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ORIGINAL PAPER

Metabolic stress response patterns in urinary compositions of idiopathic calcium oxalate stone formers, patients with chronic bowel diseases and controls

Wolfgang Berg · Sabine Gayde · Christine Uhlemann · Norbert Laube

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Abstract Emotional stress is associated with e.g. increased hormone release, high blood-sugar level and blood pressure. Stress clearly affects metabolism. Whether chronic stress exposure leads to altered urinary compositions with increased risk of CaOx; urolithiasis was examined by investigating the relation between stress burden and urine composition. 29 controls (CG), 29 CaOx stone formers (SF), and 28 patients with chronic inflammatory bowel diseases (CIBD) were advised to avoid unfavorable aliment. Any urolithiasis-related medications were stopped. At day 5, a 24-h urine was collected and comprehensive urinalysis performed. AP (CaOx) index was calculated. Subjects completed a questionnaire designed to measure perceived stress ("Trier-Inventory-of-Chronic-Stress"). Mean AP (CaOx) in CG, SF and CIBD amount to 0.8 ($\pm$0.3), 1.2 ($\pm$0.7), and 1.9 ($\pm$1.2), respectively. Increased AP (CaOx) in SF is mainly attributed to an increased effect of calcium and oxalate, whereas in CIBD this is additionally caused by a reduced effect of citrate, magnesium and volume. Stress dimensions are correlated to any investigated urinary parameter with an absolute value of $r \leq 0.600$; some correlations are statistically significant: whereas in SF only one combination, "lack of social recognition" versus calcium, shows significance, in CIBD various combinations are significantly related. In particular, sodium excretion increases with stress. In CG, some stress dimensions are directly related to citrate; with increasing stress, protection against CaOx crystallization tends to increase. It could be shown that stress load and urinary composition are related by statistical means. The observed metabolic stress response patterns in urinary compositions are different for the distinct groups, thereby, reflecting a conclusive picture. This is in particular in CIBD, for which a link between stress and inflammatory activity and between inflammatory activity and altered urinary composition is well established.

Keywords Risk of stone formation · Stress evaluation · Urinary alteration · Urolithiasis

W. Berg · S. Gayde
Clinic and Polyclinic of Urology,
Friedrich Schiller University Jena, Jena, Germany

C. Uhlemann
Clinic of Internal Medicine, Competence Center "Natural Treatment Methods", Friedrich Schiller University Jena, Jena, Germany

N. Laube (✉)
Deutsches Harnsteinzentrum, Medizinisches Zentrum Bonn, Academic Training Center of the Medical University of Bonn, Friedensplatz 16, 53111 Bonn, Germany
e-mail: n.laube@deutsches-harnsteinzentrum.de

N. Laube
Institute of Thin Film Technology, Kaiserlautern University of Technology, Rheinbreitbach, Germany

Introduction

"Stress" as a disease is a multi-stage disorder with increasing economic impact [1]. Clinically, stress is, inter alia, associated with increased hormone release, increased blood sugar level, heart rate and blood pressure, and weakening of the immune system.

Hormonal, the stress reaction is first of all characterized by an increased secretion of corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH) and cortisol, by the release of catecholamines (e.g. adrenaline, noradrenaline). But also an increased release of other hormones can be observed as a response to stress exposure;

namely, thyroid hormones, antidiuretic hormone (ADH), growth hormone, gluacon and prolactin. Furthermore, stress lowers the excretion of prostaglandins.

Stress influences the gastrointestinal, cardiorespiratory, metabolic, and immune systems. A compact overview of this topic is given in [2].

Chronic stress exposure potentially leads to various acute and chronic disorders, such as chronic exhaustion, chronic hypertension, heart attack and stomach ulcer.

Emotional stress burden, as associated with a disturbed hormone balance, clearly affects metabolism and may, therefore, significantly alter urine composition with the intensity of exposure [3–7]. For example, as cortisol, inter alia, reduces intestinal calcium absorption and thereby affecting bone metabolism, it can increase the renal Ca excretion [2]. In case of long-standing stress exposure, the then prolonged alteration of the urinary Ca concentration may influence an individual's urinary stone formation risk.

Psychological stress is widely believed to play a major role in functional gastrointestinal disorders. There is evidence that psychological stress affects disease activity and causes exacerbation of symptoms of inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease [8–12] both known as serious risk factors of calcium oxalate urolithiasis. In case of chronic disease activity, related intestinal malabsorption of water and electrolytes, e.g. of sodium, potassium, magnesium, citrate and bicarbonate, usually results in reduced urinary concentrations of magnesium and citrate as well as in low urinary pH. In many cases, patients, in particular, those also suffering from colon resection, in addition, show intestinal oxalate hyperabsorption—as a result of a fat malabsorption syndrome with related steatorrhea—and therefore commonly hyperoxaluria. Urinary compositions altered in such way subsequently result in calcium oxalate lithiasis [13–15].

