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Conference Abstract

## Mechanisms of the Influence of Uric Acid on the Precipitation of Ca-Oxalate Crystals out of Metastable Solution (Urine)\*

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### INTRODUCTION

One of the very actual problems in the urolithiasis research is the question whether and in what way raised uric acid can influence the formation of Ca-oxalate stones.

There are many clinical observations indicating an interrelation between uric acid and oxalate lithiasis. Since the early reports of Prien and Prien<sup>1</sup> as well as Gutman and Yü<sup>2</sup> in 1968 about the surprisingly high occurrence of oxalate stones in gouty patients, additional observations indicated that oxalate stone-formers were often characterized by a raised uric acid level in serum respectively in urine. This observation, made by Smith and Boyce in 1969,<sup>3</sup> was confirmed by later clinical studies by Coe,<sup>4</sup> Coe and Raisen,<sup>5</sup> Hartung,<sup>6</sup> Braun, May and Birtel<sup>7</sup> as well as Eisen, Dosch, Altwein and Hohenfellner.<sup>8</sup> The hyperuricosuria was partly accompanied by hypercalciuria, a correlation firstly observed by Dent and Sutor<sup>9</sup> in 1971.

Here, the possible mechanisms of the oversecreted uric acid on the facilitated precipitation of Ca-oxalate crystals in urine will be discussed in some detail. In addition, own experiments giving a new explanation for the uric acid: oxalate interaction will be presented briefly.

### MECHANISMS OF URIC ACID INFLUENCE ON Ca-OXALATE PRECIPITATION

Lonsdale<sup>10</sup> in 1968 published his theory that uric acid respectively sodium urate crystals facilitate the precipitation and growth of Ca-oxalate crystals by epitaxis. Robertson<sup>11</sup> in his early publication in 1971 also assumed an epitactic growth of Ca-oxalate crystals on preformed uric acid crystals.

The epitaxis between uric acid and Ca-oxalate crystals is however called in question by mineralogists working in this field.

Coe, Lawton, Goldstein and Tembe<sup>12</sup> as well as Pak and Arnold<sup>13</sup> in 1975 published their hypothesis that sodium urate induces the oxalate precipitation. Pak and Coe, carrying out experiments with radioactive labelled sodium

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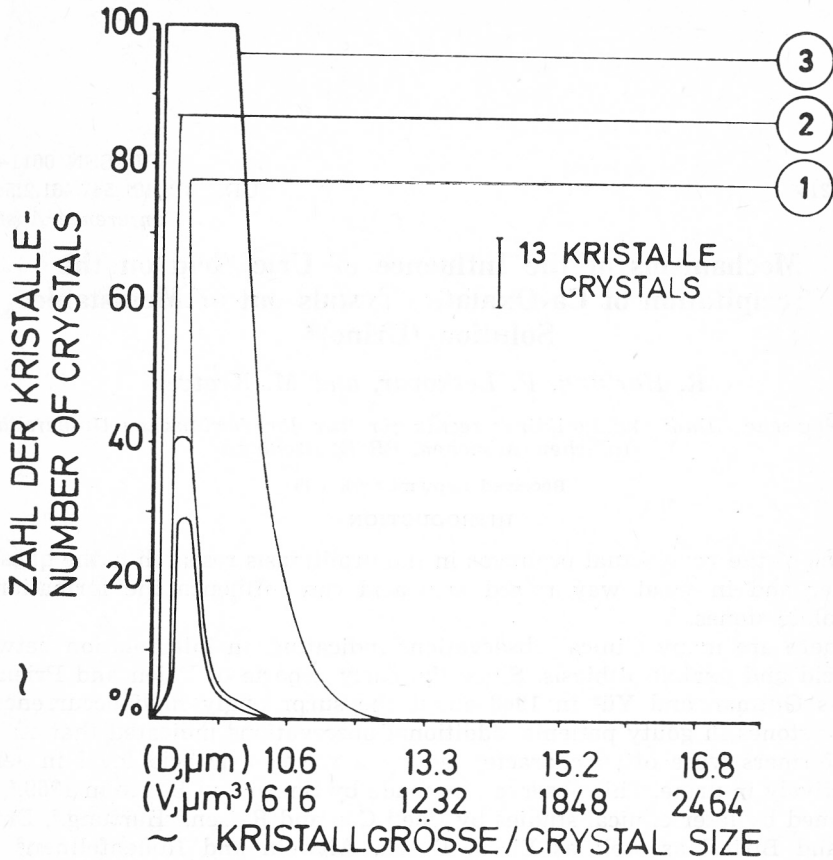


