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Advances in Medical Treatment of Renal Stones

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Advances in pharmacotherapy of renal stones are closely linked to the progress made in laboratory diagnostics. Development of lithotripters and the consequent sophisticated means of removing stones has distracted attention from the causes of lithiasis. However, removal of a renal stone only eliminates the consequences of a disease, but not its cause. There is frequently a failure to institute the most important diagnostic measure (collection of stones or disintegrates with a urinary sieve and performance of a qualified stone analysis). Various ESWL centers also do not analyse the stones or only do so by means of the intrinsically unsuitable chemical method. Thus, strategies of follow-up care are already very non-specific or wrong at the beginning of therapy.

It is indispensable to analyse every renal stone or to send all disintegrates collected for analysis. Only X-ray diffraction (7) and infrared spectroscopy (9) can provide exactly reproducible results among the methods of analysis available today. A computer program was developed for infrared spectroscopy which ensures definitive qualitative analysis and allows semiquantitative appraisals (10). By these methods of analysis, some new kinds of renal stones have been discovered (e.g. 2.8 dihydroxyadenine) and a series of sub-groups has been differentiated. The types of stones relevant for practical purposes are:

1. Cystine
   2.8 dihydroxyadenine
   Xanthine
2. Uric acid
   Ammonium urate
   Sodium urate
3. Calcium oxalate
   -Whewellite
   -Weddellite
4. Phosphates
   -Struvite
   -Carbonate apatite
   -Brushite

Particular attention must be paid to the fact that the types of renal stones of metabolic origin listed in the first group are mostly very pure, whereas two thirds of the other stone types are mixed stones. The relative urinary volume is crucial for all types of renal stones, i.e. the relative supersaturation for the respective stone type is significantly lowered with increase of urinary volume. This is shown for calcium oxalate in Figure 1.

The increase of the urine volume is of very great importance in the stone types of metabolic origin, since the lithogenic noxa is always present and constitutes a major risk especially at night.

The requirement for limitations of ascorbic acid administration in the therapy of cystine lithiasis has to be regarded as a crucial advance. By the reductive action of ascorbic acid, it was possible to induce an increased cystine excretion in almost all

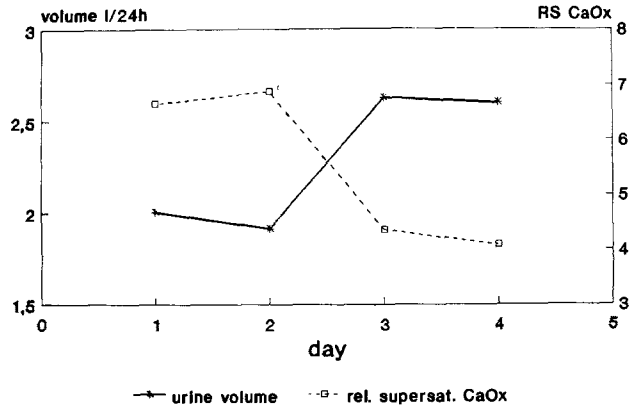

Fig. 1: Relative supersaturation with calcium oxalate as a function of 24 h-urine volume (Jahnen, 1990)

cases, but there was a therapeutic efficacy only at a cystine excretion of less than 3000 µmol/day (4). There are no new communications on the successful application of captopril (15).

Despite all our efforts, **calcium oxalate stones** remain a problem. Two thirds of all stones are calcium oxalate stones. The rate of recurrence of calcium oxalate stones without specific metaphylaxis is 67% - 74%, as confirmed once more in the most recent investigations of IGUCHI et al (1990). It has to be noted that the danger occurs in the first three years after the beginning of the lithiasis disease (12).

Diagnosis by metabolic examination

We always carry out an inpatient metabolic investigation in therapy-resistant recurrent stone formers. To eliminate dietetic infuences, the patients received a standard diet with 2400 ml of fluid for the duration of the investigtion. The evaluation of the results of 486 calcium oxalate stone patients showed that one or several risk factors were present in 92% of the women and 97% of the men. It was possible with the procedure chosen to distinguish between purely dietetic risks and risks with involvement of metabolic anomalies. The dietetic effect is manifested especially in hyperuricosuria and hypocitraturia, whereas the hypercalciuria is attributable to an intestinal hyperabsorption or a "renal leak" in the majority of cases (Fig. 2a, b).

The high rate of hyperoxaluria in male patients (60%) can be influenced by diet in only 23%, so that the intestinal hyperabsorption of oxalate and genetic factors involving oxalate formation are to be taken into consideration.

In 4.5% of the cases, a primary hyperparathyroidism could be diagnosed as the cause of calcium oxalate stone formation.

We infer from experience with inpatient metabolic investigations that very individual concepts of therapy must be drawn up on the basis of a specific diagnostics.