Despite the social impact of stress-related diseases, only scarce data dealing with the influence of negative stressors on the urinary lithogenicity are available [16–22].

The present study investigates whether chronic stress exposure and burden are related to altered urinary compositions with increased risk of CaOx stone formation.

Materials and methods

Study group

The study included 29 controls (CG), 29 recurrent idiopathic CaOx stone patients (SF), and 28 patients suffering from chronic inflammatory bowel diseases (26 Morbus Crohn, 2 idiopathic chronic inflammations, CIBD); currently, 14 of the latter also form CaOx stones. By none of the participants, an acute urinary tract infection was detected.

Based on the inventory questionings and/or medical records, any CIBD patient is indicated by ileum resection (range 20–100 cm) in the past; 4 out of the 14 stone forming ones presented additionally with partial colon resection of, however, unspecified length. During study, none of the CIBD patients suffered from an acute inflammatory episode.

Both patient groups, SF and CIBD, were chosen as they form—or are prone to form—CaOx stones due to quite different pathogenetic mechanisms, each of them presumably with a different degree of stress involvement: Whereas idiopathic stone disease is related to a more complex mechanism involving also renal handling and bone metabolism; stone formation as a consequence of chronic inflammatory bowel disease is exclusively related to dysfunctions of intestinal absorption with the kidney(s) then acting as "innocent bystander(s)".

Table 1 summarizes the epidemiologic characteristics of the investigated groups in detail clearly depicting that in SF, the risk factors of the so-called "metabolic syndrome" (e.g. overweight, diabetes mellitus, cardiovascular disease) occur more frequently than in the other (study) groups.

Prior to urine collection, all participants were kept on a self-choiced western diet which followed the general mainstream behavior. Precarious findings with respect to dietary habits which require acute advice, however, were not observed at any participant. However, they were

Table 1 Statistical key characteristics of investigated groups

Parameter (unit)	CG	SF	CIBD
Number	29	29	28
Sex (male/female)	23/6	25/4	17/11
Age (mean/SD) (years)	54/14	55/12	39/13
BMI (mean/SD) (kg/m^2)	24/4	27/4	23/3
Thyroid dysfunction (%)	3	7	0
Osteoporosis (%)	0	3	36
Diabetes mellitus (%)	3	14	0
Cardiovascular disease (%)	16	32	18
Stone episodes in the past (%)	0	100	32
Renal stone(s) at the time of study (%)	0	55	46
Family history of stone disease (%)	7	41	11
Reported morbid stress (%)	24	76	36

Remarkably, SF showed highest frequency of characteristics associated with the metabolic syndrome. The mean age of the stone formers in the CIBD group amounts to 48 $\pm$ 6.5*a*, an indication of a potentially increasing correlation between age, susceptibility to stress and inflammatory activity and stone formation

BMI body mass index, *CG* control group, *SF* calcium oxalate stone formers, *CIBD* patients suffering from chronic inflammatory bowel disease (predominantly Crohn's disease), *SD* standard deviation

advised to strictly avoid for 5 days aliments and beverages that are known to significantly alter the urinary concentrations of lithogenic components (e.g. spinach, hard cheese) or increase diuresis to an uncommon extent (e.g. coffee). All patients with stone were instructed to pause any stone metaphylaxis-related medications (e.g. alkali citrates, Ca- and Mg-preparations, cortisone). At day 5, a 24-h urine was collected, according to the recommendations of the current German Guidelines on Urolithiasis, in clean and disinfected plastic bottles (2,000 ml) containing 10 ml thymol (5% thymol-isopropanol solution) as a preservative.

Laboratory analysis

Urinary concentrations of Na, K, Ca, Mg, Cl, PO_4, oxalic acid (OA), uric acid (UA), citric acid (CIT), and creatinine, as well as urinary 24-h volume (V) and pH were measured.

Besides the individual interpretation of the urinary concentrations, which represent the physicochemically relevant variables of stone formation, the established urinalysis-based risk index AP (CaOx) for calcium oxalate stone formation was computed. AP (CaOx) requires five urine parameters: 24-h excretions of calcium, oxalate, citrate, magnesium, and V, whereby $AP\ (CaOx) = 1.9\ (Ca^{0.84} \times OA)/(CA^{0.22} \times Mg^{0.12} \times V^{1.03})$ [23]. AP (CaOX) combines the influence of the included promotors (numerator) and inhibitors (denominator) by weighing them in an appropriate manner.

