·21	1·11–6·6		
pH		6·54	0·325	5·81–7·14		
Sodium	(mmol/24 hours)	99·8	46·1	20–186	130	21
Potassium	(mmol/24 hours)	50·5	16·1	14–78	35	5
Ammonium	(mmol/24 hours)	38·1	49·45	1·4–39·4		
Calcium	(mmol/24 hours)	5·91	3·51	0·44–17·6	2·5	4
Magnesium	(mmol/24 hours)	3·69	1·32	0·55–6·5	3·3	12
Phosphate	(mmol/24 hours)	23·6	7·76	4·7–39·4	16	3
Creatinine	(mmol/24 hours)	18·3	5·57	7·2–28·2		
Citrate	(mmol/24 hours)	2·04	1·16	0·35–5·32	1·3	8
Isocitrate	(mmol/24 hours)	0·78	0·29	0·04–1·24		
Urate	(mmol/24 hours)	2·43	0·92	0·56–3·64	1·4	3
Oxalate	(mmol/24 hours)	0·33	0·154	0·05–0·72		
Pyrophosphate	(μmol/24 hours)	15·4	12·6	1·1–74·4		
Creatinine clearane	(ml/minute)	83	31·5	5–132	70	9

Table II Results of analysis of blood samples

		Mean	Standard deviation
Sodium	(mmol/l)	138·0	3·5
Potassium	(mmol/l)	4·06	0·29
Chloride	(mmol/l)	105·1	3·94
Standard bicarbonate*	(mmol/l)	24·1	1·58
Calcium*	(mmol/l)	2·29	0·103
Phosphate*	(mmol/l)	1·34	0·162
pH*	(mmol/l)	7·361	0·0619
Urea*	(mmol/l)	3·44	1·58
Glucose	(mmol/l)	4·72	0·385
Bilirubin	(mmol/l)	4·6	4·2
Magnesium	(mmol/l)	0·83	0·757
Citrate	(μmol/l)	87	30·6
Creatinine*	(μmol/l)	70	17·5
Urate	(μmol/l)	383	76·6
Albumin	(gl/l)	37·1	3·60
Haemoglobin	(g/dl)	13·2	1·22
Alkaline phosphatase	(U/l)	109	67·8
Aspartate aminotransferase	(U/l)	18·5	10·3
ESR		32·0	26·3

*Two patients in renal failure omitted

Table III Significant correlations with 24 hour urinary citrate excretion

	Correlation coefficient (r)
24 hour urine potassium	0·6615 ($p < 0·001$)
24 hour creatinine clearance	0·5992 ($p < 0·001$)
24 hour urine volume	0·4904 ($p < 0·01$)
24 hour urine magnesium	0·3780 ($p < 0·05$)

Table IV Significant differences between patients with and without a history of urinary stone disease

	Non-stone patients n=23		Stone formers n=7		
	Mean	s.d.	Mean	s.d.	
Urinary citrate (mmol/24 hours)	2·28	1·181	1·26	0·629	($p < 0·05$)
Age (years)	31·9	12·5	44·7	16·0	($p < 0·05$)
Duration‡	1·51	5·26	10·5	4·22	($p < 0·01$)
Plasma inorganic phosphate* (mmol/l)	1·38	0·140	1·20	0·172	($p < 0·02$)

* Patients in renal failure omitted (1 in each group).
‡ Duration of cord lesion (in years); logarithms were used for statistical calculation.

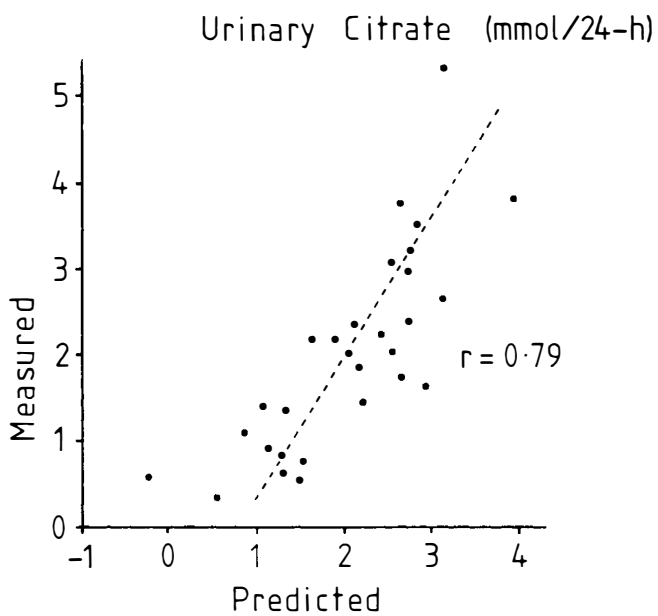

Figure 4 Results of multiple regression analysis. Urinary citrate as a function of urinary potassium, 24 hour urine volume and presence of stone disease. Predicted citrate = 0·033171.K − 1·00301.S + 0·32945.V − 0·60523. K = urinary potassium (mmol/24 hours); V = urine volume (l/24 hours); S = stone factor (no stone disease: S = 1, stone disease: S = 2).