The risk factor hypercalciuria

If the calcium excretion is in excess of 5 mmol/day irrespective of diet, we refer to the presence of hypercalciuria. By application of the calcium loading test, a classification into hyperabsorptive and renal hypercalciuria is possible. In excretion of 5 - 8 mmol calcium/day and urinary pH values less than 6.8,

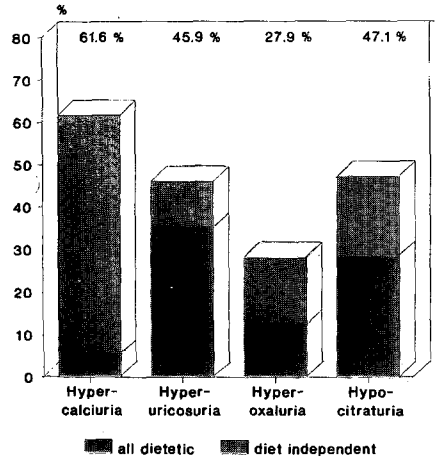

Fig. 2a:

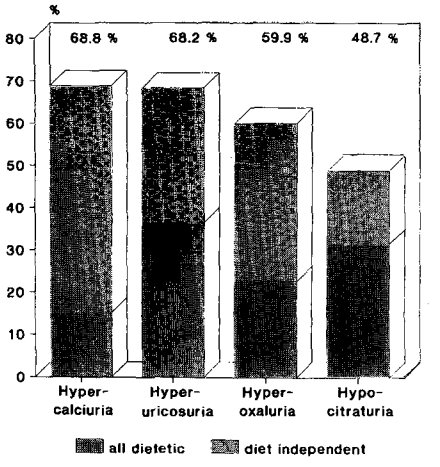

Fig. 2b:

Risk factors in calcium oxalate urolithiasis (n = 486) a) women b) men

the application of alkali citrates (e.g. potassium sodium cirate) can be very successful. C. Berg (2) attains a significant lowering of the calcium excretion by 12% by administration of 7.5 g (27 mmol) potassium sodium citrate (RenapurR, OxalytR). In our investigations, a reduction of 23% was found with 9 g potassium sodium citrate (8).
If the excretion of calcium is in excess of 8 mmol/day, the administration of hydrochlorothiazide is to be considered. This medication is to be prefered especially in renal hypercalciuria. If a pronounced hyperabsorption of calcium was diagnosed, the application of ion exchangers is indicated, especially in the form of dietary fibers. Various brans have a good calcium-lowering effect, and good clinical effects were attained with a mixed bran preparation. The rate of stone passage fell from 1.5 to 0.15 per year (5).

Risk factor hyperuricemia/hyperuricosuria

Raised uric acid in the serum frequently results in a raised excretion in the urine, but normal values may also be present in the serum owing to rapid renal elimination, even in raised uric acid formation. Uric acid blocks the GAGs as inhibitors of calcium oxalate crystallization. It is mostly excreted to an increasing extent in consequence of high-protein diet. A diet high in methionine leads to an additionally raised urinary acid excretion. The serum uric acid values are to be lowered to subnormal values by allopurinol. The urinary pH is raised to 6.8 to 7.0 by alkali citrates, and a high solubility of uric acid is thereby attained.

Risk factor hypocitraturia

In the international literature, 2 mmol/day is specified as the minimum limit for hypocitraturia. We prefer the limit value of 3 mmol/day for the commencement of therapy. Citrate excretion is enhanced by 80% to 100% by administration of 7.5 to 9 g potassium sodium citrate per day (6).
On the basis of the circadian rhythm of the pH value of the correlating citrate excretion in the urine, the greatest risk of calcium oxalate stone formation can be established as being in the night. The lowest urine volume was measured at night as an additional risk. It is therefore a good prophylactic strategy against recurrences to eliminate particularly the risks of nocturnal lithogenesis. Increase of urine dilution is very important. However, pharmacotherapy can also be very effective. Thus the "single evening dose" of alkali citrate brings about a highly significant lowering of the risk of lithogenesis in the night (2). The advantage of the therapeutic approach for the night is the good compliance of the patients. For this reason, it is our strategy to restrict alkalization therapy to the morning and evening in many cases.