Windows software was used for statistical analysis; a $p < 0.05$ was considered to be statistically significant.

Stress assessment

Subjective stress levels were assessed with a German version of the "Trier Inventory for the Assessment of Chronic Stress" (TICS) [24]. The TICS questionnaire is widely used, and has shown high internal consistency and validity [25–28].

It is a standardized 57-item self-report scale for differentiated assessment of the different specifications of chronic stress. The items were combined to nine dimensions: (1) job overload (jobo); (2) social overload (soco); (3) pressure to succeed (pts); (4) lack of work satisfaction (lws); (5) too much work (tmw); (6) lack of social recognition (lsr); (7) social stress (socs); (8) social isolation (soci); (9) chronic worrying (chrw). Furthermore, a 12-item screening scale for estimating a summing-up measure of sensed stress (sscs) is calculated.

To evaluate stress load, subjects were asked to answer each of the 57 items on a 5-point rating scale regarding how frequently they have experienced specific emotionally stressful situations during the past 3 months.

Linear regressions of urinary concentrations of selected components versus stress dimensions according to the TICS were performed and statistically evaluated.

Results and limitations

Table 2 lists the scores of the different stress dimensions according to the TICS which were observed for each test groups. For each stress dimension, mean, median and standard deviation is given. Statistically significant differences with $p \leq 0.05$ are obtained only between SF and CIBD at stress dimensions "chronic worrying" and "screening scale chronic stress".

Table 3 summarizes the statistical key numbers of lithogenically important urinary excretions of various parameters and AP (CaOx) of each of the test groups and depicts the results of the inter-group comparisons by means of statistical significances.

The renal OA excretions of the control group (0.3 ± 0.1 mmol/day) are significantly lower than those observed in SF (0.5 ± 0.1 mmol/day, $p < 0.01$) and CIBD (0.6 ± 0.4 mmol/day, $p < 0.05$). The latter group (presumably) reflecting the result of intestinal oxalate hyperabsorption which is often found in patients suffering from inflammatory bowel diseases [13, 29]. In fact, 11 out of the 28 CIBD patients are hyperoxaluric (OA > 0.5 mmol/day); from those 14 CIBD patients already forming CaOx stones, nine show hyperoxaluria (OA 0.87 ± 0.37 mmol/day).

Corresponding to the different major risk factors and related aetiopathogenesis of stone formation in SF and in

Table 2 Comparison of the stress burdens of the investigated groups

Group	CG			SF			CIBD		
Dimension	Mean	MD	SD	Mean	MD	SD	Mean	MD	SD
Jobo	10.9	9	8.5	10.9	9	7.3	13.8	14	6.3
soco	9.5	10	5.6	9.8	9	5.7	10.1	11	4.8
pts	15.7	16	7.3	13.2	11	8.4	15.3	15	7.5
lws	7.6	7	3.7	6.9	6	4.8	9.3	10	4.4
tmw	4.8	5	3.0	4.0	4	2.8	5.6	6	3.1
lsr	3.9	4	2.6	4.3	3	3.6	4.1	4	3.1
socs	5.7	6	3.5	5.8	5	4.0	7.5	7	4.4
soci	5.7	5	4.6	4.8	5	3.8	6.5	6	4.1
chrw	5.7	6	3.4	4.9	5	2.8	6.7	7	3.0
sscs	13.6	13	7.7	12.4	11	7.5	17.3	16	6.4

The higher the value, the more pronounced the persons' suffer from the particular stress dimension. Statistically significant differences with $p \leq 0.05$ are obtained only between SF and CIBD at stress dimensions "chrw" and "sscs"

For abbreviations (see text and Table 1)

MD median

Table 3 Selection of lithogenically relevant urinary parameters and AP (CaOx) index for calcium oxalate stone formation for the three test groups

Parameter (unit)	CG		SF		CIBD		*P* value
	Mean	SD	Mean	SD	Mean	SD	
24-h *V* (L)	2.34	0.88	2.57	0.69	1.83	0.74	*b*+, *c*++
pH	6.10	0.74	6.01	0.72	6.02	0.84	*b*+
Ca (mmol/day)	4.78	1.81	6.96	4.10	4.30	2.34	*a*+, *c*+
Mg (mmol/day)	4.86	1.51	5.01	1.58	2.09	1.17	*b*++, *c*++
OA (mmol/day)	0.34	0.12	0.48	0.12	0.57	0.38	*a*++, *b*+
UA (mmol/day)	2.89	0.49	3.79	1.58	2.84	1.37	*a*+, *c*+
CIT (mmol/day)	2.38	1.79	2.50	1.25	1.34	0.98	*b*+, *c*++
AP (CaOx) $(\text{mmol/day})^{1.5}\ \text{L}^{-1.03}$	0.77	0.33	1.23	0.69	1.90	1.20	*a*+, *b*++, *c*+