Figure 1.

oxalate, also could show that concentrations of monosodium urate as low as 20 mg/l, occurring physiologically in urine, were able to accelerate essentially the Ca-oxalate precipitation so that the latent time before the start of the precipitation could be reduced from 50 to 10 minutes. In this way, the crystallization times became comparable with the passage time of urine in the upper urinary tract (3 to 5 minutes), as calculated by Brown and Britton.

Robertson however, studying the influence of sodium and ammonium urate, couldn't confirm the theory of Pak. He, in the first line couldn't observe in urine the corresponding urates respectively the high uric acid oversaturations leading to the formation of monosodium urate. The role of uric acid in the facilitated oxalate precipitation Robertson saw in the binding of acid mucopolysaccharides as potent inhibitors by the semicolloidal uric acid. The same effect, the reduced activity of inhibitors in presence of uric acid, we also observed.

In addition, the so called »salting-out« effect of uric acid on Ca-oxalate crystals, reported by Kallistratos and Fenner<sup>14</sup> in 1971, should be mentioned. Kallistratos, adding uric acid to urinary samples with increasing pH values, found that at pH = 5.5 uric acid, at pH = 6.0—6.5 oxalate and at pH = 7.0 phosphate precipitated. This »salting-out« effect of uric acid led to repeated

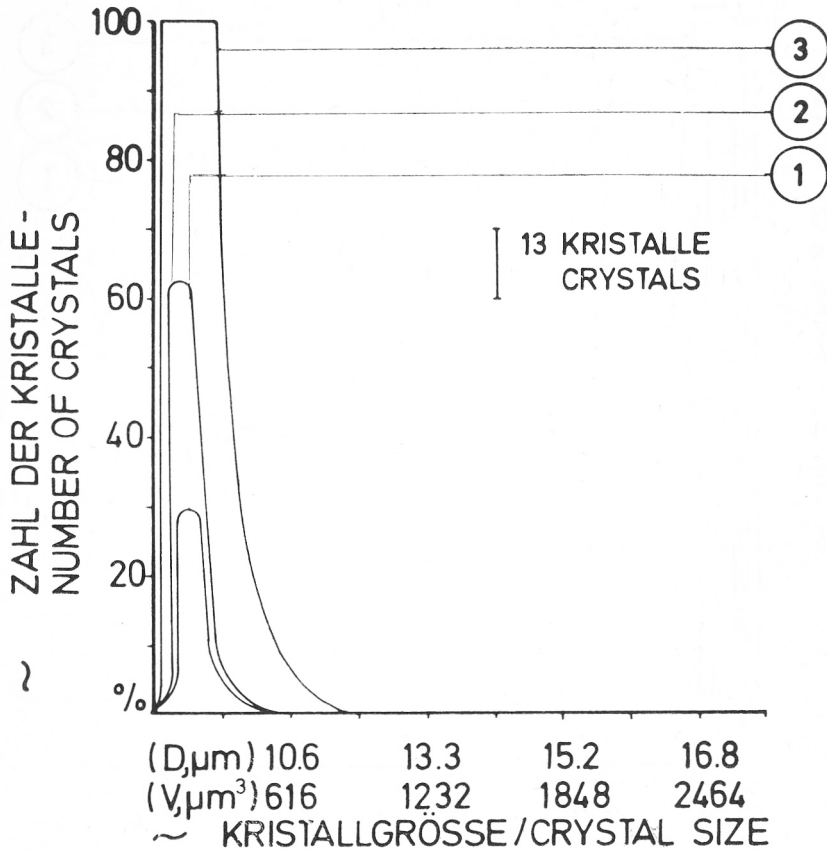


Figure 2.

discussions because of the problematic use of the term »salting-out« in this connection.

