

## EVOLUTION OF POST-ESWL RESIDUAL LITHIASIS DEPENDING ON THE TYPE OF CALCULUS AND URINE COMPOSITION

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**Summary.-** OBJECTIVES: Extracorporeal shock wave lithotripsy (ESWL) is one of the most commonly used procedures for removal of renal calculi from the upper urinary tract, but complete expulsion of the fragments generated is not always achieved. This can lead to new lithiasic episodes, and it is considered that 10-26% of fragmented calculi can undergo regrowth. This in vitro study investigated the influence of fragment and urinary composition on post-ESWL growth of fragments, with the aims of establishing the effect and importance of these parameters, and identifying effective prophylactic measures.

**METHODS:** Fragments collected from patients immediately following expulsion after ESWL treatment were selected for regrowth experiments. The particles included 24 calcium oxalate monohydrate (COM) fragments, 48 calcium oxalate dihydrate (COD), 24 hydroxyapatite (HAP), and 16 uric acid.

**RESULTS:** In all treatments, calculi fragments showed a considerable capacity to induce growth of calcium oxalate and calcium phosphate. Under normocalciuria conditions, new COM crystals formed; both COM and COD crystals developed under hypercalciuria conditions at a urinary pH < 6.0; and in hypercalciuric conditions and urinary pH > 6.0 both HAP and brushite (BRU) crystals were formed. The highest growth rates were observed for COD calculi fragments under hypercalciuria conditions and at a urinary pH of 6.5, followed by growth on COM and HAP fragments under the same conditions; growth rates under other conditions tested were similar but 10-fold lower. With regard to the role of crystallization inhibitors, phytate exhibited inhibitory effects under all assay conditions. However, citrate had little effect, even at the highest concentration tested (1,000 mg/L).

**CONCLUSIONS:** This study demonstrates the importance of avoiding heterogeneous nucleant retention (pre-existing solid microparticles) in renal cavities, as these can act as very efficient inducers of the formation of new calculi, the composition of which is mainly dependant on the urine composition.

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**Resumen.-** OBJETIVOS: La eliminación de cálculos renales mediante ondas de choque (LEOC) suele dar buenos resultados, aunque no siempre se consigue la expulsión completa de los fragmentos generados, que pueden inducir nuevos episodios litíasicos. Así, se considera que entre el 10 y el 26% de los cálculos fragmentados pueden experimentar procesos de re-crecimiento. En este trabajo se presenta un estudio "in vitro" de la influencia de la composición del fragmento y de la orina en el crecimiento de los fragmentos post-LEOC, con la finalidad de conocer los efectos de ambos parámetros, valorar su importancia y así poder plantear medidas profilácticas efectivas.

MÉTODOS: Para ello se seleccionaron fragmentos post-LEOC de cálculos de oxalato cálcico monohidrato (24), oxalato cálcico dihidrato (48), hidroxipatita (24) y ácido úrico (16). Todos los fragmentos utilizados fueron expulsados el mismo día de la aplicación de las ondas de choque.

RESULTADOS: En todas las situaciones, los fragmentos de cálculos estudiados presentaron una notable capacidad para inducir el crecimiento del oxalato cálcico o/y fosfato cálcico, de manera que en condiciones de normocalciuria se generaron cristales de oxalato cálcico monohidrato (COM), con hipercalcemia y pH inferior a 6.0 crecieron cristales de COM y oxalato cálcico dihidrato (COD) y en condiciones de hipercalcemia y pH superior a 6.0 crecieron cristales de hidroxipatita (HAP) y brushita (BRU). Es de destacar que las velocidades de crecimiento más elevadas se observaron sobre fragmentos de COD, en condiciones de hipercalcemia y pH = 6.5, y le siguen en orden de magnitud las velocidades de crecimiento sobre fragmentos de COM y HAP en condiciones de hipercalcemia y pH = 6.5. Las demás velocidades de crecimiento son parecidas y del orden de 10 veces inferiores a las primeras. En cuanto al papel de los inhibidores de la cristalización, el citrato exhibió efectos muy notables en todas las condiciones ensayadas. El citrato, sin embargo, incluso para elevadas concentraciones (1000 mg/L), manifestó efectos inhibidores débiles.

CONCLUSIONES: Estos estudios demuestran la importancia de evitar la retención de nucleantes heterogéneos (micropartículas sólidas preexistentes) en las cavidades renales ya que actúan muy eficazmente como inductores de la formación de nuevos cálculos, cuya composición depende en gran medida de la composición de la orina.

**Palabras clave:** Fragmentos post-LEOC. Litiasis residual. Crecimiento de fragmentos. Mecanismos. Oxalato cálcico. Fosfatos cálcicos. Ácido úrico.

## INTRODUCTION

Extracorporeal shock wave lithotripsy (ESWL) is one of the most commonly used procedures to remove renal calculi from the upper urinary tract of lithiasic patients. However, expulsion of the generated fragments does not take place immediately, and in a significant number of cases residual fragments can be detected. Thus, whereas efficient fragmentation of calculi by ESWL to particles less than 5 mm has been described in 85-96% of patients (1, 2), residual fragments have been detected in 20-35% of patients 3 months after ESWL application (3-5). It is considered that a fragment has regrown if the size is over 1/3 of the original size, and various data suggest that 10-26% of fragmented calculi undergo regrowth (6, 7).