Furthermore, the results of each urinary parameter of each test group were compared with each other and the related significance levels of the differences are given

Pairs of inter-group comparisons: *a* SF versus CG, *b* CIBD versus CG, *c* SF versus CIBD. Significance levels: +, $p \leq 0.05$; ++, $p \leq 0.01$. For example, the difference in urinary pH is statistically significant between CIBD and CG with $p \leq 0.05$

Abbreviations according to Table 1 and 24-h *V*: 24-h urine volume; *OA* oxalic acid, *UA* uric acid, *CIT* citric acid, *AP* (*CaOx*) urinary ion activity product of calcium oxalate [23]

CIBD, the latter show significantly ($p < 0.05$) lower Ca excretions (4.3 ± 2.3 vs. 7.0 ± 4.1 mmol/day) and UA excretions (2.8 ± 1.4 vs. 3.8 ± 1.6 mmol/day). In addition, the excretions of CIT (1.3 ± 1.0 vs. 2.5 ± 1.2 mmol/day) and magnesium (2.1 ± 1.2 vs. 5.0 ± 1.6 mmol/day) are significantly ($p < 0.01$) lowered in CIBD as compared to SF (Table 3).

Relative to CG, an increased lithogenic risk for SF—and even more clearly for CIBD can be derived from calculating AP (CaOx); as to be expected, the mean AP (CaOx) is lowest in CG and highest in CIBD; the SFs' mean AP (CaOx) lies in between both the groups. The AP (CaOx) of CG is significantly different from that of SF ($p \leq 0.05$) and CIBD ($p \leq 0.01$) (Table 3).

In Fig. 1, the numerator of AP (CaOx) is plotted versus 1/denominator of AP (CaOx) for each of the investigated groups. Here, increasing *y* values indicate an increase in the excretion of promotors of CaOx stone formation, whereas increasing *x* values refer to an increasing lack of inhibitor excretion. Dashed hyperbolae indicate constant AP (CaOx) of, from inside to outside, 0.5, 1.0, 2.0 and 4.0, respectively. Data of SF and, in particular, of CIBD show broader scatter than those obtained from CG. According to the interpretation scheme, stone formation risk in SF is mainly attributed to an increased excretion of promotors with respect to CG. In contrast, increase in AP (CaOx) in CIBD is caused by both increased effect of Ca and, in particular, OA, and lowered excretions of the inhibitory risk factors CIT, Mg and *V* (Table 3); an outcome which coincides well with the intestinal malabsorption patterns from which this patient group commonly suffers. The highest positive linear correlation coefficient observed was 0.600, found at the combination "social stress" and nominator of AP (CaOx) in SF. The lowest negative linear correlation with $r = -0.498$ was obtained at the combination "job overload" and OA concentration in CIBD. The stress dimension "lack of social recognition" showed at any of the investigated groups highest positive correlation coefficients with concentrations of urinary components (CG $r = 0.591$ in CIT, SF $r = 0.370$ in Ca, CIBD $r = 0.544$ in Na). With respect to negative correlations, an unequivocal picture evolves. Here, lowest values were found in CG for the combination "pressure to succeed" versus Mg concentration; in SF and CIBD, the combinations "social overload" versus K and "job overload" versus OA concentration are indicated with the lowest intra-group linear correlation coefficients, with values of −0.363 and −0.498, respectively.

Figure 2 shows the significance levels of correlation coefficients *r* obtained from linear regression of urinary concentrations of selected components versus stress dimensions according to TICS. Significance levels for *r* of $p \leq 0.05$ and $p \leq 0.01$ for $n = 28$ samples (CIBD) are reached at $r \geq 0.374$ and $r \geq 0.479$; for $n = 29$ (CG, SF), these significance levels are already reached at $r \geq 0.367$ and $r \geq 0.471$, respectively.