Evaluating the own experiments to this problem, we could define the facilitated Ca-oxalate precipitation in presence of uric acid as a special case of a more general phenomenon, the induction of heterogeneous precipitation from metastable urine by preformed crystals of accompanying scarcely soluble urinary salts.

#### METHODS

Our experiments were carried out by means of the Coulter Counter/Size Distribution Analyzer (P 128)-technique and should be presented in the following figures.

#### RESULTS

In Figure 1, the promotion of phosphate precipitation out of a metastable solution by uric acid crystal seeds is demonstrated. Curve 1 represents the metastable Ca-phosphate solution, curve 2 the suspension of uric acid crystals and the curve 3 the metastable Ca-phosphate solution incubated with uric acid crystals.

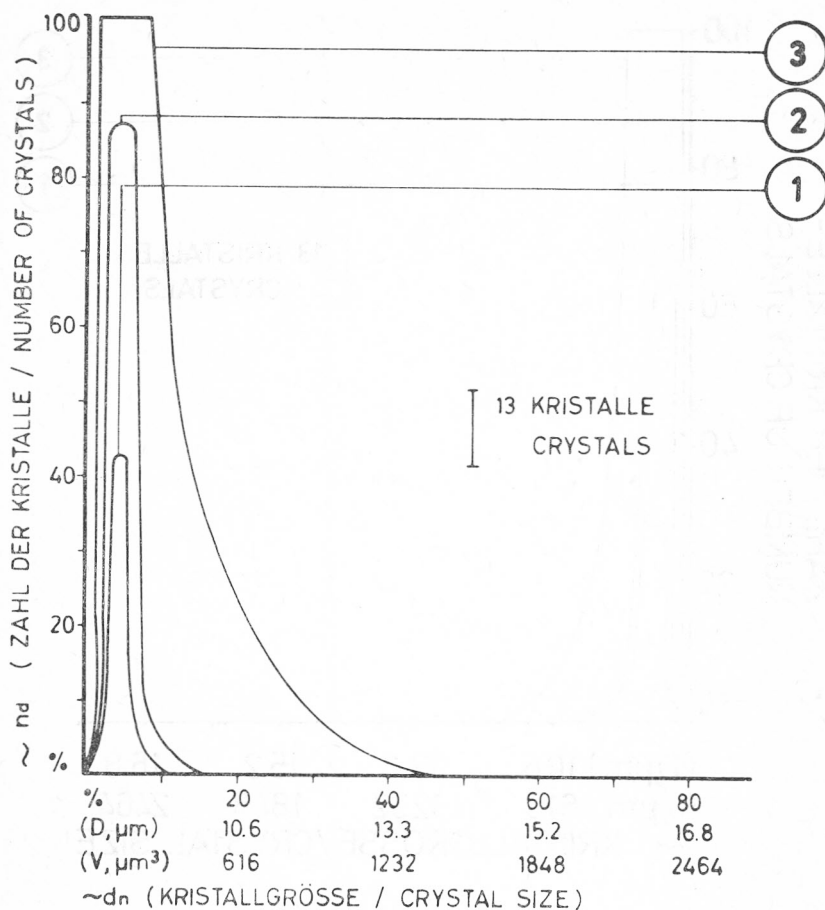


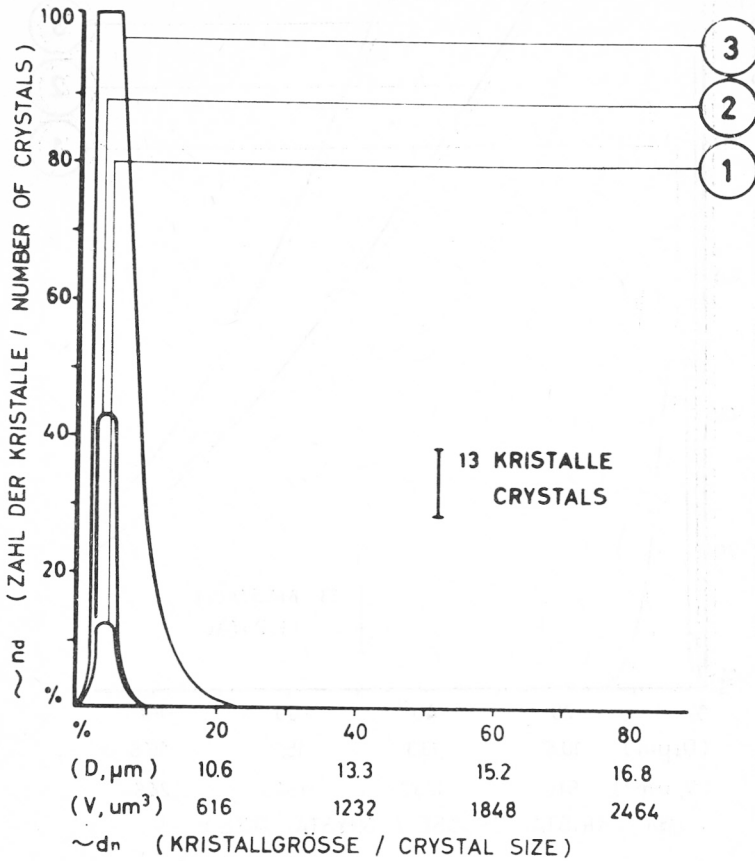
Figure 3.

