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SYMPOSIUM PAPER

Relevance of the BONN Risk Index for metabolic monitoring of patients with calcium oxalate urolithiasis: a clinical application study of the Urolizer®

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Abstract The BONN Risk Index (BRI) successfully determines the calcium oxalate (CaOx) crystallization risk from urine samples. The BRI is based on a standardized crystallization test performed on native urine. A BRI-measuring device, the "Urolizer®", has been developed, operating automatically and requiring only a minimum of preparative efforts. In this study, the Urolizer® is evaluated regarding its analytical and diagnostic practicability for metaphylaxis control in the framework of the daily routine of a stone surgery. From 51 CaOx recurrent stone-formers, 24 h urines were collected at the beginning and after 3 months of metaphylaxis. As much as 27 patients were indicated to suffer from "mild hypercalciuria", low urinary pH or hypocitraturia, and 24 patients from "hypercalciuria". The former were treated with alkaline citrate (AC), and the latter with hydrochlorothiazide (HCT). Analyses of urines collected before and during treatment, BRI using the Urolizer®, and urinalysis-based risk indices were evaluated. In both patient groups, BRI decreased significantly, while metaphylaxis ($P<0.001$) in the AC group decreased from 1.08 (±0.58) to 0.56 (±0.39) L^{-1} and in the HCT-group from 3.30 (±1.15) to 1.60 (±0.52) L^{-1}. In most patients, urinary parameters changed as desired and related risk indices decreased appropriately. The clinical utility of the easy-to-determine BRI is demonstrated. By quantifying the "overall" therapy effect within 15 min, the innovative analysis device may be especially suited for practitioners specializing in urolithiasis treatment.

Keywords Metabolic workup · Nephrolithiasis · Calcium oxalate · Risk evaluation · Metaphylaxis control

Abbreviations

AP_{CaOx}	Ion activity product index for calcium oxalate
BRI	BONN Risk Index
CaOx	Calcium oxalate
RSS	Relative supersaturation

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Introduction

Urolithiasis is an entity of rising prevalence and increasing impact on the health-care systems in developed countries [1–4]. Changes in lifestyle factors, in particular, during the past decades are considered causative for the dramatic increase in the occurrence of urolithiasis [5]. Calcium oxalate represents by far the most frequent mineral phase found in uroliths with a frequency of approximately 70–75% [6, 7]. Owing to the high recurrence rate of calcium oxalate stone formation (approximately 50%) [3] in case of insufficient metaphylactic treatment, evaluation of the individual causes of calcium oxalate urolithiasis and improved possibilities for metaphylaxis monitoring in the framework of follow-up programs are not only of utmost clinical importance, but also highly appreciated by more than half of the urolithiasis patients [8].

The usual methods of estimating the individual causes of urinary CaOx calculus formation and the risk of recurrence are based on single urinary parameter assessment or combinations of several analysis-based urinary parameters with a formula based either on empirical determinations or on commonly accepted thermodynamic equilibrium models. These risk parameters refer mainly to renal excretions parameters, urinary pH and 24 h urine volume. A variety of parameter-combining approaches were developed [9]. The AP_{CaOx}, an established approximate measure of the urinary ion activity with respect to CaOx [10], was chosen for this study. This parameter requires five input data: urinary volume, renal 24 h excretions of calcium, oxalic acid, magnesium and citric acid. The empirical formula for 24 h urines, $AP_{CaOx} = (1.9 \times Ca^{0.84} \times Ox)/(Mg^{0.12} \times Cit^{0.22} \times V^{1.03})$, combines these data to a manageable measure of the CaOx formation risk.

The most sophisticated urinalysis-based index requires input of at least 12 urinary parameters potentially involved in the process of stone formation. From these, a model value of the urine's relative CaOx supersaturation, RSS, is iteratively computed by the EQUIL II-program via determining the systematic interaction of these components within the framework of existing physico-chemical boundary conditions [11, 12]. The input variables are the urinary concentrations of Na, K, Ca, Mg, NH_4, Cl, PO_4, SO_4, uric acid, oxalic acid, and citric acid as well as the urinary pH.

Limits to these (computational) approaches include an overly complex pathological reality as well as the economic costs of detailed urinalysis in order to obtain a more realistic scenario. Risk indices that consider the overall effect of all urine components offer a possible solution to the aforementioned dilemma.