There were too many different combinations of drugs and of urinary organisms for separate statistical analysis. Instead, merely the presence or absence of infection was included in the analysis.

Ambient temperature measured several times each day in the vicinity of the patient's bed was in the range 17–25°C.

Table I gives the results of the analysis of the urine samples, including the number of patients in whom the mean of the two samples fell below the expected normal range. Table II shows the results of blood analysis.

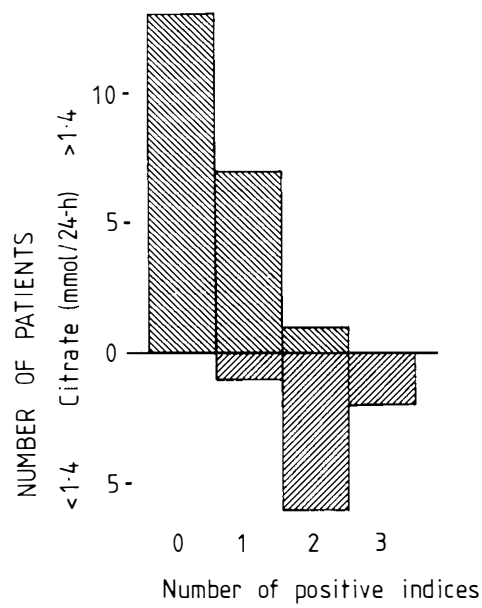

Figure 5 Numbers of patients with citrate excretion above or below 1·4 mmol/24 hours in relation to the numbers of citrate indicators. Citrate indicators: potassium < 40 mmol/24 hours; volume < 2·5 l/24 hours; plasma magnesium < 0·74 mmol/l; history of urinary stone.

Urinary citrate was significantly related to 24-hour urine volume, potassium, magnesium and creatinine clearance (Table III). The stone formers had significantly lower citrate excretion than the patients with no history of stone disease. They had also been paraplegic for longer and were older. Plasma phosphate was significantly reduced in the stone formers if the two patients in renal failure (who also had hyperphosphataemia) were excluded (Table IV).

Multiple regression analysis revealed that the only significant predictors of citrate excretion were urinary potassium and volume and the presence or absence of stone disease (Fig. 4). When the stone disease component was omitted from the multiple regression analysis, potassium alone remained as a significant contributor to the rate of citrate excretion.

Figure 5 shows the contribution of four 'citrate indicators' to urinary citrate excretion. The citrate indicators are: urinary potassium and volume and serum magnesium less than 40 mmol/24-h, 2·5 1/24-h and 0·74 mmol/l respectively and a positive history of urinary stone. When 0 or 1 citrate indicators were present urinary citrate was below 1·4 mmol/24-h in 20/21 patients. When 2 or 3 citrate indicators were present urinary citrate was over 1·4 mmol/24-h in 8/9 patients. This result was highly significant ($p < 0·001$).

Discriminant analysis yielded 100% discrimination between stone and non-stone patients (Fig. 6). The data required for this were urinary citrate and sodium, plasma citrate concentration and the results of urine culture. Discrimination improved further if the duration of the cord lesion was included (Fig. 7).

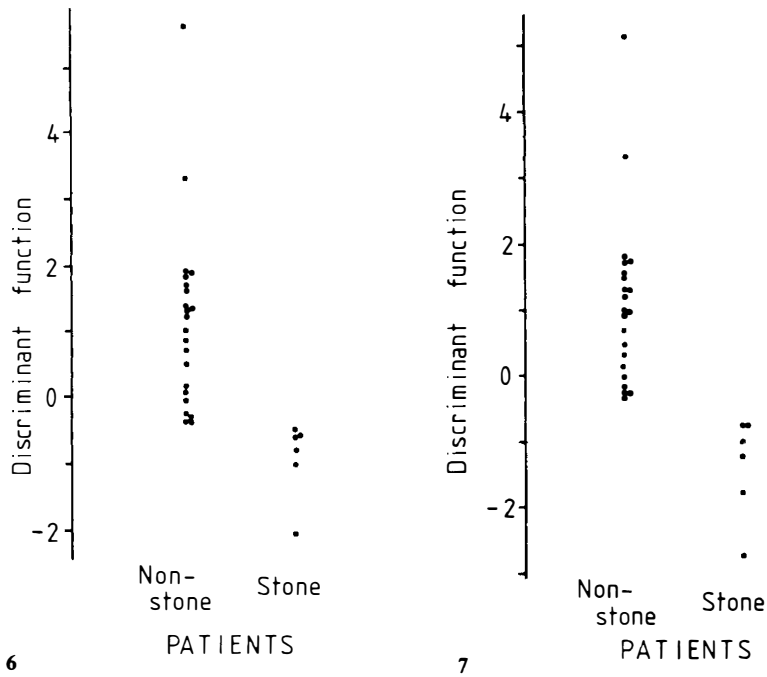

Figure 6 Results of discriminant analysis. Discriminant function = Cit − 0·011397.Na + 0·020667.SCit − 1·262.Cult. Cit = urinary citrate (mmol/24 hours); Na = urinary sodium (mmol/24 hours); SCit = plasma citrate (μmol/l); Cult = bacterial culture (no growth: Cult = 1; organisms present: Cult = 2).

