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Urinary Oxalate in Summer and Winter in Normal Subjects and in Stone-Forming Patients with Idiopathic Hypercalciuria, Both Untreated and Treated with Thiazide and/or Cellulose Phosphate

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Summary. Urinary oxalate excretion has been measured by a specific enzymatic method in normal subjects and stone formers with idiopathic hypercalciuria. In every group studied urinary oxalate was higher in the summer than in the winter. These differences were slight and not significant in normal subjects but were considerable and statistically significant in the stone formers both untreated and when treated with thiazide. Thiazides raise urinary oxalate only very slightly but cellulose phosphate leads to large rises in urinary oxalate both in the summer and the winter. The highest values of urinary oxalate were seen in the summer in patients treated with cellulose phosphate. The mean rise in this group was 70 % above normal and this must be viewed with some anxiety.

Key words: Urine - Oxalate - Seasons - Thiazides - Cellulose phosphate.

Calcium oxalate is the most frequently found ingredient of renal calculi both in this country and some overseas areas (18). While it is generally agreed that urinary calcium is frequently raised in calcium oxalate lithiasis, the role of oxalate is still in some doubt. Recent papers from Czechoslovakia (12), France (16), and Leeds, England (7) have all reported that urinary oxalate has been some 20 % higher in calcium oxalate stone formers than in normal subjects. The French group (16) also observed that the rise in urinary oxalate could be continuous but was sometimes paroxysmal. Spanish opinion has been divided with one group (17) having found no difference in urinary oxalate values between normal subjects and stone formers, while another group (10) found urinary oxalate values as high as 62 to 99 mg/24 h in patients with recurrent calcium oxalate lithiasis compared with normal values of 7 to 40 mg/24 h.

The reason for this disagreement could be in part technical and in part climatic. Thus, oxalate determination has been notoriously difficult and unreliable (5). Furthermore, seasonal variations in urinary oxalate have recently been recognised in London (14, 4) and in Leeds (13). This means that in assessing urinary oxalate, time of year should be taken into account whereas this has not been done in the past. Moreover, if seasons of the year affect urinary oxalate then geography might do so as well.

Drugs which are able to lower urinary calcium have been used for many years as treatment for calcium oxalate lithiasis. Cellulose phosphate was advocated as long ago as 1964 (2) and extensive trials have been carried out (1, 8, 14, 15). Thiazide diuretics have also been used extensively, (15, 19, 20). Information however on the effect of these drugs on urinary oxalate has been scanty, conflicting and has not taken account of time of year. A Spanish group found that urinary oxalate was not changed by cellulose phosphate (11) but in Poland considerable rises were observed after cellulose phosphate (9) and this has been comfirmed in a small study on six patients in the U. S. A. (6). Thiazides were found to lower urinary oxalate in the Netherlands (3) but this was not confirmed in Canada (19). A new simple and reliable enzymatic technique for estimation of urinary oxalate was introduced into these hospitals three years ago, and it was therefore thought appropriate to report the effects of treatment with thiazide and/or cellulose phosphate on urinary oxalate of hypercalciurics with calcium oxalate lithiasis.

METHODS

The studies were made on out-patients referred to a Metabolic Stone Clinic and who were found to have idiopathic hypercalciuria in association with calcium-rich renal calculi. Many of the patients were included in a previous study (15) but many new patients have been included since that time. The general conditions, criteria for inclusion in the study and most of the methods are as described previously except that urinary oxalate was measured by the enzymatic method (5) and the method for urinary calcium was changed to flame spectrophotometer atomic absorption in 1975. Most patients were treated with thiazides or cellulose phosphate or both, but a few were untreated for various reasons. However, all patients were studied for a period prior to drug therapy so providing additional data for untreated patients. It is emphasized that most of the patients were undergoing long-term follow up and were studied on numerous occasions at different times of the year. Hence the study on the patients may be regarded as longitudinal rather than cross-sectional.

Several sources of material were used in order to obtain data from normal subjects. One contribution was from a small group of individuals working in the hospitals each of whom collected a 24 h urine sample each month for 13 consecutive months. Other substantial contributions were from Hospitals Doctors and General Practitioners elsewhere who kindly cooperated in two different surveys of normal urinary constituents. In these surveys each individual appears only once.