Since its first publication in 2000, the BRI in vitro test has been successful in determining the CaOx crystallization risk from unprocessed urine samples [13–18]. Recent studies have shown that BRI can be determined not only from fresh urine, but also from urine stored over a period of 24 h at moderate temperature ($T = 4°C$ and $T = 24°C$) without significant loss in analytical quality (data presented at the 11th symposium on urolithiasis 2008, Nice, France).

By determination of the native concentration of free urinary calcium ions, $[Ca^{2+}]$, and controlled induction of a crystallization process within the urine sample itself, BRI considers (non-specifically) all urine components in their native quantity proportions. The ratio calculated from $[Ca^{2+}]$ and (Ox^{2-}), the amount of ammonium oxalate required for crystal formation, is termed the BRI, that is $BRI = [Ca^{2+}]/(Ox^{2-})$. By definition, a cut-off value of 1 L^{-1} separates urines from CaOx stone formers and urines from controls [14].

Despite limited analytical efforts and minimal expenditure of time (approximately 15 min), high significance is reached by the BRI in discriminating between persons "without risk" and persons "at risk" [14, 17, 18]. Though defined by only two parameters, the BRI discriminates more specifically between healthy people and individuals prone to forming stones than the commonly used risk indices such as AP_{CaOx} or RSS [14, 15, 19].

To date, BRI determination was almost exclusively performed within the set-ups of scientific laboratories. This was due to the relatively laborious manual efforts, which are considered acceptable only in proven centers specializing in urolithiasis treatment ("stone clinics"). In order to bring the BRI to a broad application within a clinical routine setting, a measuring device has been developed that operates fully automatically (i.e., no expertise required) and thereby requiring only a minimum of preparative and cleaning efforts (i.e., low analytical costs).

In recent months, the so-called "Urolizer®" for BRI determination has reached marketing status (developed by NTTF GmbH, Rheinbreitbach, Germany; distributor: Raumedic AG, Helmbrechts, Germany). A pilot run Urolizer® has been made available to each of the working groups. Evaluation of the BRI precision of the Urolizer® in the run-up to this study revealed a mean intra-sample variation coefficient for BRI in the clinically important range between 1.0 and 5 L^{-1} (i.e. "increased" to "very high" risk [14]) of 10.1% (MV = 1.49 L^{-1}; mean intra-series SD = 0.15 L^{-1}). Including those samples with BRI $\leq$ 1.0 L^{-1}, mean CV amounts to 11.8% at a mean BRI of 0.85 L^{-1} and a corresponding mean intra-series SD of 0.10 L^{-1} (detailed data in [20]). In this study, the Urolizer® was tested regarding its analytical and diagnostic practicability for metaphylaxis control using the BRI in the framework of the daily routine of a stone surgery.

Materials and methods

For this study, 24 h urines from 51 recurrent CaOx stone formers with no indication of urinary tract infection (negative test with respect to nitrite and leucocytes, Combur^{10} Test® strips for visual reading; Roche Diagnostics) were collected without preservatives on two occasions: at the beginning of metabolic workup and after 3 months of ongoing metaphylaxis. The patients were grouped into two sub-groups according to the initially analyzed renal calcium excretion ("baseline"):

1. Of all the patients, 27 (19 males, age 57 ± 13 years; 8 females, age 56 ± 21 years) showed calcium excretions

Table 1 Individual results of urinalyses of 24 h urine samples of calcium oxalate stone formers suffering from inter alia, mild hypercalciuria