The recurrence of renal calculi is much higher in patients treated by ESWL than in those receiving percutaneous nephrolithotomy. This is attributed to the movement of small particles generated during fragmentation of the calculus to cavities with low urodynamic efficacy, where they act to induce genesis of new calculi (7).

Growth of post-ESWL fragments can impede their spontaneous removal, and this constitutes a serious additional complication of ESWL that has necessitated the establishment of adequate prophylactic measures to prevent regrowth of post-ESWL fragments (8-10). Thus, it has been observed that administration of thiazides reduces the regrowth of residual post-ESWL fragments, and favors their spontaneous expulsion. The effect of thiazides is very significant in patients with hypercalcemia (11). It has also been reported that therapy with potassium citrate reduced oxalocalcic stone formation after ESWL treatment (12). In this in vitro study we investigated the influence of fragment and urinary composition on the growth of post-ESWL fragments, with the aims of establishing the effect and importance of these parameters, and identifying effective prophylactic measures.

## MATERIALS AND METHODS

Samples of fragments spontaneously passed by patients on the day following ESWL treatment were collected, and representative fragments (2-4 mm in size) were assigned to one of four treatment groups. The fragments were as follows: fragments from calcium oxalate monohydrate (COM) renal calculi (n=24), fragments from calcium oxalate dihydrate (COD) renal calculi (n=48), fragments from hydroxyapatite (HAP) renal calculi (n=24), and fragments from uric acid (UA) renal calculi (n=16).

Regrowth of post-ESWL fragments was studied using the system shown in Figure 1. Three fragments from each sample were placed without any prior pre-treatment into flow chambers (3 cm diameter and 4 cm high) in a temperature-controlled (37°C) chamber. Freshly prepared synthetic urine was introduced into the flow chamber using a multichannel peristaltic pump, and the system was operated for varying time periods to allow the growth of new crystals on the fragments. Fragment growth was evaluated by

weight increase using a precision balance. Growth of the different renal calculi fragments was normalized by calculating the relative mass increase, to avoid the effects of differences in surface area on the growth rate. The system was also used to evaluate the effect of various crystallization inhibitors on fragment regrowth. The concentration of various substances in of assayed urine corresponded to typical physiological values. The composition of the synthetic urine used is indicated in Table I.

In experiments in which the effect of citrate ions was evaluated, a calcium supplement was added to achieve the same calcium oxalate supersaturation value as was found in the absence of citrate, because the high concentration of citrate used was able to complex calcium ions.

## RESULTS

The growth rates of the post-ESWL fragments at different calcium concentrations and pH values are summarized in Tables II and III. Crystals that developed under the various conditions tested are shown in Figures 2-6 and details appear in Table IV. Under normocalciuric conditions ( $[Ca^{2+}] = 150 \text{ mg/L}$ ) COM crystals grew on COM calculi fragments. Under hypercalciuric conditions ( $[Ca^{2+}] = 250 \text{ mg/L}$ ) at  $\text{pH} < 6$ , COM and COD crystals grew on both COM and COD calculi fragments. Under hypercalciuric conditions ( $[Ca^{2+}] = 250 \text{ mg/L}$ ) at  $\text{pH} > 6$ , HAP and brushite (BRU) crystals grew on both COM and COD calculi fragments. Under normocalciuric conditions ( $[Ca^{2+}] = 250 \text{ mg/L}$ ) at  $\text{pH} > 6$ , COM crystals grew on HAP calculi fragments, whereas under hypercalciuric conditions ( $[Ca^{2+}] = 250 \text{ mg/L}$ ) at  $\text{pH} > 6$ , BRU crystals grew on HAP calculi fragments. Under normocalciuric conditions COM crystals grew on uric acid calculi fragments.

The highest growth rates were observed on COD calculi fragments under hypercalciuric conditions at  $\text{pH} 6.5$ , followed by growth rates on COM and HAP calculi fragments under the same conditions. The growth rates under other treatment conditions were similar, but 10-fold lower than the fastest growth rates observed.

Turning to crystallization inhibitors, the effects of phytate on growth of the various types of calculi fragments under differing conditions of calciuria and pH are summarized in Table V. Phytate had marked effects under all conditions studied, but even at the highest assayed concentration (1,000 mg/L) citrate had only weak inhibitory effects.