For the purpose of this study the year was divided up into 6 months of winter, October to March, and 6 months of summer, April to September.

RESULTS

The results of this study are summarised in Figure 1. which shows 24 h urinary oxalate results in the normal subjects and the various groups of patients according to treatment and time of year. These results have been analysed for statistical significance of differences between groups and the analysis is shown in Table 1. The results are also shown in more detail in Figures 2-5 which show distribution of urinary oxalate values within each group.

The main points revealed by these figures are as follows: -

1. No statistical difference can be detected in urinary oxalate values between summer and winter either in normal subjects or in stone formers undergoing treatment with cellulose phosphate with or without added thiazide. It should be noted however, that in each group the mean summer value is higher than the mean winter value.

2. Both untreated and thiazide treated stone formers show mean urinary oxalate values that are higher in the summer than in the winter and these differences are statistically significant.

3. Mean urinary oxalate in untreated stone formers is the same as for the normal group in the winter but higher in the summer.

4. Thiazide treatment of stone formers appears to raise urinary oxalate very slightly but this not statistically significant in the summer and is barely statistically significant in the winter.

5. Cellulose phosphate treatment raises urinary oxalate considerably both in the summer and winter and these changes are statistically highly significant.

DISCUSSION

The results reported here seem to shed new light on the question of urinary oxalate in idiopathic hypercalciuria and the effects of treatment. Firstly Figure 1 and Table 1 show that when consideration is given to season of the year, changes in the same direction can be seen in every group of subjects studied, with a higher excretion in the summer than in the winter. The magnitude of the changes varies greatly. Thus in normal subjects it was so small as to be not statistically significant. We have already postulated (4) that these different behaviours by normal subjects and stone formers could be due to the greater availability in the latter group of the increased oxalate intake in the summer months. It is now seen that statistically significant seasonal changes also occur in urinary oxalate stone formers treated with thiazide while the changes with cellulose phosphate nearly achieve statistical significance and probably would have done so if the numbers had been larger.

It is clear that although seasonal factors are unimportant when considering urinary oxalate of normal subjects, they are important when considering stone formers and effects of treatment. Thus, if normal subjects and stone formers are considered in the winter, there is virtually no difference in urinary oxalate, but in the summer the stone formers excrete 30% more oxalate than normal subjects. Treatment with thiazide leads to a rise in urinary oxalate but Figure 1 shows that this rise is rather small and in fact achieves statistical significance only in the winter with a rise of 9% compared to a mere 6% in the summer. It must be doubtful whether rises in urinary oxalate as small as this can be important in the context of stone formation. On the other hand, the effect of cellulose phosphate on urinary oxalate is considerably greater. The rise in the winter figure is of 44% and in the summer the figure is of 31% over the pre-treatment levels. The corresponding rises however above the normal levels are

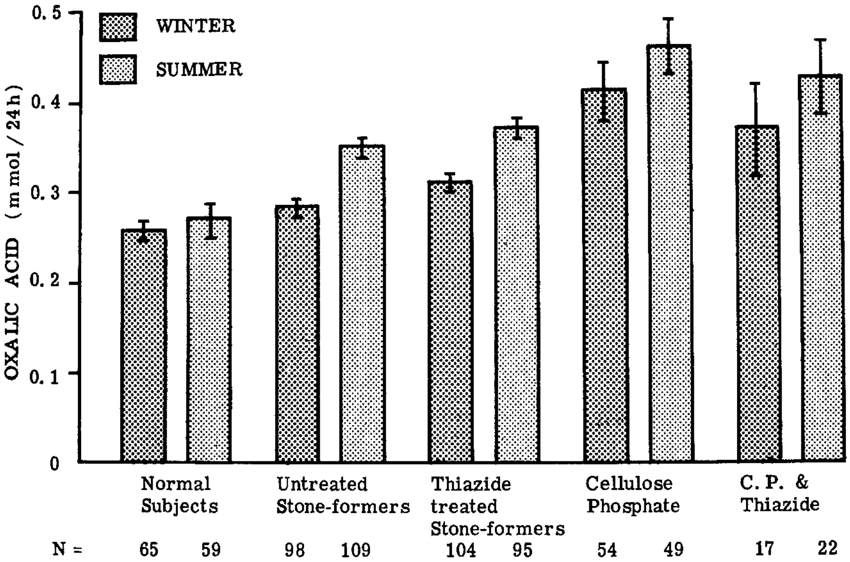

Fig. 1. Urinary oxalate excretion during summer and winter by stone formers with or without treatment, and by normal subjects. Each column shows the mean, S. E. M. and the number of urine samples studied