No.	Sex	Stage 0									
		BRI	AP	RSS	24 hV	pH	Ca^{2+}	Ca	Mg	OA	CA
1	m	1.10	0.86	5.28	2.50	5.6	0.45	4.6	4.3	0.52	2.93
2	f	1.90	1.27	7.64	2.60	6.6	0.83	7.8	3.0	0.46	2.26
3	m	1.20	1.36	5.12	2.60	5.5	0.60	5.4	2.5	0.44	0.47
4	f	0.40	0.87	2.52	3.60	6.4	0.33	3.0	9.7	0.71	0.36
5	m	1.00	0.85	4.70	2.20	5.5	0.48	2.0	4.5	0.63	0.79
6	m	1.70	2.35	13.97	1.90	5.9	0.64	7.2	5.6	0.64	1.82
7	m	2.10	3.59	17.86	1.80	6.0	0.71	9.3	3.1	0.72	2.12
8	m	1.30	0.97	4.23	4.20	5.5	0.71	7.2	9.5	0.66	2.14
9	m	1.00	0.76	3.61	3.60	6.2	0.53	5.8	4.1	0.47	1.98
10	m	0.70	0.52	3.88	1.90	5.5	0.48	2.0	2.5	0.35	1.29
11	f	0.70	0.69	3.37	1.70	6.0	0.38	1.9	1.1	0.46	2.91
12	m	0.40	0.51	3.11	3.10	6.0	0.23	1.3	0.9	0.63	0.53
13	f	2.50	1.37	10.30	1.00	5.8	0.79	5.0	4.3	0.26	2.01
14	f	0.90	0.84	9.61	3.20	6.3	0.48	6.3	3.2	0.46	3.10
15	m	1.20	1.66	7.49	1.50	5.7	0.60	5.1	4.5	0.38	0.75
16	m	1.10	1.27	7.92	2.40	6.0	0.63	6.5	4.1	0.52	3.36
17	m	1.10	1.69	9.09	2.30	5.7	0.60	7.1	5.9	0.66	3.52
18	m	0.90	1.15	6.46	1.40	5.6	0.53	3.6	6.3	0.42	1.75
19	m	0.80	0.68	2.97	3.00	6.1	0.49	5.0	3.1	0.40	2.37
20	f	0.70	0.93	6.68	1.50	6.1	0.41	3.0	2.5	0.44	3.74
21	f	1.50	0.84	4.14	3.00	5.8	0.64	7.3	4.4	0.44	5.01
22	m	0.70	1.58	9.61	2.20	5.8	0.41	4.6	4.2	0.82	3.67
23	m	1.10	1.27	7.81	1.10	5.7	0.44	4.6	3.6	0.26	1.47
24	f	0.50	0.69	4.27	2.60	6.1	0.38	3.9	3.7	0.50	4.24
25	m	1.50	1.87	11.41	1.50	5.5	0.63	6.3	3.0	0.45	2.64
26	m	2.40	1.86	10.51	1.90	5.6	0.69	7.1	2.5	0.44	1.41
27	m	1.10	0.92	4.28	2.00	5.8	0.56	5.6	6.0	0.35	2.36
MV	–	1.05	1.23	6.96	2.31	5.86	0.54	5.13	4.15	0.50	2.26
MD	–	1.10	0.97	6.46	2.20	5.80	0.53	5.10	4.10	0.46	2.14
SD	–	0.55	0.65	3.64	0.79	0.29	0.14	2.01	2.02	0.14	1.18
No.	Sex	Stage AC									
		BRI	AP	RSS	24 hV	pH	Ca^{2+}	Ca	Mg	OA	CA
1	m	0.30	0.61	2.46	3.50	6.7	0.32	4.7	3.6	0.50	4.45
2	f	1.60	1.17	7.44	1.90	6.7	0.62	6.7	3.4	0.44	2.11
3	m	0.90	0.87	3.90	2.90	6.3	0.48	5.3	2.7	0.44	2.00
4	f	0.20	0.48	2.22	2.90	6.7	0.29	2.4	4.9	0.49	1.71
5	m	0.80	1.57	6.84	2.90	6.4	0.46	4.7	3.2	0.84	1.45
6	m	0.90	1.36	8.23	2.30	6.7	0.46	5.6	5.0	0.63	3.74
7	m	1.50	2.86	14.46	1.90	6.5	0.63	9.1	3.1	0.74	4.86
8	m	0.70	0.56	2.35	3.50	6.4	0.48	4.9	14.9	0.61	7.74
9	m	0.40	0.55	2.59	3.80	6.7	0.32	5.5	4.6	0.46	4.48
10	m	0.50	0.29	1.34	2.00	6.6	0.32	1.6	2.8	0.32	3.82
11	f	0.20	0.30	1.08	2.60	7.1	0.25	1.5	1.5	0.45	4.56
12	m	0.10	0.27	0.97	3.40	6.7	0.10	1.0	1.1	0.61	2.21
13	f	1.40	0.49	2.75	1.90	6.8	0.58	4.8	5.5	0.23	4.87
14	f	0.80	0.67	3.43	3.00	6.7	0.46	6.5	3.2	0.38	5.64