Figure 7 Results of discriminant analysis with addition of term relating to duration of spinal cord lesion. Discriminant function = Cit − 0·011397.Na + 0·020667.SCit − 1·262.Cult − 0·4600.$\log_{10}$ (Dur). Dur = duration of cord lesion (years).

Discussion

The most important factor related to citrate excretion was urinary potassium. Citrate excretion also tended to be reduced in patients with impaired renal function, lower urinary volume and reduced excretion of magnesium. Multiple regression analysis showed that the only variables that contributed significantly to variation in urinary citrate were urinary potassium and volume and urinary stone history (Fig 4). When the occurrence of hypocitraturia was related to the presence of two or more citrate indicators only 2 patients were wrongly categorised (Fig. 5).

Urinary potassium or volume have not always been considered in studies of citrate excretion. Significant correlations between citrate and several urinary minerals were noted by Marangella *et al.* (1987) who, however, did not carry out multiple regression analysis. Our findings demonstrate the importance of determining or controlling all factors that might influence a metabolic process being studied as well as the value of multiple regression analysis in interpreting results. Other factors which have been reported to influence citrate excretion, such as drug therapy, diet or urinary infection, were without significant effect in this

study. This may have been because their effects on citrate metabolism were mediated by other variables that were measured, e.g. potassium or magnesium status. However, the number of patients in this study was small in relation to the number of variables. Other factors may achieve statistical significance if the number of patients is greatly increased.

Hypocitraturia is known to occur when there is overt deficiency of either potassium or magnesium, probably as a result of potassium-induced intracellular acidosis (Fourman and Robinson, 1953; Rudman *et al.*, 1980; Simpson, 1983; Schwille *et al.*, 1982). Marangella and Linari (1987) observed that urinary potassium was lower in hypocitraturic stone formers than it was in normocitraturic stone formers. Jaeger *et al.* (1988) suggested that potassium depletion contributed to hypocitraturia in patients who complained of regularly passing soft stools. The 2 patients in this study with acidosis of renal failure both had low urinary potassium and citrate.

Mild potassium depletion in spinal patients is readily explained. During the first few weeks following a spinal cord injury there is marked loss from the body of metabolites including potassium and magnesium. At the same time anorexia is common and food intake is reduced. Subsequently lost minerals are repleted. If appetite is slow to improve, if sweating is severe, or if the use of aperients results in passage of persistently soft stools over a long period, mineral depletion may persist. The high proportion of low urinary sodium values in our patients as well as the occurrence of some low values for phosphate and urate excretion suggests that this was the case, since the excretion of these metabolites is principally diet-dependent. Hypomagnesaemia was present in 4 patients (serum magnesium $< 0{\cdot}75$ mmol/l).

Discriminant analysis resulted in complete separation of the patients with a history of stone disease from those who had never formed a stone (Fig. 6). The stone formers tended to have lower plasma and urinary citrate and higher urinary sodium. Whether these features preceeded or followed the onset of stone disease is a matter for further study. Schwille *et al.* (1982) reported hypocitraturia and raised plasma citrate in a group of normocalciuric stone formers. All except one of our stone formers had urinary infection. The stone formers also tended to have lower urinary pH and higher urine volumes than the patients without a history of stone disease. These features were probably due to the management of the condition.

Inclusion in the discriminant analysis of duration of the cord lesion improved separation between the two groups of patients (Fig. 7). This may have been because the stone formers were not matched for age or duration of lesion with non-stone patients, or because risk factors require time to produce stone disease in susceptible individuals. At the outset the project was intended as a study of citrate excretion, not of stone disease. The predictive power of the discriminant function will need to be established by application to a much larger number of patients.

Citrate is a well-recognised complexing agent and inhibitor of crystallisation. Its role as a factor in calcium stone disease is well understood (Fleisch, 1978; Nicar *et al.*, 1983). Crystallisation inhibitors have not previously been implicated in infection stone disease. However, the majority of infection stones are also calcium stones. When the multiple regression analysis was carried out with the stone disease component ommitted only potassium contributed significantly to citrate excretion. Therefore the role of stone disease as an influence on citrate excretion

could not be explained by any other variable measued. There is a need for further study of the role of citrate metabolism in all types of urinary stone disease.

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