Table 1. Statistical analysis of differences between mean urinary oxalate values in various groups

		T	P
Normal subjects:	Winter : Summer	0.56	< 0.10
Stone formers:	Untreated - Winter : Summer	4.14	> .001
	On thiazides - Winter : Summer	4.93	> .001
	On cellulose phosphate - Winter : Summer	1.2	< 0.10
	On both drugs - Winter : Summer	0.91	< 0.20
Winter:	Untreated : cellulose phosphate treated	3.74	> .001
	Untreated : thiazide treated	2.13	< .01
	Normal subjects : untreated	1.25	< 0.10
Summer:	Untreated : cellulose phosphate treated	3.90	> .001
	Untreated : thiazide treated	1.18	< 0.10
	Normal subjects : untreated	4.3	> .001

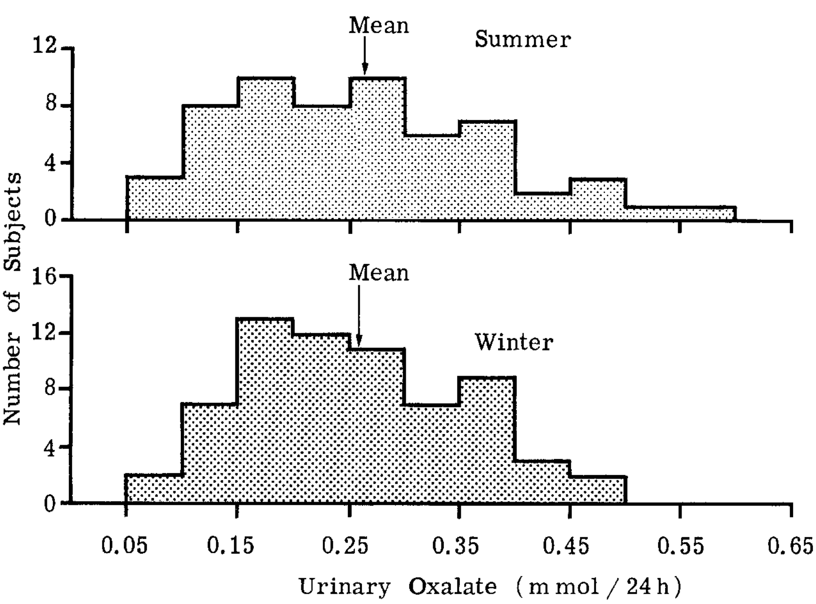

Fig. 2. Histogram of urinary oxalate in normal subjects in summer and winter

Urol. Res., Vol. 4, No. 4 (1976)

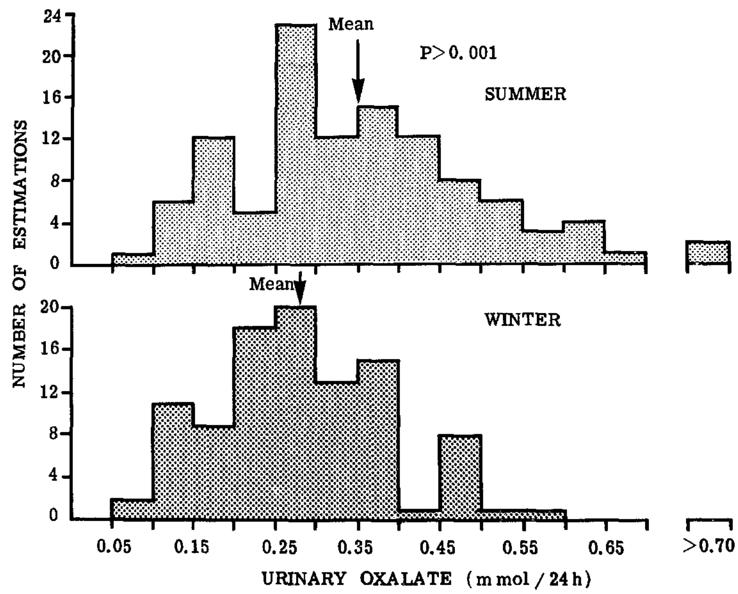

Fig. 3 Histogram of urinary oxalate in stone formers treated with thiazide in summer and winter