Table 1 continued

No.	Sex	Stage AC									
		BRI	AP	RSS	24 hV	pH	Ca^{2+}	Ca	Mg	OA	CA
15	m	1.00	1.27	6.05	1.80	7.0	0.52	5.2	4.2	0.40	1.86
16	m	0.80	0.90	4.73	2.50	7.2	0.60	6.2	3.8	0.42	3.88
17	m	0.70	1.37	7.71	2.40	6.8	0.48	5.8	7.1	0.68	3.58
18	m	0.50	0.62	3.24	2.00	6.6	0.41	2.8	6.5	0.48	4.04
19	m	0.20	0.37	2.20	4.00	6.8	0.31	4.4	3.2	0.35	3.20
20	f	0.30	0.71	2.78	2.30	7.1	0.38	3.4	2.2	0.48	4.51
21	f	0.50	0.69	3.91	3.40	6.7	0.34	7.1	5.0	0.44	5.82
22	m	0.40	0.78	3.24	2.80	7.0	0.34	4.4	4.0	0.58	5.20
23	m	0.60	0.58	3.32	2.20	6.9	0.38	5.0	3.8	0.28	3.68
24	f	0.50	0.71	3.33	2.50	6.6	0.32	4.0	3.2	0.48	4.43
25	m	0.60	1.03	5.95	2.40	6.4	0.44	5.8	3.4	0.48	4.08
26	m	1.20	1.30	7.42	2.80	6.8	0.51	6.6	2.2	0.56	2.88
27	m	0.40	0.52	2.85	3.20	6.6	0.35	5.0	8.5	0.41	3.84
MV	–	0.56	0.85	4.33	2.70	6.72	0.41	4.81	4.32	0.49	3.88
MD	–	0.60	0.69	3.32	2.60	6.70	0.41	5.00	3.60	0.48	3.88
SD	–	0.39	0.52	2.83	0.61	0.22	0.12	1.82	2.60	0.13	1.40

The scenarios at the beginning of therapy (stage 0) and after 3 months of alkaline citrate therapy (AC) are presented. BRI (L^{-1}), 24 hV (L), Ca^{2+} (mmol/l), and all other data in mmol/24 h

MV mean value (BRI geometric mean, otherwise arithmetric mean), *MD* median value, *SD* standard deviation, *m* male, *f* female

between 5 and 8 mmol/day (i.e. mild hypercalciuria) or a pH-value in the 24 h urine below the optimum pH range for calcium oxalate stone metaphylaxis of 6.5 to 7.0, or low citrate excretion of less than 2.5 mmol/day (Table 1).

2. A total of 24 patients (16 males, age 54 ± 11 years; 8 females, age 57 ± 11 years) showed calcium excretions exceeding the lower limit value for hypercalciuria of 8 mmol/day (Table 2).

In accordance with the German guidelines for stone treatment [21], the first group was primarily treated with $KHCO_3$/citric acid/Na_3 citrate preparations (Blemaren®) in order to increase both urinary pH and urinary citrate excretion. After extensive counseling by a urologist, the patients were advised to evaluate the individually required alkaline citrate dosage according to the results of regular self-checking of actual urinary pH using indicator paper ($5.4 < pH < 7.4$). Under therapy conditions, the urinary pH should then reach values between 6.5 and 7.0.

The second group was primarily treated with hydrochlorothiazide each morning and evening (each 12.5 mg); in case of hypercalciuria with Ca > 10 mmol/day, additionally a third dose was given at midday for effective lowering of the renal calcium excretion. From each urine, BRI and the lithogenically significant parameters as required for EQUIL II calculations were throrougly analyzed. RSS values and AP_{CaOx} values were computed from the urinary concentrations and from the thus derived renal excretions, respectively. Geometric means for BRI ($= (x_1 \times x_2 \times \cdots \times x_n)^{1/n}$) and arithmetic means for the other parameters were calculated.

Analyses of urines collected before and during treatment and risk indices of each of both groups were statistically compared using two-sided non-parametric Wilcoxon test for dependent variables. A P value of <0.05 was considered to be significant. Changes in BRI, AP_{CaOx}, RSS and urinary concentrations/excretions after 3 months of metaphylaxis were investigated, i.e. 104 24 h urines were collected and analyzed.