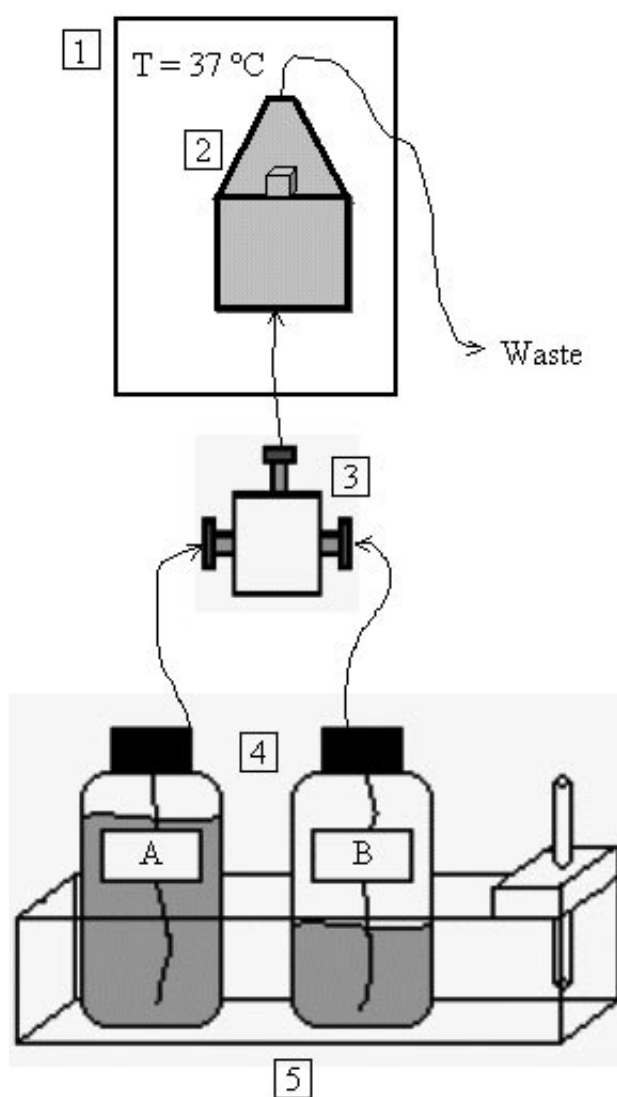


FIGURE 1. Diagram of the experimental flow system device used for crystallization studies with post-ESWL calculi fragments. (1) Temperature-controlled chamber. (2) Flask containing the post-ESWL calculi fragments. (3) Three-way T mixing chamber for solutions A and B. (4) A and B solutions for artificial urine. (5) Peristaltic pump.

TABLE I. COMPOSITION OF SYNTHETIC URINE.

| Solution A (mM)                                     |        | Solution B (mM)                                      |        |
|---|--------|--|--------|
| $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ | 19.34  | $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$  | 15.45  |
| $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$           | 5.93   | $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ | 15.64  |
| $\text{NH}_4\text{Cl}$                              | 86.73  | $\text{NaCl}$  | 223.08 |
| $\text{KCl}$  | 162.60 | $\text{Na}_2\text{C}_2\text{O}_4$                    | 0.57   |

Different volumes of 1 M calcium solution (prepared by dissolving calcium carbonate with hydrochloric acid) were added to solution A to obtain a final calcium concentration in the range of 140- 250 mg/L.

## DISCUSSION

This study demonstrates that renal calculus fragments composed of COM, COD, HAP, or UA can undergo substantial regrowth over a long period in the presence of lithogenic urine (high calcium concentration;  $\text{pH} > 6$ ; inhibitors deficit). For example, 200 mg fragments of COM, COD, or UA would increase their weight by 30 mg during 1 month in contact with normocalciuric urine at  $\text{pH} \leq 5.5$ , but COD fragments in contact with hypercalciuric urine at  $\text{pH} \geq 6.5$  for the same time period would increase their weight by 500 mg.

This study also shows that it is necessary to apply prophylactic treatment to avoid regrowth of post-ESWL calculus fragments, irrespective of the composition of the fragment. However, special care has to be taken when planning such treatments if the fragments are composed of COD, the patient is hypercalciuric, and the urinary pH is high ( $> 6.0$ ).

It can be also concluded that the use of crystallization inhibitors, including citrate and phytate, is

TABLE II. RATE GROWTH  $\text{mg}/(\text{mg} \cdot \text{h})$  OF POSTESWL CALCULI FRAGMENTS DEPENDING ON THEIR COMPOSITION, CALCIUM CONCENTRATION AND ASSAYED PH.

| Rate growth (expressed in $\text{mg} / \text{h} \cdot \text{mg}$ of fragment) |                                       |                                       |                                       |                                       |
|---|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Fragments composition   | $\text{pH} = 5.5$                     |                                       | $\text{pH} = 6.5$                     |                                       |
|   | $[\text{Ca}^{2+}] = 150 \text{ mg/l}$ | $[\text{Ca}^{2+}] = 250 \text{ mg/l}$ | $[\text{Ca}^{2+}] = 150 \text{ mg/l}$ | $[\text{Ca}^{2+}] = 250 \text{ mg/l}$ |
| COM   | $0.21 \pm 0.03$                       | $0.30 \pm 0.03$                       | $0.31 \pm 0.02$                       | $1.65 \pm 0.27$                       |
| COD   | $0.22 \pm 0.04$                       | $0.32 \pm 0.03$                       | $0.35 \pm 0.05$                       | $3.87 \pm 0.43$                       |
| HAP   | -                                     | -                                     | $0.36 \pm 0.10$                       | $1.87 \pm 0.22$                       |

TABLE III. RATE GROWTH  $\text{mg}/(\text{MG}\cdot\text{H})$  OF POST-ESWL URIC ACID CALCULI FRAGMENTS DEPENDING ON THE CRYSTALLINE PHASE AND INTERNAL STRUCTURE. RATE GROWTH OBSERVED FOR  $[\text{CA}^{2+}] = 140 \text{ MG/L}$  AND  $\text{PH} = 5.0$ .

