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Urolithiasis, Inhibitors and Promoters

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Summary. The aim of this work is to evaluate the role and importance of inhibitors and promoters in urolithiasis. Carrying in mind theoretical considerations, we conclude that in urolithogenic processes, inhibitors and promoters could only play a decisive role in the "idiopathic" oxalocalcic urolithiasis. We classify the "idiopathic" oxalocalcic stone-formers into three main groups, considering inhibitory and promoting factors. It is shown that such classification is in good agreement with the clinical results observed in a group of 88 "idiopathic" oxalocalcic stone-formers.

Key words: Urolithiasis, promotion, inhibition

Introduction

Many factors have been advanced to explain formation of stones in the urinary tract. In recent years, an important role seems to be assigned in general to the so-called inhibitors and promoters of the crystallization (1, 2). Nevertheless, it must be considered that in the formation of crystalline masses, both factors inhibitors (nucleation or crystal growth) and promoters (basically, heterogeneous nucleants), only can be decisive when being in non-excessive supersaturation. It must be considered that at high supersaturation the nucleation is homogeneous and crystal growth could take place mainly controlled by surface nucleation or by diffusion, and consequently inhibitors would cause little effect or even cause no effect. Thus, in urolithogenic processes, inhibitors and promoters could only play a decisive role in the "idiopathic" oxalocalcic urolithiasis (nor hypercalciuria, nor hyperoxaluria). It must be taken into account that, generally, in uric, phosphatic and cistinic urolithiasis important degrees of supersaturation are found. The object of this report is to demonstrate the role and importance of inhibitors and promoters on "idiopathic" oxalocalcic urolithiasis.

Material and Methods

Our study included 88 patients with calcium oxalate urolithiasis, without hypercalciuria (excretion of calcium < 250 mg/24 h) and hyperoxaluria (excretion of oxalate < 40 mg/24 h). In all cases the group of subjects was selected to comprise an equal number of women and men, and ages between twenty and sixty-five years. All subjects were on free diets at the time of urine collection and none of the stone-formers were undergoing pharmacologic treatment of any kind. All of them had been subjected to metabolic evaluation, including calcium, oxalate, uric acid and citrate. Urinary calcium was determined by atomic absorption spectroscopy; uric acid, citrate and oxalate by the Boehringer Mannheim kits No. 704156, 139076 and 755699, respectively. Composition of the calculus was determined for each patient by infrared spectroscopy.

Results and Discussion

In accordance with our experience, considering "in vivo" and "in vitro" results, the most important inhibitors and promoters of "idiopathic" calcium oxalate urolithiasis appear in Table 1. Taking into account the above mentioned results, we propose the classification of the "idiopathic" oxalocalcic stone-formers into three main groups.

Thus, in a first group we include individuals with tendency to urinary pH < 5.5 (favoured by Protein rich, lipid rich and glucid rich diets). In this group promotion would be clearly favoured by heterogeneous nucleation on uric acid and the inhibition of calcium oxalate crystallization disfavoured due to low citrate excretions (as a consequence of acidic blood pH). It is also possible that in some cases the presence of low urinary glycosaminoglycans concentrations favour the heterogeneous nucleation of calcium oxalate on uric acid.

In a second group, we include the individuals with tendency to urinary pH values between 5.5 - 6.5

Table 1: Main inhibitors and promoters in "idiopathic" calcium oxalate urolithiasis

Inhibitors	Cause important effects	Cause some inhibitory effects
- Nucleation:	Glycosamino-glycans (3, 4) Pyrophosphate (3, 4)	Citrate (4)
- Crystal Growth:	Citrate (5-7)	Magnesium(8) Glycosamino-glycans (7, 9, 10) Pyrophosphate (7, 11)

Promoters

- uric acid as heterogeneous nucleant, urinary pH < 5.5 (3)
- calcium phosphates as heterogeneous nucleants, urinary pH > 6.5 (3)
- other heterogeneous nucleants: mucoproteins, drugs, ... (3)

References appear between brackets

(favoured by balanced diets), in which an important deficit of inhibitors of calcium oxalate crystallization could be detected (probably related to low urinary citrate excretion). In some cases uncommon types of heterogeneous nucleation could appear (i.e. mucoproteins, drugs, ...).

Finally, in a third group, we would include individuals with tendency to urinary pH > 6.5 (favoured by vegetarian diets). In this case, the promotion would be clearly favoured by heterogeneous nucleation on calcium phosphates. In some cases deficit of inhibitors could be found. Thus, low pyrophosphate excretion would enhance the heterogeneous nucleation of calcium oxalate on calcium phosphate particles.