Results

Linear best-fit regression of BRI versus AP_{CaOx} and BRI versus RSS revealed linear regression coefficients r of 0.68 and 0.71, respectively. In every patient of both patient groups, BRI decreased during metaphylaxis (Tables 1, 2). Consequently, a distinct lowering of mean BRI (±SD) was observed (Figs. 1, 2, 3) in the alkaline citrate group from 1.08 (±0.58) to 0.56 (±0.39) L^{-1} and in the HCT-group from 3.30 (±1.15) to 1.60 (±0.52) L^{-1}. Both differences are statistically significant with $P < 0.001$. Also, the urinalysis-based indices AP_{CaOx} and RSS decreased in both treatment

Table 2 Individual results of urinalyses of 24 h urine samples of calcium oxalate stone formers suffering from inter alia, hypercalciuria

No.	Sex	Stage 0									
		BRI	AP	RSS	24 hV	pH	Ca^{2+}	Ca	Mg	OA	CA
1	m	5.00	2.18	11.88	2.40	6.1	1.45	13.1	12.4	0.41	2.33
2	m	2.90	2.61	9.05	2.70	5.6	0.76	8.7	6.2	0.55	1.63
3	m	2.00	3.39	10.47	3.30	5.9	0.62	15.4	9.6	1.11	4.07
4	f	2.40	1.98	8.76	3.60	6.0	0.83	15.2	5.1	0.67	4.46
5	f	3.90	2.02	9.64	2.90	6.1	0.93	12.5	2.7	0.56	2.00
6	f	3.00	1.87	11.10	1.80	5.9	0.76	8.2	2.4	0.42	1.24
7	m	4.00	2.10	12.02	2.20	6.2	1.00	10.6	4.9	0.54	3.32
8	m	6.40	2.56	13.44	1.70	6.2	1.23	11.5	2.8	0.45	3.17
9	m	2.30	1.56	9.22	2.70	6.0	0.68	8.9	3.3	2.22	2.39
10	m	3.10	1.76	6.37	4.60	6.2	0.89	14.5	7.0	0.60	1.70
11	f	1.90	1.82	9.74	4.20	5.8	0.74	8.2	5.1	1.19	1.98
12	m	3.80	2.36	13.64	2.80	6.1	0.89	9.6	3.2	0.81	3.44
13	m	4.50	2.89	13.82	1.50	5.6	1.07	10.8	7.5	0.54	3.93
14	m	3.20	1.59	8.71	2.60	5.7	0.81	8.9	3.6	0.51	4.50
15	M	4.10	1.74	10.73	2.50	5.7	0.96	8.2	4.8	0.62	3.03
16	f	2.30	1.74	9.42	4.00	6.6	0.81	10.2	4.3	0.88	4.08
17	f	3.20	2.25	12.88	4.00	6.4	1.00	16.3	6.1	0.87	4.36
18	m	3.80	2.88	14.89	1.80	6.1	1.05	13.5	6.5	0.56	5.13
19	m	5.90	1.69	10.17	2.30	6.0	1.32	10.9	3.0	0.37	1.86
20	m	2.60	2.21	10.38	2.20	5.8	0.83	14.8	6.6	0.50	5.63
21	f	3.70	1.91	11.97	2.00	6.1	0.89	8.1	2.2	0.47	2.40
22	f	2.80	1.15	6.35	4.00	6.5	0.93	11.2	5.5	0.46	2.92
23	m	4.20	2.43	23.76	2.60	6.2	0.98	9.6	3.5	0.57	0.82
24	m	2.30	2.34	11.75	3.00	6.2	0.69	15.0	8.9	0.67	3.44
MV	–	3.30	2.13	11.26	2.81	6.04	0.92	11.41	5.30	0.69	3.08
MD	–	3.20	2.06	10.60	2.65	6.10	0.89	10.85	5.00	0.56	3.10
SD	–	1.15	0.49	3.37	0.85	0.26	0.20	2.64	2.47	0.38	1.24
No.	Sex	Stage HCT									
		BRI	AP	RSS	24 hV	pH	Ca^{2+}	Ca	Mg	OA	CA
1	m	1.30	1.78	7.22	3.00	6.7	0.59	10.2	10.7	0.59	1.91
2	m	0.60	1.29	6.76	2.00	6.1	0.49	5.8	5.7	0.48	2.60
3	m	1.00	1.77	5.98	4.00	6.4	0.46	10.2	8.5	0.97	4.07
4	f	1.10	1.36	5.97	3.40	6.3	0.50	8.7	2.7	0.74	8.50
5	f	1.80	1.68	6.51	3.00	6.3	0.63	10.0	4.3	0.63	3.84
6	f	2.40	1.47	8.39	2.30	5.9	0.68	6.4	2.6	0.51	1.88
7	m	1.70	1.81	9.73	2.40	6.4	0.71	8.5	6.4	0.66	4.03
8	m	1.90	1.13	7.13	2.50	6.4	0.56	7.3	5.0	0.42	2.33
9	m	1.30	1.21	6.88	2.60	6.3	0.45	5.4	1.1	0.46	1.56
10	m	2.10	1.54	5.89	4.20	6.0	0.74	10.1	7.2	0.87	1.75
11	f	1.00	1.48	5.26	5.00	6.5	0.49	8.0	5.2	0.54	2.28
12	m	2.10	1.61	9.31	2.80	6.3	0.72	7.0	2.5	0.71	3.67
13	m	2.30	1.59	8.21	2.00	5.8	0.78	8.2	8.0	0.51	4.02
14	m	1.50	0.85	5.12	2.80	5.7	0.60	5.4	3.4	0.50	4.30
15	M	2.00	1.09	6.31	3.00	5.8	0.68	6.4	4.5	0.58	3.20
16	f	1.20	1.16	6.08	4.00	6.5	0.54	7.9	4.3	0.72	3.87
17	f	2.10	1.33	7.48	4.00	6.2	0.70	10.8	5.8	0.68	4.47