| Rate growth (expressed in $\text{mg} / \text{h} \cdot \text{mg}$ of fragment) |                   |
|---|-------------------|
| Crystalline phase and inner structure   |                   |
| Compact anhydrous uric acid   | $0.048 \pm 0.013$ |
| Porous anhydrous uric acid  | $0.067 \pm 0.016$ |
| Compact dihydrate uric acid   | $0.075 \pm 0.011$ |
| Porous dihydrate uric acid  | $0.161 \pm 0.040$ |

an important prophylactic measure to prevent the regrowth of calculi fragments. Phytate is a very effective crystallization inhibitor of calcium salts (13-16), and if the urinary pH is lower than 5.5, use of citrate avoids the formation of uric acid microcrystals as citrate induces an increase in pH, and an increase in citraturia would contribute to decrease calcium oxalate supersaturation because of the formation of stable complexes between calcium ion and citrate (17-18).

Nevertheless, when administering citrate it is recommended that urinary pH be monitored to avoid pH values exceeding 6.0.

Finally, this study demonstrated the importance of avoiding the retention of heterogeneous nucleants (pre-existing solid particles) in renal cavities, because they efficiently act as inducers of the formation of new calculi, whose composition depends to a great extent on urine composition.

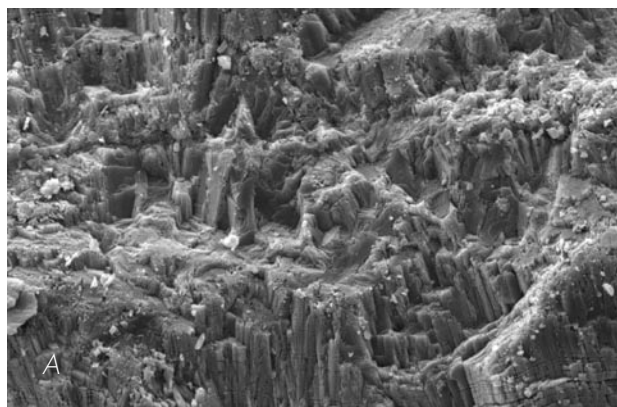


FIGURE 2A. Post-ESWL fragments of COM renal calculi.

A). Before the regrowth study, in normocalciuric (150  $\text{mg/L}$ ) and normooxaluric (25  $\text{mg/L}$ ) conditions at pH 5.5.

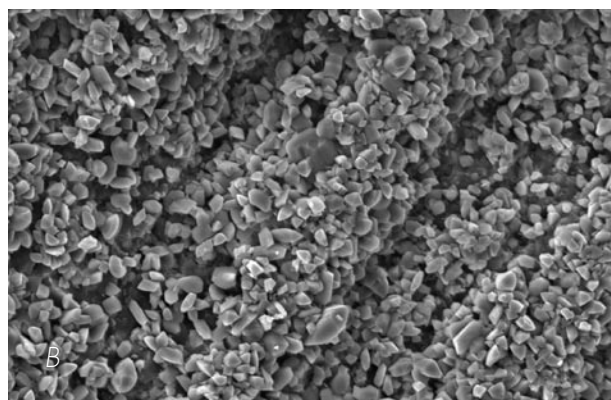


FIGURE 2B. Post-ESWL fragments of COM renal calculi.

B). After 144 h, with new, small COM crystals evident.

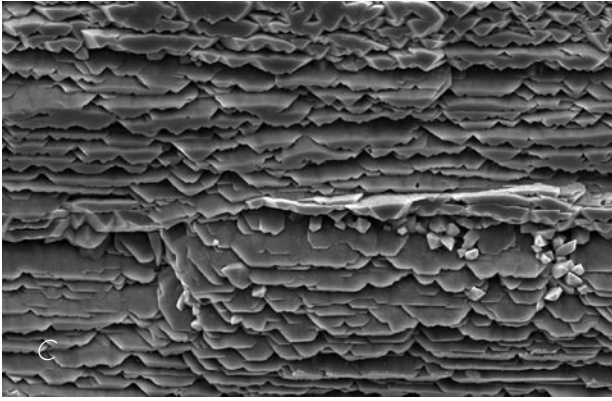


FIGURE 2C. Post-ESWL fragments of COM renal calculi.

C). After 240 h, with COM columnar crystals evident.