Whereas in SF only one combination, "lack of social recognition" versus Ca concentration, shows statistical significance, in CIBD, a multitude of combinations are significantly related. In particular, Na concentration is affected by increasing stress perception with positive and significant linear correlations ($0.409 \leq r \leq 0.544$) to six stress dimensions (Fig. 2). However, OA concentration is inversely correlated ($r = -0.498$) to "job overload"; and

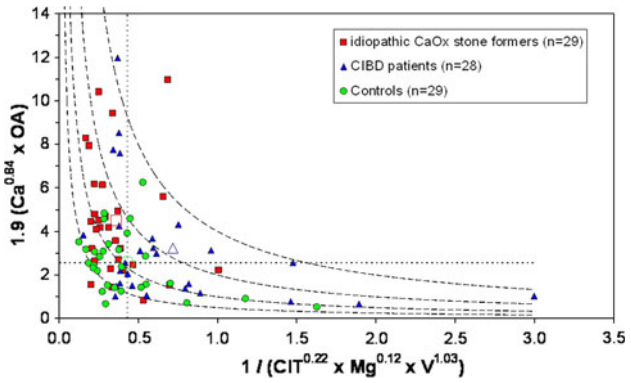

Fig. 1 Plot of numerator of AP (CaOx) versus 1/denominator of AP (CaOx) for the different investigated groups. Increasing *y* values indicate an increase in excretion of promotors of CaOx stone formation, whereas increasing *x* values refer to an increasing lack in inhibitor excretion. *Dashed hyperbolae* indicate constant AP (CaOx) of, from inside to outside, 0.5, 1.0, 2.0 and 4.0, respectively. *Dotted lines* pass through the center (*green open circle*) of the control group's data. *Open red square* and *open blue triangle* mark centers of idiopathic SF and CIBD patients' data, respectively. Ca, OA, CIT, Mg and V: 24-h excretions of calcium, oxalic acid, citric acid and magnesium, and 24-h urine volume (further details, see text)

statistically significant ($p \leq 0.01$). This suggests, contrary to one's expectations, that an increased psychological pressure on the job is not statistically related to an increase in OA concentration. In fact, the opposite occurs.

In controls, the important inhibitor of CaOx formation, CIT, is directly related to four stress levels, i.e. in case of an increasing burden in these stress dimensions, protection against urinary stone formation tends to increase. However, an increase in "pressure to succeed" is significantly related to a decrease in the urinary concentrations of K and Cl, and, unfortunately, also of Mg, an inhibitor of Ca-stone formation.

Figure 3 depicts correlation coefficients calculated from linear regression of the AP (CaOx)'s numerator and reciprocal value of the AP (CaOx)'s denominator versus stress dimensions obtained from TICS sorted by test groups. Obviously, the different groups show different patterns that coincide with the general picture of Figs. 1 and 2. However, correlation coefficients are also "small" ($0.1 \leq r \leq 0.3$) or "medium" ($0.3 \leq r \leq 0.5$) [30], some showing also high statistical significance.

The group of idiopathic CaOx stone formers is indicated by nearly any stress dimension positively correlated to both AP (CaOx) numerator and reciprocal AP (CaOx) denominator. A positive correlation to the AP (CaOx)'s numerator can be interpreted as an increase in the effect of the most pronounced promotors of CaOx stone formation (Ca, OA). However, at increased stress levels, such a correlation to the reciprocal AP (CaOx)'s denominator indicates an overall decrease in the effect of the important inhibitors CaOx stone formation, CIT, Mg, and *V*.

Different pictures evolve in CIBD and CG: most of the stress dimensions show direct correlations to the AP (CaOx)'s numerator, but negative correlations to its reciprocal denominator. A clear indication of a markedly influence of increased stress load at this patient group is not only statistically associated with an increase in promotoric effect of Ca and OA, but also with a counteracting increase in the combined inhibitory effect of CIT, Mg, and *V*.

Discussion

The test groups are indicated by different (mean) urinary compositions as well as by quite different relations between values of stress dimensions and urinary parameters. This is especially shown in Fig. 2 where different metabolic stress response patterns evolve. The highest number of significant correlations ($n = 18$) is observed in