Table 2 continued

No.	Sex	Stage HCT									
		BRI	AP	RSS	24 hV	pH	Ca^{2+}	Ca	Mg	OA	CA
18	m	1.40	1.46	8.47	2.00	6.3	0.57	6.8	8.6	0.60	5.87
19	m	2.50	1.17	6.91	3.00	6.0	0.78	7.2	3.8	0.52	2.45
20	m	1.80	1.03	6.08	2.60	6.0	0.61	7.4	6.8	0.48	4.89
21	f	2.10	1.26	7.39	2.70	6.2	0.70	6.5	2.2	0.50	2.20
22	f	2.00	0.92	4.82	4.00	6.5	0.71	8.5	5.4	0.46	2.84
23	m	2.40	1.57	4.80	2.50	6.4	0.74	7.8	4.5	0.54	2.24
24	m	1.10	1.60	8.85	2.60	6.4	0.32	9.7	8.6	0.58	3.76
MV	–	1.60	1.38	6.90	3.02	6.23	0.61	7.93	5.33	0.59	3.44
MD	–	1.80	1.41	6.82	2.80	6.30	0.62	7.85	5.10	0.56	3.44
SD	–	0.52	0.27	1.35	0.78	0.25	0.12	1.57	2.37	0.13	1.53

The scenarios at the beginning of therapy (stage 0) and after 3 months of hydrochlorothiazide therapy (HCT) are presented. Units and abbreviations, see Table 1

groups in most patients (two exceptions), and considering all data, decreases were significant with $P < 0.001$.

BRI, AP_{CaOx} and RSS decreased in the alkaline citrate group in the mean by 56.3% (±21%), 69.6% (±27%) and 63.4% (±26%), respectively. Similar changes could be observed in the HCT group. Here, data changed by 50.8% (±14%), 66.7% (±13%) and 64.3% (±13%), respectively.Alkaline citrate medication leads in most patients to expected changes in the urinary concentrations of free calcium ions, [Ca^{2+}], and the renal excretions of the urinary target parameters total calcium, citric acid and hydrogen ions (Ca, CA and pH, respectively). In the alkaline citrate group all 27 patients showed a decrease in Ca^{2+}, 20/27 showed a decrease in Ca and 26/27 and 27/27 patients showed an increase in CA and pH, respectively (Table 1). These four changes are statistically significant with $P < 0.001$ (Fig. 1).

Similar results were obtained in the HCT group: in all patients, [Ca^{2+}] and Ca decreased under medication (P<0.001 for both parameters). Slight increases in pH (17/24) and CA (15/24) were observed, whereas changes in pH were statistically significant with P<0.05 (Table 2; Fig. 2).