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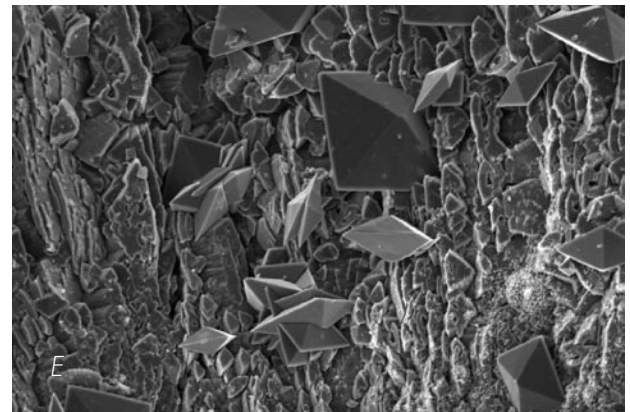
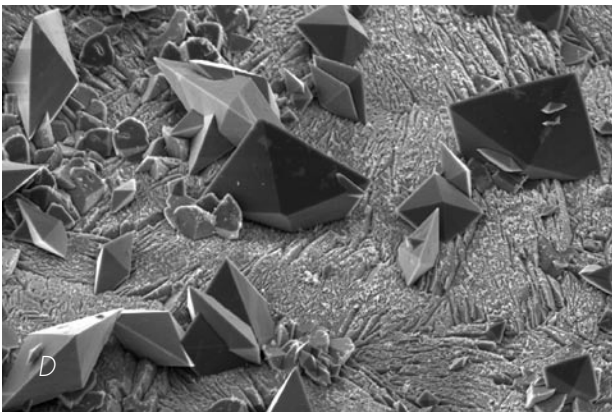


FIGURE 2D and E. Post-ESWL fragments of COM renal calculi.

D and E). After 192 h in hypercalciuric (250 mg/L) and normooxaluric (25 mg/L) conditions at pH 5.5, with new COM and COD crystals evident.

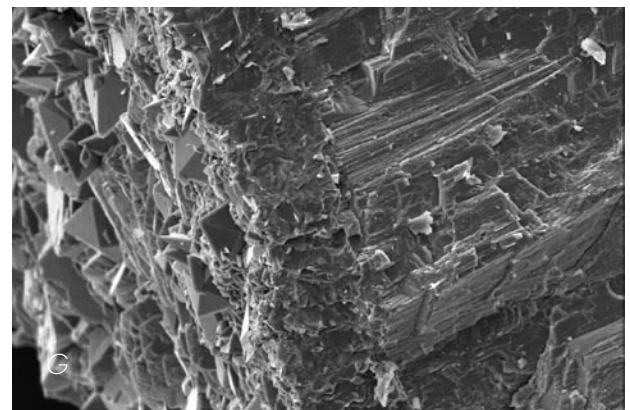
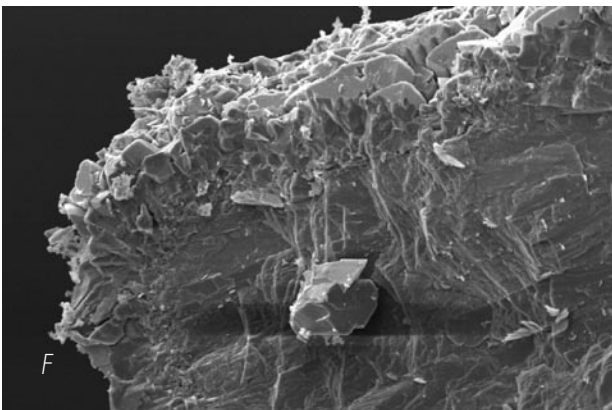


FIGURA 2F and G. Post-ESWL fragments of COM renal calculi.

F and G). Sections of calculi after regrowth in hypercalciuric conditions at pH 5.5, with new compact layers of columnar growth evident.

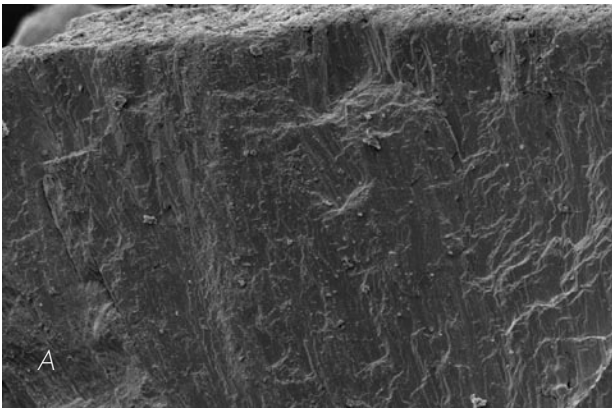


FIGURE 3A. Post-ESWL fragments of COM renal calculi.

A). Before the regrowth study, after 192 h in normo-oxaluric (25 mg/L) conditions at pH 6.5.

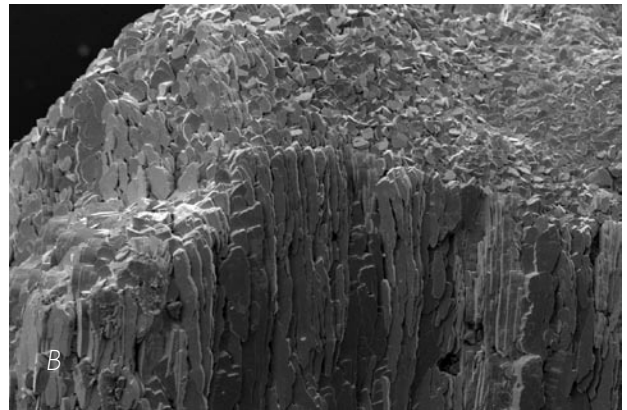


FIGURE 3B. Post-ESWL fragments of COM renal calculi.

B). In normocalciuria (150 mg/L) conditions, with formation of COM columnar crystals evident.