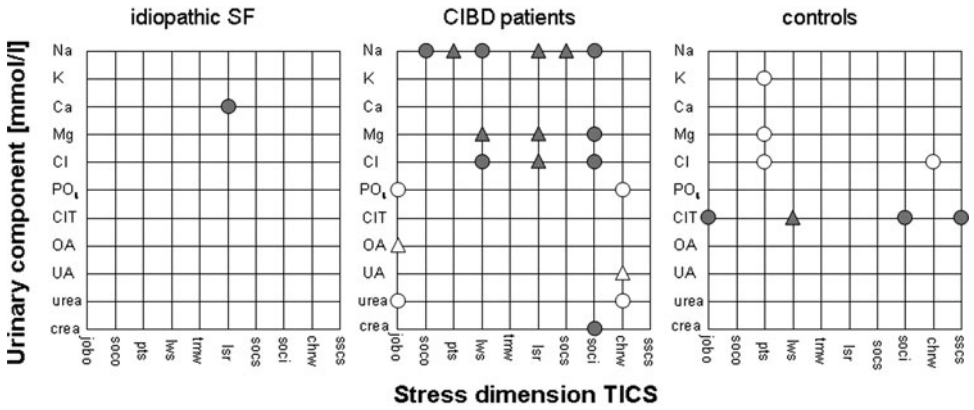

Fig. 2 Plots indicating significance levels of correlation coefficients *r* obtained from linear regression of urinary concentrations of selected components versus stress dimensions according to TICS. *Circles* and *triangles* indicate significance levels for *r* of $p \leq 0.05$ and $p \leq 0.01$, respectively. *Filled symbols* indicate positive correlation, *open symbols* show negative correlations. *CIT*, *OA*, *UA*, and *crea* indicate citric acid, oxalic acid, uric acid and creatinine, respectively (for further abbreviations and details see text)