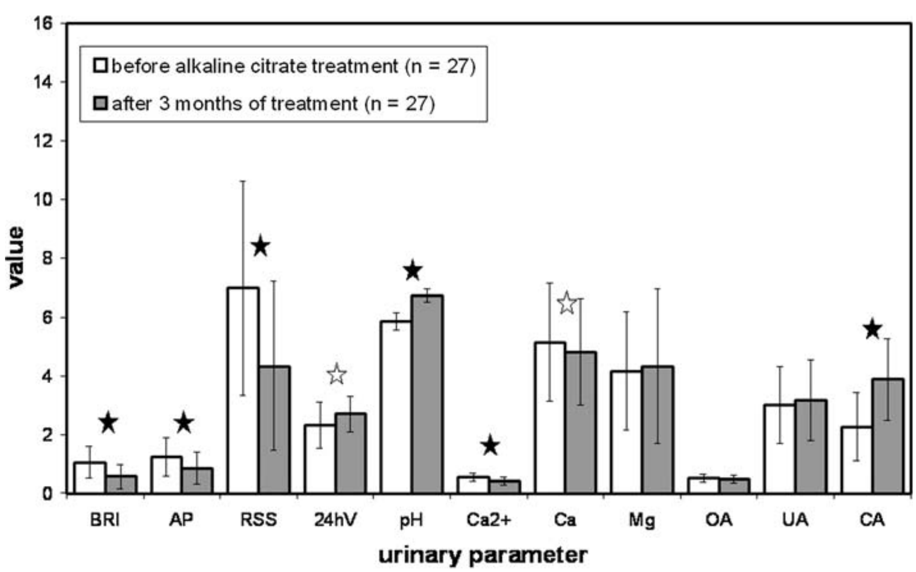

Fig. 1 Results of urinalyses from 24 h urines of recurrent calcium oxalate stone formers with Ca excretions of 5–8 mmol/day, or Ca excretions below 5 mmol/day and pH<6.8, or citrate excretions below 2.5 mmol/day (Table 1) given as mean values ± SD (BRI geometric mean, otherwise arithmetric mean). Risk indices for calcium oxalate crystallization (BRI, AP_{CaOx}, RSS) and urinary parameters with: 24 hV, 24 h urine volume (L); pH, urinary pH; and Ca^{2+}, unbound urinary calcium (mmol/L). *Ca* total calcium, *Mg* magnesium, *OA* oxalic acid, *UA* uric acid, *CA* citric acid [all data in (mmol/d)]. Statistically significant differences are indicated with *black* and *white stars* for $P < 0.01$ and $P < 0.05$, respectively

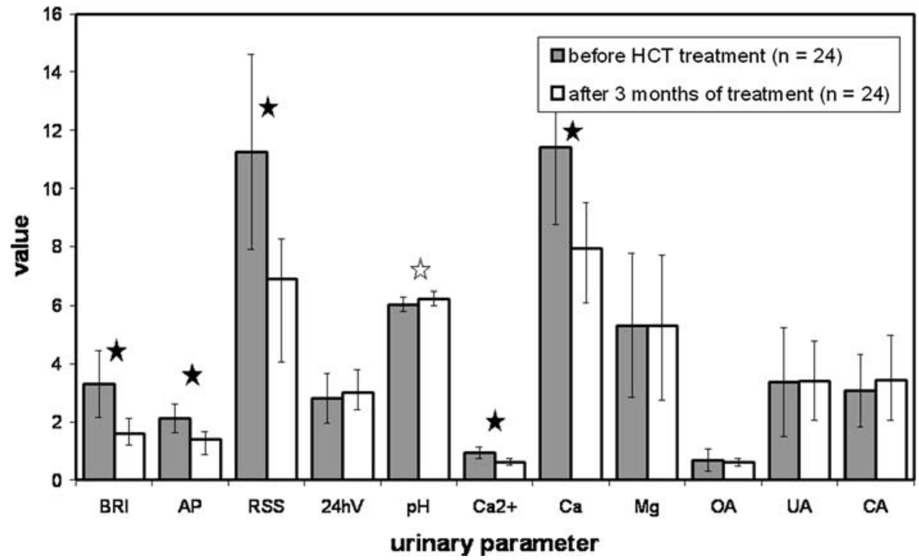

Fig. 2 Results of urinalyses from 24 h urines of calcium oxalate stone formers with Ca excretions exceeding 8 mmol/day (Table 2). Abbreviations, units and symbols, see Fig. 1