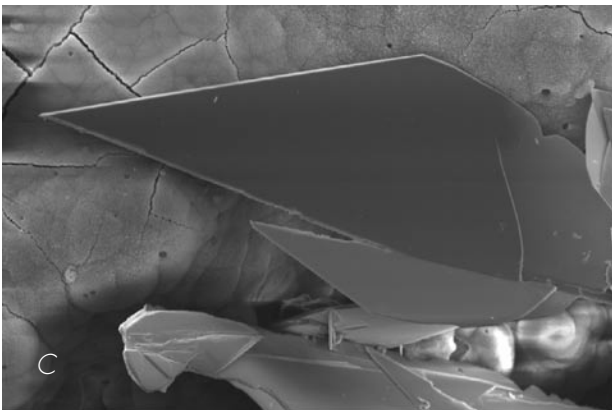


FIGURE 3C. Post-ESWL fragments of COM renal calculi.

C) In hypercalciuria (250 mg/L) conditions, with formation of hydroxyapatite and big brushite crystals evident.

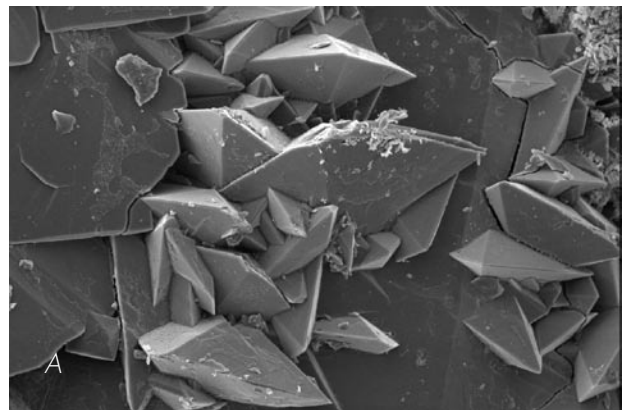


FIGURE 4A. Post-ESWL fragments of COD renal calculi.

A). Before the regrowth study, after 192 h in normo-oxaluric (25 mg/L) conditions.

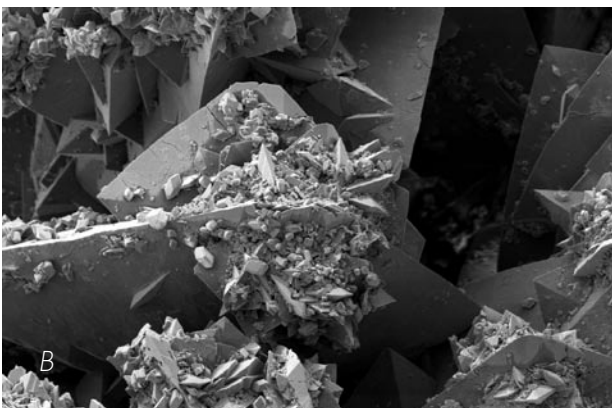


FIGURE 4B. Post-ESWL fragments of COD renal calculi.

B). In normocalciuria (150 mg/L) conditions at pH 5.5, with formation of COM crystals evident.

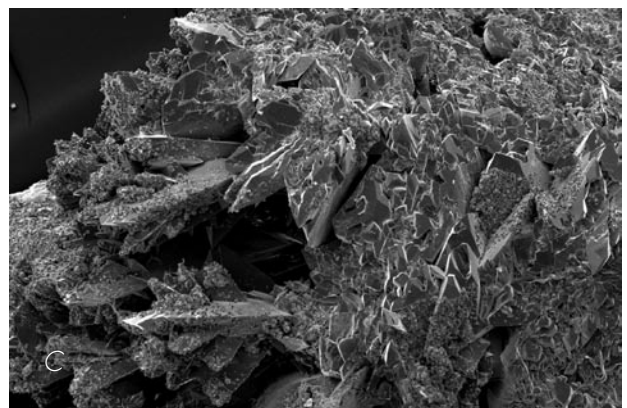


FIGURE 4C. Post-ESWL fragments of COD renal calculi.

C). In hypercalciuria (250 mg/L) conditions at pH 5.5, with formation of COM and new COD crystals evident.



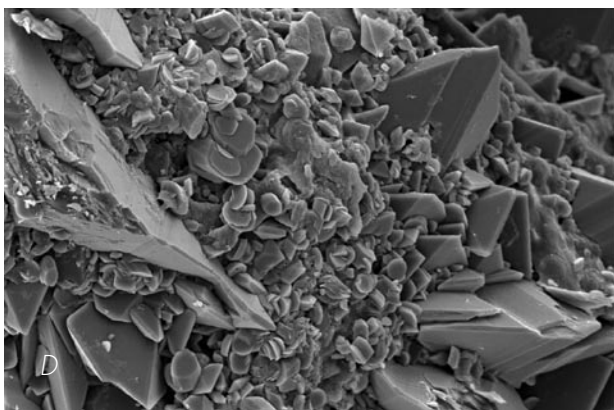


FIGURE 4D. Post-ESWL fragments of COD renal calculi.

D) In normocalciuria (150 mg/L) conditions at pH 6.5, with formation of COM and new COD crystals evident.