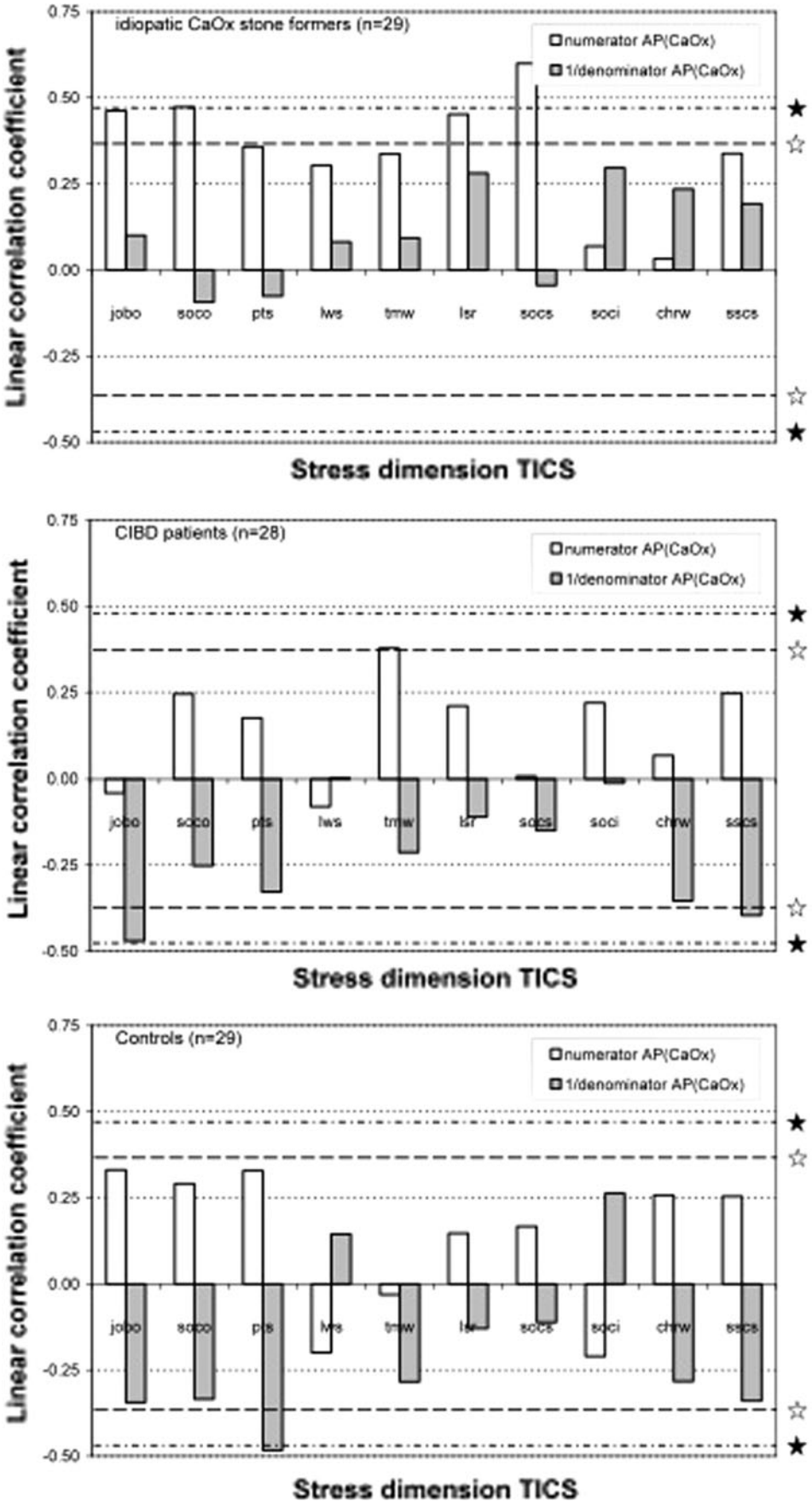

Fig. 3 Correlation coefficients calculated from linear regression of the AP (CaOx)'s numerator and reciprocal value of the AP (CaOx)'s denominator versus values of stress dimensions obtained from TICS, respectively, sorted by groups. Stress dimensions (see Fig. 2). *Lines* marked with *open* and *closed stars* indicate significance levels $p \leq 0.05$ and $p \leq 0.01$, respectively (for further details see text)

CIBD between a value of a particular stress dimension and a concentration of a particular urinary component—eight significant combinations were obtained in CG, but only one in SF.

Even statistically significant on a considerably high level, the obtained linear correlations at all investigated parameter combinations are at best "medium". Therefore, a factual scientific relationship of such a combination is not proved.

It remains difficult to decide, whether stone formation in CIBD is the result of bowel disease prior to stress burden or whether persistent stress elicits in fact bowel disease leading to pathologically altered urine compositions. However, it is remarkable that stress perception is most associated with altered urinary compositions in this patient group; an observation which is in line with the etiological course with respect to CaOx urolithiasis: stress, inflammatory bowel disease, oxalate hyperabsorption and CaOx stone formation [8–12].

It cannot be clarified whether stress is the primary cause of disturbed urinary compositions or whether the observed correlations are only randomly pronounced characteristics in these patients.

The results suggest that urinary alteration due to persistent psychological stress is mainly related to CIBD. In contrast, SF show although characterized by highest frequency of experienced morbid stress (Table 1), no significant data set except for the positive correlation between value of stress dimension "lack of social recognition" and Ca concentration ($p \leq 0.05$). Surprisingly, CG shows a multitude of statistically significant relations between stress perception and urinary component. However, urinary alterations, if any, are generally directed towards compositions which are indicated by the lowest mean AP (CaOx) found in the tested groups. This may be mainly attributed to the CIT concentration which is directly related to increasing values of four stress dimensions (Fig. 2).

Beside the restricted number of participants, a limitation of this study is that although obtaining considerable statistical significances at some combinations of stress dimensions with urinary parameters, the absolute values of the related linear correlation coefficients are small.

Conclusion

The influence of chronic stress on urinary risk factors of stone formation was investigated in three different study groups for the first time using an extensive and validated inventory for the assessment of chronic stress.

The observed patterns of statistical relationships between urinary components and specific stress dimensions make some explanations much more plausible than others. However, a clear causal relationship (or absence of causality) for any of the correlations observed, could not be determined. The occasionally observed high statistical significances for some combinations of stress dimensions and urinary parameters are clear indications of an underlying cause and effect relationship between stress load and alteration of urinary composition. However, this complex relationship is yet to be discovered.

Therefore, examining a patient having stone suffering from emotional stress, the urologist should take into consideration that this emotional load might be a strong, but less aware influential factor in that patient's stone etiology.

However, in CIBD, the number of significant correlations between value of stress dimension and urinary parameters might coincide also with a clinical relevance. Until now separately made observations of a stress-induced increase in intestinal inflammatory activity and of a clear evidence of increased stone formation risk in these patients (e.g. due to increased intestinal oxalate absorption) are in this study for the first time conclusively linked.