In Figure 2, the same metastable phosphate solution was incubated with powdered uric acid stone. Again, the comparison of curve 3 and curve 1 shows the clear promotion of phosphate precipitation by the crystalline material of uric acid stone.

In Figure 3, the facilitated Ca-oxalate precipitation out of metastable solution by uric acid crystal seeds is presented. Curve 1 represents the metastable oxalate solution without and curve 3 that one with uric acid crystal seeds added. The acceleration of the precipitation process by uric acid crystals is obvious.

The comparison of curve 1 and curve 3 in Figure 4 shows that the crystalline material of disintegrated uric acid stones is also efficacious in promoting the nucleation and growth of Ca-oxalate crystals out of metastable solution. Curve 2 represents the suspension of powdered uric acid stone used.

In Figure 5, the influence of uric acid crystal seeds on the precipitation of Ca-oxalate crystals out of a highly oversaturated, instable solution is de-



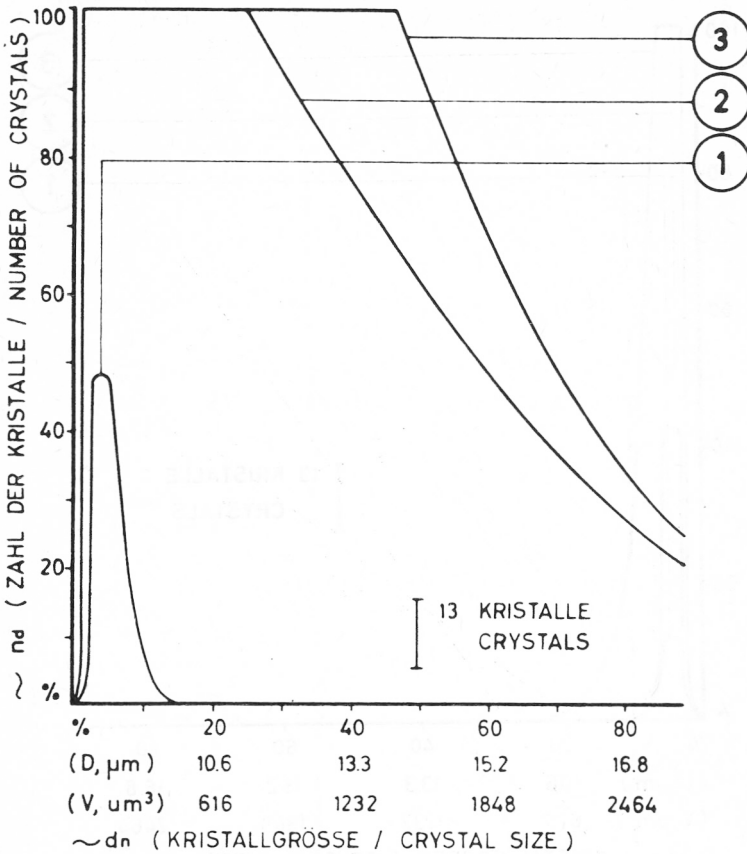
INCREASED FORMATION OF Ca-OXALATE-CRYSTALS IN PRESENCE OF POWDERED URIC-ACID-CALCULUS

- 1.....SUSPENSION OF POWDERED URIC-ACID-STONE (BLANK)
- 2.....METASTABLE Ca-OXALATE-SOLUTION
- 3.....METASTABLE Ca-OXALATE-SOLUTION + SUSPENSION OF POWDERED URIC-ACID-STONE

Figure 4.

monstrated. The comparison of curve 2 and 3 shows that even at such a oversaturation crystal seeds accelerate the precipitation of oxalate crystals. Curve 1 represents the uric acid suspension used.