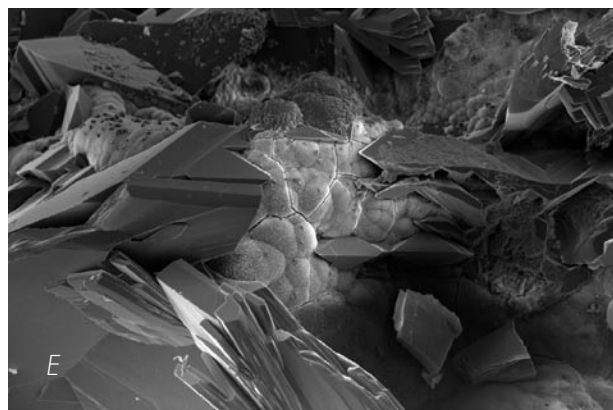


FIGURE 4E. Post-ESWL fragments of COD renal calculi.

E). After 48 h in normoocaluric (25 mg/L) and hypercalciuric (250 mg/L) conditions at pH 6.5, with formation of hydroxyapatite and big brushite crystals evident.

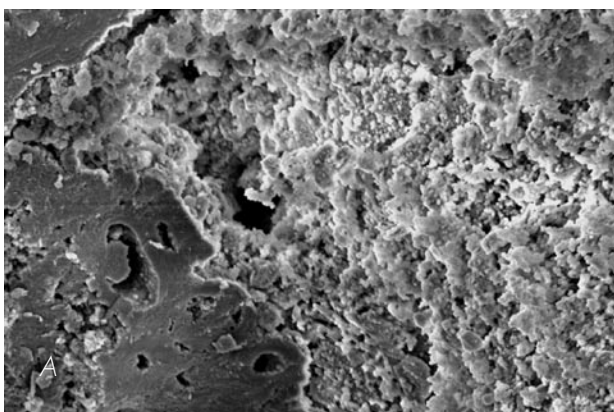


FIGURE 5A. Post-ESWL fragments of HAP renal calculi.

A). Before the regrowth study, in normoocaluric (25 mg/L) conditions at pH 6.5.

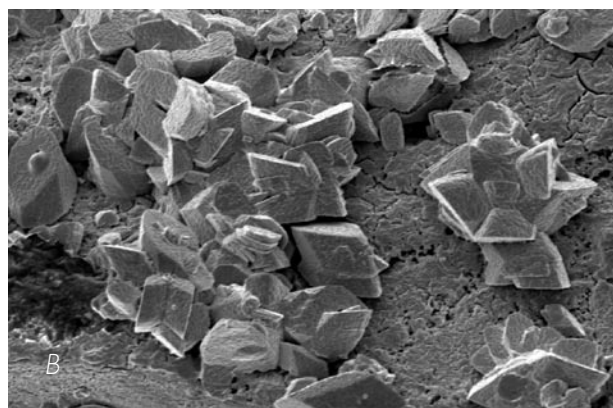


FIGURE 5B. Post-ESWL fragments of HAP renal calculi.

B). After 192 h in normocalciuria (150 mg/L) conditions, with formation of COM crystals evident.

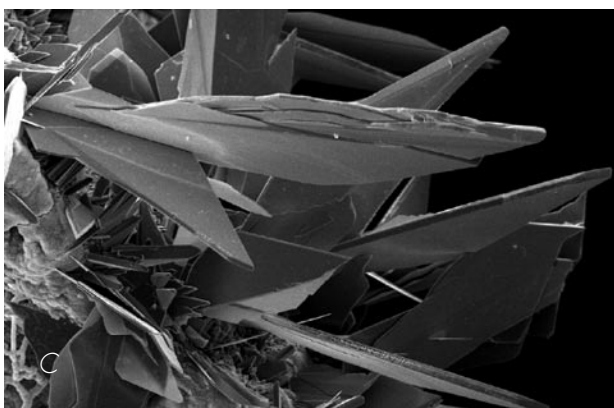


FIGURE 5C. Post-ESWL fragments of HAP renal calculi.

C). After 48 h in hypercalciuria (250 mg/L) conditions, with formation of hydroxyapatite and big brushite crystals evident.

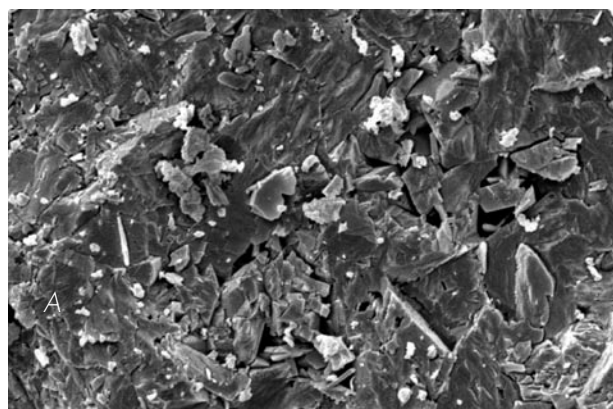


FIGURE 6A. Post-ESWL fragments of anhydrous uric acid renal calculi.

A). Before the regrowth study.