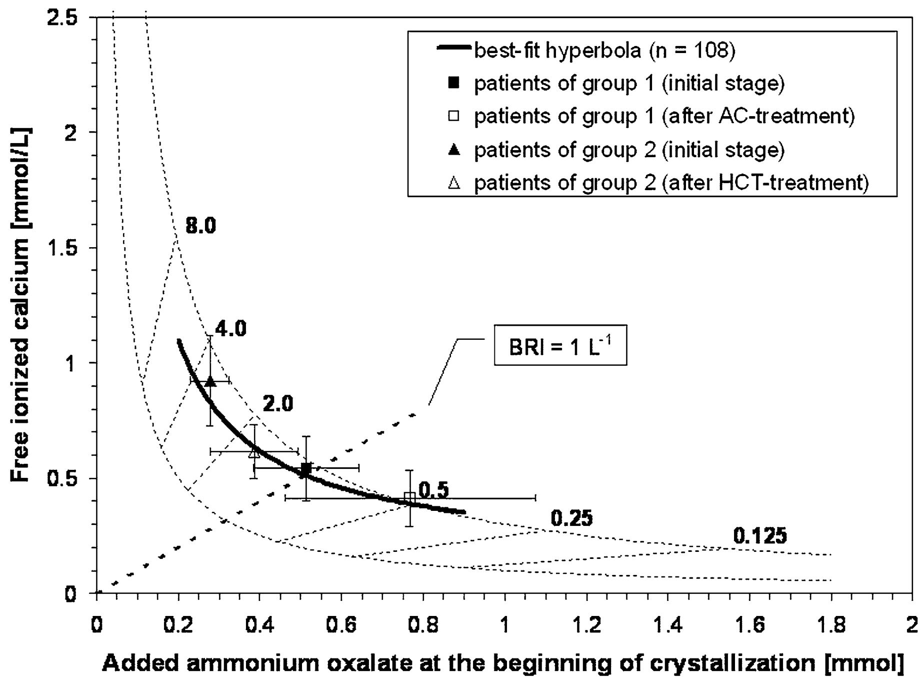

Fig. 3 Mean ± SD [Ca^{2+}] and (Ox^{2-}) values in calcium oxalate stone formers at different stages of treatment, investigated using the Urolizer®. [Ca^{2+}] and (Ox^{2-}) values were hyperbolically related. Calculation of best fit hyperbola from 108 included samples revealed [Ca^{2+}] = 0.1916/(Ox^{2-}) + 0.138 ($r = 0.85$). Values 0.125, 0.25, 0.5, etc. indicate lines of constant BRI. From line to line BRI risk doubled or halved. A BRI of 1 L^{-1} statistically separates calcium oxalate stone formers (BRI > 1 L^{-1}) from healthy subjects or adequately treated patients. Individual data are given in Tables 1 and 2

Discussion

The clinical utility of the easy and rapid-to-determine BRI is conclusively demonstrated in two groups of patients with recurrent CaOx urolithiasis before and during metaphylactic treatment with alkaline citrate and hydrochlorothiazide, respectively.

While the results of AP_{CaOx} and RSS reflect the same tendencies, they are determined with considerably more analytical effort and expenditure of time. Modern concepts of stone metaphylaxis and metaphylaxis control, however, are not only evaluated on their quality, but will also increasingly be benchmarked according to the related costs for the health systems.

Our test results revealed that in the urological outpatient surgery, the pilot-run Urolizer® can be reliably used for diagnosing the metabolic risk of CaOx stone formation according to the BRI method. BRI thereby serves more as a control of metaphylaxis success rather than as a parameter primarily for therapy finding.

By quantifying the "overall" therapy effect of introduced metaphylaxis within 10–15 min, this innovative analysis device may be especially suited for practitioners specializing in urolithiasis treatment. Possibility for urine storage at moderate temperatures without loss of analysis quality further improves applicability of the BRI method [20].

However, as for any analytical method, limitations exist for the Urolizer®. For example, BRI evaluation is less reliable when performed from dimmish urines (e.g. in the course of acute urinary tract infection), or when determined from urines in which previous to BRI measurement crystal formation occurred (e.g. during a too-cold storage).

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Conflict of interest statement None of the authors has any financial interest in the company that makes the product discussed in the article.

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