In addition, the high positive correlation between urinary calcium and uric acid we calculated on the basis of data from single urinary samples, collected during 6 weeks in the group of recurrent oxalate stone patients and their controls, should be demonstrated (Figure 6). This parallelism in the uric acid and calcium excretion we found with recurrent oxalate stone-formers is a support of our hypothesis that uric acid, especially if overproduced, leads to



INFLUENCE OF URIC-ACID-SUSPENSION ON MARKED OVERSATURATED Ca-OXALATE-SOLUTION

- 1.....URIC-ACID-SUSPENSION (BLANK)
- 2.....OVERSATURATED Ca-OXALATE-SOLUTION
- 3.....OVERSATURATED Ca-OXALATE-SOLUTION + URIC-ACID-SUSPENSION

Figure 5.

a latent metabolic acidosis and mediately to the mobilisation of the bone base reserve. In this way, the bone calcium occurs in urine.

CONCLUSION

From our experimental data it can be concluded that uric acid promotes the precipitation of Ca-oxalate crystals out from metastable solutions like urine, the mechanism being the induced heterogeneous precipitation. An additional result is the high positive correlation between urinary calcium and uric acid, supporting our hypothesis that overproduced uric acid mobilises the bone calcium.

• CaOX-STEINBILDNER / STONE-FORMERS (—)  
 ○ KONTROLLPERSONEN / CONTROLS (---)  
 $r$  CaOX-STEINB. = 0.85  
 CaOX-STONE-F  
 $P <$  0.001  
 $r$  KONTROLLEN = 0.44  
 CONTROLS  
 $P <$  0.02

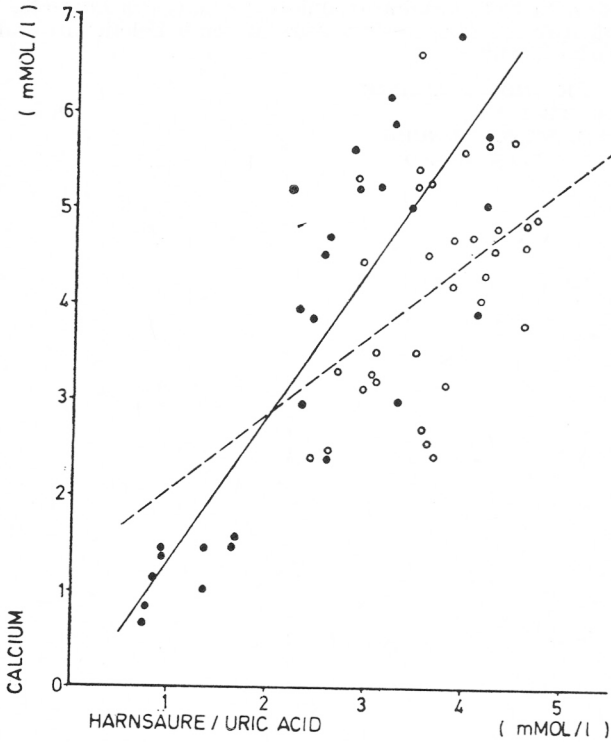


Figure 6.

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**SAŽETAK****Mehanizmi utjecaja urinske kiseline na taloženje kristala kalcijeva oksalata iz metastabilnih otopina (urina)**

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Potaknuti opažanjem da pacijenti sa hiperurikemijom i hiperurikozurijom često pokazuju pojave stvaranja bubrežnih oksalatnih kamenaca, provedena su ispitivanja mehanizama utjecaja urinske kiseline na taloženje kalcijeva oksalata. Raspravlja se i o pojavama inducirano, odnosno ubranog taloženja kalcijeva oksalata u prisutnosti kristala urinske kiseline.

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