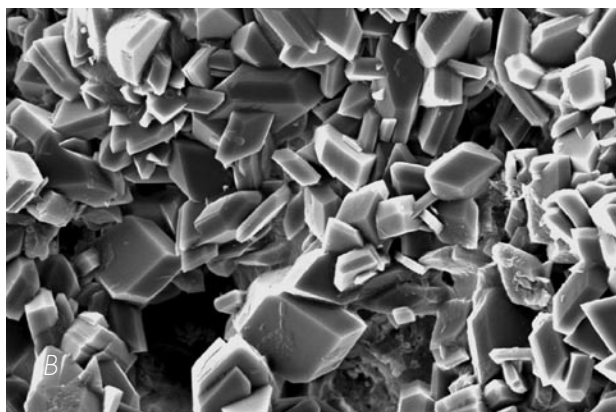


FIGURE 6B. Post-ESWL fragments of anhydrous uric acid renal calculi.

B) After 48 h in normoocaluric (25 mg/L) and normocalciuric (140 mg/L) conditions at pH 5.0, with formation of COM crystals evident.

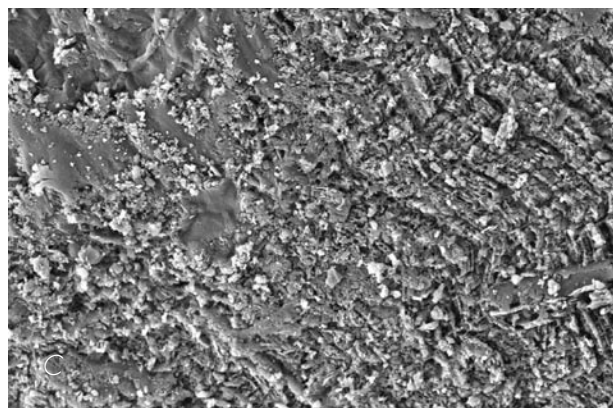


FIGURE 6C. Post-ESWL fragments of anhydrous uric acid renal calculi.

C) Post-ESWL fragments of dihydrate uric acid renal calculi before the regrowth study.

TABLE IV. TYPE OF FORMED CRYSTALS ON THE DIFFERENT KIND OF CALCULI FRAGMENTS DEPENDING ON THE STUDIED EXPERIMENTAL CONDITIONS.

| Type of formed crystals   |                              |                              |                                |                              |
|---------------------------|------------------------------|------------------------------|--------------------------------|------------------------------|
| Type of calculi fragments | pH = 5.5                     |                              | pH = 6.5                       |                              |
|                           | [Ca <sup>2+</sup> ]=150 mg/l | [Ca <sup>2+</sup> ]=250 mg/l | [Ca <sup>2+</sup> ] = 150 mg/l | [Ca <sup>2+</sup> ]=250 mg/l |
| COM                       | COM                          | COD                          | COM                            | HAP / BRU                    |
| COD                       | COM                          | COM/COD                      | COM                            | HAP / BRU                    |
| HAP                       | -                            | -                            | COM                            | BRU                          |

TABLE V. PHYTATE CONCENTRATIONS THAT AVOID DURING 192 H THE INCREASE OF THE POSTESWL CALCULI FRAGMENTS WEIGHT (N = 12) DEPENDING ON THE FRAGMENTS COMPOSITION, CALCIUM CONCENTRATION AND ASSAYED PH.

| [phytate] (mg / L)    |                              |                              |                                |                               |
|-----------------------|------------------------------|------------------------------|--------------------------------|-------------------------------|
| Fragments composition | pH = 5.5                     |                              | pH = 6.5                       |                               |
|                       | [Ca <sup>2+</sup> ]=150 mg/l | [Ca <sup>2+</sup> ]=250 mg/l | [Ca <sup>2+</sup> ] = 150 mg/l | [Ca <sup>2+</sup> ]=250 mg/l* |
| COM                   | 1                            | 1.5                          | 1                              | 6                             |
| COD                   | 1                            | 1.5                          | 1.5                            | 3                             |
| HAP                   | -                            | -                            | >1.5                           | >6                            |

(\*) in hypercalciuric conditions and pH = 6.5, the period of growth study was 48 h owing the high observed weight increase.

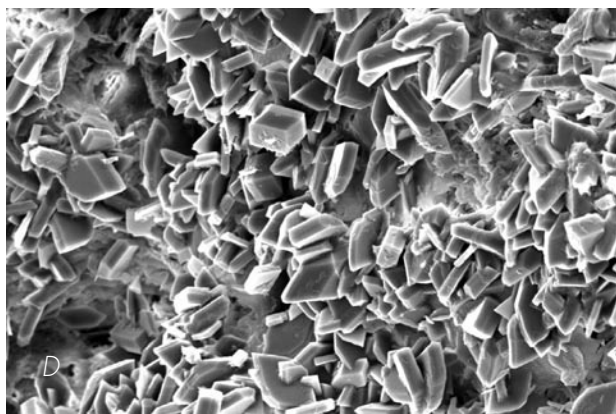


FIGURE 6D. Post-ESWL fragments of anhydrous uric acid renal calculi.

D). After 48 h in normooxaluric (25 mg/L) and normocalciuric (140 mg/L) conditions at pH 5.0, with formation of COM crystals evident.

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