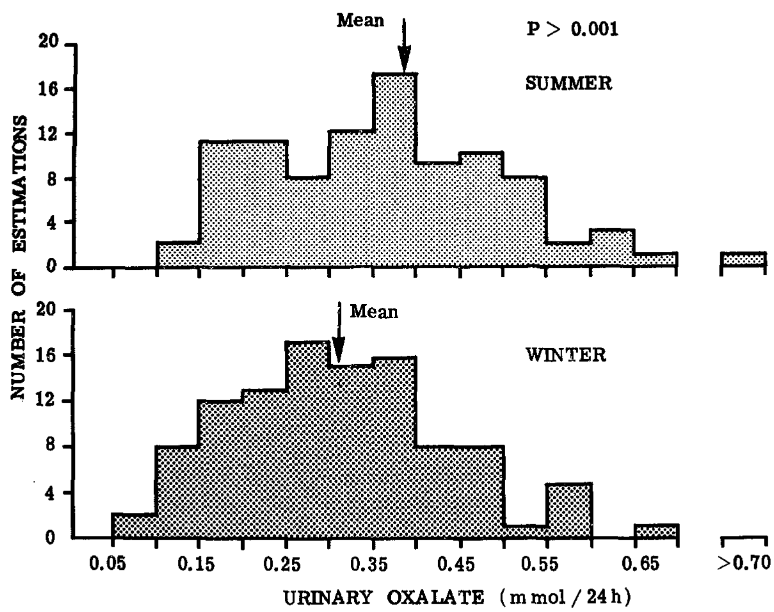

Fig. 4. Histogram of urinary oxalate in stone formers treated with thiazide in summer and winter

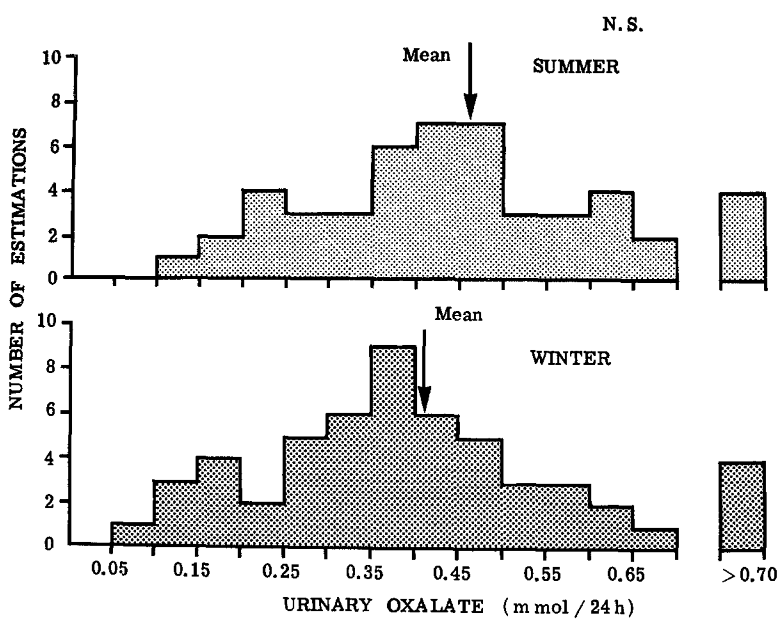

Fig. 5. Histogram of urinary oxalate in stone formers treated with cellulose phosphate in summer and winter

even higher at 68 % and 70 % respectively. These high levels of urinary oxalate may well be important in relation to calculus formation and the question posed by these figures is whether rises in urinary oxalate following treatment with cellulose phosphate are sufficient to off-set the benefit from the fall in urinary calcium. In other words, what is the net change with regard to saturation of calcium oxalate? This is a question which, in our view, has not yet been satisfactorily answered and further work is therefore in progress.

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