Relating to the aggregation, we think that considering the "crystalline concentration" of calcium oxalate in real human urine, it becomes difficult to explain the crystalline aggregation phenomena based exclusively on a crystalline trapping and retaining action of the agglomerants (secondary aggregation). Recent experimental results indicated primary aggregation as a feasible mechanism of the calculi development (12). Primary agglomeration represents a sort of crystal malgrowth that takes place on the surface and/or tips of already developed crystals, the so-called parent crystals (13). This process results in concretions consisting of intergrown crystals with a complex crystal arrangement that closely resembles the structure of certain types of calcium oxalate monohydrate renal calculi. Primary agglomeration of calcium oxalate monohydrate crystals forming a stone in combination with an effect of mucoproteins adsorbed on the exposed calculus surface (acting as a heterogeneous nucleant) apparently can constitute a feasible mechanism of certain types of renal calculi development (14). Consequently, inhibitors of aggregation would be related to inhibitors of crystal growth and to inhibitors of heterogeneous nucleation. In Table 2, we show the biochemical parameters found in urine of 88 oxalocalcic "idiopathic" stone-formers as well the calculus composition of such patients. As can be seen, they are classified according to the above commented postulates and the obtained results are in good agreement with the established hypotheses.

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Table 2: Mean biochemical parameters of the studied oxalocalcic "idiopathic" stone-formers (n = 88).

Ca	Diuresis	Ox	Uric acid	Citrate	Calculus composition		
					CaOx + uric	pure CaOx	CaOx + Phos.
mg/24h	ml/24h	mg/24h	mg/24h	mg/24h			
Group I (n_1 = 33): pH < 5.5							
189 ± 58.7	1530 ± 489	27.8 ± 4.3	600.6 ± 139.0	545.2 ± 247.5	3	30	-
Group II (n_2 = 39): pH 5.5-6.5							
170 ± 50.6	1658 ± 640	24.1 ± 6.1	548.8 ± 147.3	452.7 ± 186.8	-	30	9
Group III (n_3 = 16): pH > 6.5							
208 ± 42.9	1663 ± 660	27.4 ± 5.0	619.0 ± 170.4	681.8 ± 266.5	-	9	7

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Role of Citric Acid in Primary Hyperparathyroidism with Renal Lithiasis

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Summary. Nephrolithiasis is presented in 18-40% of patients with primary hyperparathyroidism. Our work suggests that citrate, an inhibitor of calcium salts, could be involved in the presence of renal lithiasis because hyperparathyroid stone formers show less citrate elimination than nonstone formers.

Key words: Primary hyperparathyroidism, renal lithiasis, citrate

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Primary hyperparathyroidism (pHPT) is a disease characterized by skeletal involvement and/or renal lithiasis (RL) as main complications (1, 2, 3, 4). In diseases with increased bone resorption, bone components are released to extracellular fluid. Bone is the main reservoir of citric acid, and it is known that citrate inhibits both nucleation and crystal growth of calcium salts (1, 5). The aim of the present work is to evaluate the role of citric acid in the development of RL in patients with pHPT and the possible role of parathormone (PTH) on citric acid metabolism.

Material and Methods

Diagnostic criteria: We defined pHPT after surgical findings (adenoma or hyperplasia) and/or biochemical parameters (hypercalcemia with elevated iPTH serum levels). RL was confirmed by X-ray or echographic techniques or by recent history of at least one calculi passed. Bone involvement (BI) was defined if alkaline phosphatase serum levels were higher than 13 K.A.U. or urinary hydroxyproline/creatinine ratio above 0.035. We defined hypocitraturia when urinary citrate elimination was less than 320 mg/24 hours. Patients: Forty three unselected patients with pHPT were chosen. Nineteen had RL (9 men, 10 women) and 24 did not have RL (4 men and 20 women). We excluded patients who had a secondary metabolic disease associated with RL.
Methods - Serum and 24 hours-urine: Creatinine was assessed by Jaffe's reaction, citrate by citrate lyase, calcium and magnesium by atomic absorption spectrophotometry and phosphate by Fiske and Subbarrow. Serum: Alkaline phosphatase by Bessey Lowry, and iPTH by RIA. In 24 h-urine: Diuresis, pH by glass electrode, and hydroxyproline by the Kivirikko method.

Results and Discussion

RL is a complication in pHPT and its incidence is 18-40% (1, 2, 3, 4, 6) in that pathology. We found that 40% of patients with pHPT were stone formers. We, like Pak (3), found a female preponderance in nonstone formers group, whereas the two sexes have an equal incidence in patients with pHPT with RL.