Risk factor hyperoxaluria

It was indicated in the Introduction that hyperoxaluria was diagnosed in 60% of male and 28% of female kidney stone patients by metabolic investigations. About one third of the cases of hyperoxaluria can be normalized by dietetic measures. Hyperoxaluria constitutes a substantial risk and should always be considered above all in therapy-resistant patients. It is known from various observations that 40% to 50% of hyperoxalurias are attributable to a hyperabsorption of oxalate. In these cases, restriction of calcium is to be avoided. Administration of magnesium may be a therapy promising good prospects of success. According to an investigation of W. Berg (3), the intestinal absorption of oxalate is inhibited by magnesium. The effect of magnesium therapy on the growth of calcium oxalate crystals in the urine is controversial. However, a good prophylactic effect against recurrences has been demonstrated clinically by some authors. It is hence probable that the effect of magnesium already begins in the intestine. The administration of pyridoxine is indispensable in metabolic hyperoxaluria.
We consider that it is necessary to commence specific therapy with the first stone episode. It can be inferred from a previous evaluation of our metabolic patients that reoperations or nowadays lithotripter treatments and nephrectomies have not uncommonly resulted from nonspecific metaphylaxis. The latter are especially frequent in uric acid (14.1%) and in particular in infection stone conditions (32%).
The therapeutic guidelines are the most effective for **uric acid stone conditions**. However, this good efficacy also results in inconsistency of compliance on the part of the patient (and frequently also of the physicians). The high rates of nephrectomy of 14% provide a clear example of the consequences.
The complications in **infection stone** are very much more dramatic. The cause of the lithogenesis, the infection with urease-forming bacteria, can only be treated successfully in complete freedom from stones. Complete primary clearance of the stones is hence necessary in this case. Checks of the freedom from infection, as well as possibly bacterial suppression and dilution of the urine are important secondary measures. Since the formation of infection stone (struvite/carbonate/apatite) can only take place in alkaline medium, the urine is always to be acidified to pH values less than 6.2 as an immediate measure before stone removal. In use of antibiotics, the acidification has the additional advantage that the efficacy of these drugs is increased in the acid pH range.
A physiological acidification is possible by administration of l-methionine (acimethine). This drug has a rapid effect and high bioavailability of more than 89% (1).
The rate of recurrences in stone patients could be drastically reduced with a specific metaphylaxis after the metabolic investigation. Owing to the greatest danger of recurrence in the first year of the stone condition (40%) and the possible complications (14), we advocate comprehensive diagnostics on manifestation of the first stone (Fig. 3). This can also be carried out under outpatient conditions and at certain centers as a service. We have offered a follow-up program for almost three years which communicates the results of diagnostics to doctors and makes recommendations for therapy. About 1500 patients are being attended by about 200 doctors at present (11).
Every stone episode which does not occur also entails

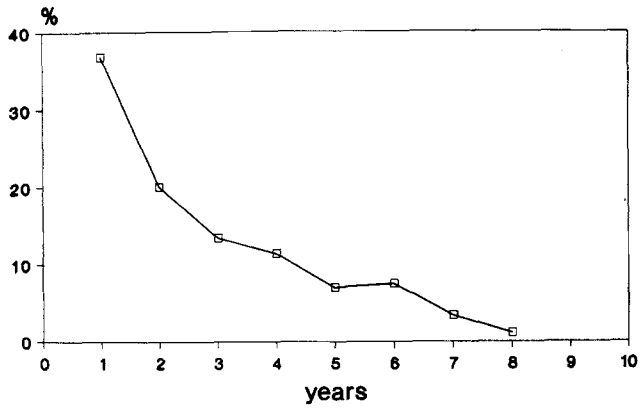

Fig. 3: Recurrent stone formation as a function of time (Schneider, 1985)

a lowering of costs. Compared to the average costs of a lithotripter treatment with stay in hospital, absence from work and resulting costs for the insurance funds, the annual costs for specific medication prophylaxis are low.

Effective principles of therapy are available for the majority of the metabolic anomalies to be corrected. It would be a particular advance in pharmacotherapy of urolithiasis if these were applied consistently and specifically (Fig. 4).

It is thus our duty to make these advantages accessible to all stone patients by appropriate organization of diagnostics and by assuring dissemination of the principles of treatment. The message is simple, but we must all be prepared to understand it.

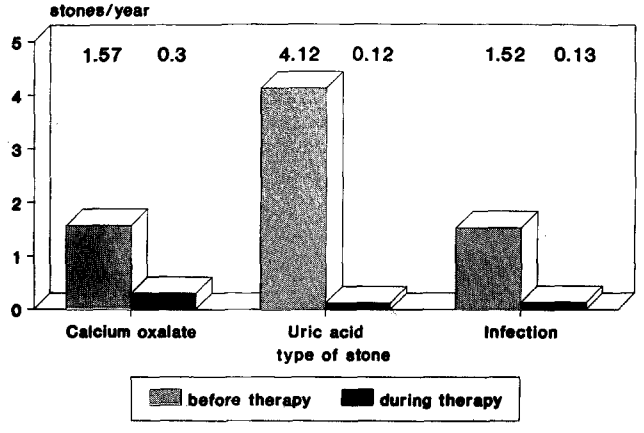

Fig. 4: Frequency of relapse before and during therapy (observation period 19.5 months)

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