References

1. Kalia M (2002) Assessing the economic impact of stress—the modern day hidden epidemic. Metabolism 51:49–53
2. Chrousos GP, Gold PW (1998) Editorial: a healthy body in a healthy mind–and vice versa–the damaging power of "uncontrollable" stress. J Clin Endocrinol Metab 83:1842–1845
3. Vitaliano PP, Scanlan JM, Krenz C, Schwartz RS, Marcovina SM (1996) Psychological distress, caregiving, and metabolic variables. J Gerontol B Psychol Sci Soc Sci 51:290–299
4. Kyrou I, Tsigos C (2007) Stress mechanisms and metabolic complications. Horm Metab Res 39:430–438
5. Tsatsoulis A, Fountoulakis S (2006) The protective role of exercise on stress system dysregulation and comorbidities. Ann NY Acad Sci 1083:196–213
6. Goldsmith RS (1972) Calcium metabolism under stress and in response. Life Sci Space Res 10:87–101
7. Ferrari P (2003) Cortisol and the renal handling of electrolytes. Role in glucocorticoid-induced hypertension and bone disease. Best Pract Res Endocrinol Metab 17:575–589
8. Mawdsley JE, Rampton DS (2006) The role of psychological stress in inflammatory bowel disease. Neuroimmunomodulation 13:327–336
9. Maunder RG, Levenstein S (2008) The role of stress in the development and clinical course of inflammatory bowel disease: epidemiological evidence. Curr Mol Med 8:247–252
10. Gareau MG, Silva MA, Perdue MH (2008) Pathophysiological mechanisms of stress-induced intestinal damage. Curr Mol Med 8:274–281
11. Bitton A, Dobkin PL, Edwardes MD et al (2008) Predicting relapse in Crohn's disease: a biopsychosocial model. Gut 57:1386–1392
12. Bhatia V, Tandon RK (2005) Stress and the gastrointestinal tract. J Gastroenterol Hepatol 20:332–339
13. Worcester EM (2002) Stones from bowel disease. Endocrinol Metab Clin North Am 31:979–999

14. Hoppe B, Leumann E, von Unruh G, Laube N, Hesse A (2003) Diagnostic and therapeutic approaches in patients with secondary hyperoxaluria. Front Biosci 8:437–443
15. McConnell N, Campbell S, Gillanders I, Rolton H, Danesh B (2002) Risk factors for developing renal stones in inflammatory bowel disease. BJU Int 89:835–841
16. Brundig P, Berg W, Schneider HJ (1981) Stress and risk of urolith formation. Urol Int 36:265–273
17. Berg W, Gayde S, Huschke T, Uhlemann C, Laube N (2009) Metabolic stress response patterns in urinary compositions of idiopathic calcium oxalate stone formers, stone formers with chronic bowel diseases and controls. 6th European Lithiasis Society (eULIS) Symposium, Como, Italy. Arch It Urol Androl 81:154–155
18. Diniz D, Schor N, Blay SL (2006) Stressful life events and painful recurrent colic of renal lithiasis. J Urol 176:2483–2487
19. Grases G, Pérez-Castelló JA, Sanchis P et al (2006) Anxiety and stress among science students. Study of calcium and magnesium alterations. Magn Res 19:102–106
20. Najem GR, Seebode JJ, Samady AJ, Feuermann M, Friedmann L (1997) Stressful life events and risk of symptomatic kidney stones. Int J Epidemiol 26:1017–1023
21. Schmucki O, Asper R, Zortea C (1984) Stress and urolithiasis. Urol Int 39:159–164
22. Walters DC (1986) Stress as a principal cause of calcium oxalate urolithiasis. Int Urol Nephrol 18:271–275
23. Tiselius HG (1997) Risk formulas in calcium oxalate urolithiasis. World J Urol 15:176–185
24. Schulz P, Schlotz W, Trierer Inventar zur Erfassung von chronischem Stress (TICS): Skalenkonstruktion, teststatistische Überprüfung und Validierung der Skala Arbeitsüberlastung (1999) The Trier Inventory for the Assessment of Chronic Stress (TICS): scale construction, statistical testing, and validation of the scale work overload. Diagnostica 45:8–19
25. Kudielka BM, Buchtal J, Uhde A, Wüst S (2007) Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. Biol Psychol 74:92–103
26. Pruessner M, Hellhammer DH, Pruessner JC, Lupien SJ (2003) Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. Psychosom Med 65:92–99
27. Nierop A, Bratsikas A, Klinkenberg A, Nater UM, Zimmermann R, Ehlert U (2006) Prolonged salivary cortisol recovery in second-trimester pregnant women and attenuated salivary α-amylase responses to psychosocial stress in human pregnancy. J Clin Endocrinol Metab 91:1329–1335
28. Oltmanns KM, Dodt B, Schultes B et al (2006) Cortisol correlates with metabolic disturbances in a population study of type 2 diabetic patients. Eur J Endocrinol 154:325–331
29. Trinchieri A, Lizzano R, Castelnuovo C, Zanetti G, Pisani E (2002) Urinary patterns of patients with renal stones associated with chronic inflammatory bowel disease. Arch Ital Urol Androl 74:61–64
30. Cohen J, Cohen P, West SG, Aiken LS (2003) Applied multiple regression/correlation analysis for the behavioral sciences, 3rd edn. Lawrence Erlbaum Associates, Hillsdale