

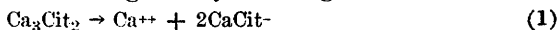
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Urinary Citrates in Calcium Urolithiasis.

BEN KISSIN AND M. OWEN LOCKS. (Introduced by B. Kramer.)

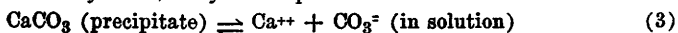
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The existence of a soluble, non-ionized calcium citrate complex has been established by the work of many investigators.¹⁻⁷ The dissociation of calcium citrate is given by Hastings, McLean, *et al.*:⁸



Thus, in equation 2, the more citrate present, the more CaCit^- complex is formed and the less calcium is present in the form of calcium ion (Ca^{++}).

The equilibrium of an insoluble calcium salt, as for example CaCO_3 , in a water system, may be expressed as:



The addition of citrate ion ($\text{Cit}^\equiv$) to the system removes the Ca^{++} by uniting with it, as in equation 2, to form CaCit^- , thus displacing equation 3 to the right. This is equivalent to an increased solubility of the relatively insoluble salt. Greenwald⁹ determined the exact increases in apparent solubility product of $\text{Ca}_3(\text{PO}_4)_2$ and CaCO_3 with a given citrate concentration, and found large increases in solubility with small concentrations of citrate. Albright, Sulkowitch and Chute¹⁰ demonstrated the solution of $\text{Ca}_3(\text{PO}_4)_2$ stones *in vitro* and *in vivo* with alkaline citrate solutions.

The daily excretion of citrates in the urine of normal individuals as determined by Ostberg¹¹ varied from 140 mg to 1,340 mg expressed in terms of citric acid. However, these were the extreme variations and the great majority of the determinations were close to the average of 530 mg. This is a larger concentration than that

¹ Greenwald, *J. Biol. Chem.*, 1926, **67**, 1.

² Hastings, Murray and Sendroy, *J. Biol. Chem.*, 1926-27, **71**, 723.

³ Clark, Percival and Stewart, *J. Physiol.*, 1928, **66**, 346.

⁴ Shelling and Maslow, *J. Biol. Chem.*, 1928, **78**, 661.

⁵ Shear and Kramer, *J. Biol. Chem.*, 1928, **79**, 161.

⁶ Shear, Kramer and Reznikoff, *J. Biol. Chem.*, 1929, **83**, 721.

⁷ Whittier, *J. Biol. Chem.*, 1938, **123**, 283.

⁸ Hastings, McLean, Eichelberger, Hall and DaCosta, *J. Biol. Chem.*, 1934, **107**, 351.

⁹ Greenwald, *J. Biol. Chem.*, 1938, **124**, 437.

¹⁰ Albright, Sulkowitch and Chute, *J. Am. Med. Assn.*, 1939, **113**, 2049.

¹¹ Ostberg, *Skand. Arch. Physiol.*, 1931, **62**, 81.

used by Greenwald⁹ and should have some effect on the solubility of calcium in urine. The purpose of this experiment was to determine the daily urinary excretion of citrates in patients with calcium urolithiasis to see whether this condition might be associated with a decrease in that component.

Method. Sixteen cases of calcium urolithiasis, proven by X-ray or postoperative analysis, were chosen from 4 hospitals. All patients were on normal house diets with little or no medication. Sixteen other patients were carefully picked as controls from the same hospitals, an effort being made to match the lithiasis patients as to age, sex, diet and bed regimen. In most instances each patient had a comparable control. Twenty-four-hour specimens of urine were collected under toluene, and determinations of citrate made according to the method of Pucher, Sherman and Vickery.¹²

To check the reliability of the method used, determinations were made on solutions containing known amounts of citric acid. In addition, quantities of citric acid corresponding to the amounts found in urine were added to samples of urine. Our analyses showed quantitative recovery within the limits of error reported by the authors (Pucher, Sherman and Vickery). In Table I we give the concentration of citrate and the 24-hour excretion in the urines of 16 patients suffering with calcium stones and in an equal number of patients who, clinically and by X-ray, were found to be free of such stones.

TABLE I.
The 24-hour Citric Acid Excretion of Ca Stone Patients and Controls.

Patient	Conc. HCit, mg/cc	Total HCit, mg	Control	Conc. HCit, mg/cc	Total HCit, mg
1	.02	30	1	.12	180
2	.03	45	2	.08	192
3	.10	57.5	3	.19	270
4	.04	71.2	4	.20	300
5	.13	84.5	5	.17	438
6	.08	120	6	.88	485
7	.08	144	7	1.65	495
8	.08	152	8	.30	525
9	.17	153	9	1.10	550
10	.06	162	10	.98	637
11	.12	192	11	.57	855
12	.12	204	12	.48	864
13	.09	216	13	.49	906.5
14	.18	270	14	.64	1024
15	.55	302	15	1.01	1060.5
16	.19	342	16	.84	1260
Avg	.13	165.3		.61	627.6

¹² Pucher, Sherman and Vickery, *J. Biol. Chem.*, 1936, **113**, 235.

Discussion. According to these determinations, the concentration of citric acid in the urine of calcium urolithiasis patients is, on the whole, exceptionally low. Fifteen of the 16 cases excreted less than .20 mg per cc of urine. In the control group, only 5 cases excreted less than .20 mg per cc. The average concentration for the patients was .13 mg per cc and that for the controls, .61 mg per cc. As regards the total daily citric acid output, all the calcium stone patients excreted less than 350 mg. 11 patients with less than 200 mg. Only 4 of the controls excreted less than 350 mg daily, the others ranging much higher. The average daily excretion for the patients was 165.3 mg, while that of the control group was 627.6 mg.

The spread of the values among the controls compares well with that found by Ostberg for normal individuals. It compares well, also, with the results of Sherman, Mendel and Smith,¹³ who, with the same method used in this paper, found the normal spread to be from 356 mg to 1,180 mg daily. The fact that only one determination was made for each patient is probably not of very great significance since Ostberg found a marked tendency for these values to remain about the same from day to day.

The value of this experiment lies in the fact that it presents a possible etiological factor in the formation of calcium urinary stones. Furthermore, increasing the citrate concentration of urine, by the administration of citrates or of dicarboxylic acids which, according to Orten and Smith,¹⁴ are converted to urinary citrates, may offer a new prophylactic or even therapeutic measure.

The authors express their thanks to Dr. Benjamin Kramer, who suggested this problem and under whose supervision the work was done.

Conclusions. The daily urinary citrate content and concentration of patients with calcium urolithiasis is much lower than those of normal individuals. This finding may be of etiological importance.

¹³ Sherman, Mendel and Smith, *J. Biol. Chem.*, 1936, **113**, 247.

¹⁴ Orten and Smith, *J. Biol. Chem.*, 1937, **117**, 555.