Chronic Stress and Calcium Oxalate Stone Disease: Influence on Blood Cortisol and Urine Composition

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OBJECTIVE To evaluate the influence of chronic stress (CS) on urine composition of calcium oxalate (CaOx) stone patients and controls.

METHODS This case-control study enrolled 128 patients during a period of 20 months. The cases were CaOx stone formers with a recent stone episode. Controls were matched by sex and age. Dimensions of CS were evaluated in cases and controls by validated self-report questionnaires measuring stressful life events, perceived stress, anxiety, depression, burnout, and satisfaction with life. Blood and urine samples were collected to determine cortisol levels and urinary composition.

RESULTS More relations between CS dimensions and blood and urine parameters were observed in cases than in controls. In cases, the blood cortisol level was related positively with the number of stressful life events ($P = .03$), intensity of these events ($P = .04$), and anxiety ($P = .04$). In addition, urinary magnesium ($P = .03$) and pyrophosphate ($P = .05$) levels were positively related with satisfaction with life and burnout, respectively. In contrast, urinary magnesium levels were negatively related with perceived stress ($P = .01$), anxiety ($P = .016$), and depression ($P = .03$). In controls, the number of stressful life events and the intensity of stressful life events was related positively with magnesium ($P = .06$, $P = .02$) levels and negatively with blood cortisol levels ($P = .03$, $P = .004$).

CONCLUSION Based on the variation between cases and controls in relations between CS dimensions and biochemical parameters, we hypothesize that CS may trigger a differential biological response in CaOx stone formers and controls, which in turn may promote or protect against CaOx stone formation. UROLOGY 82: 1246–1254, 2013. © 2013 Elsevier Inc.

Nephrolithiasis is a common disorder, with multifactorial causes and a high risk of recurrence.[1] Calcium oxalate (CaOx), the most common type of stone, has been associated with several risk factors, including psychological stress.[2-7] Stress activates the hypothalamic-pituitary-adrenocortical axis, inducing major variations in blood levels of cortisol, aldosterone, and catecholamines.[8] Cortisol can increase urinary calcium excretion by competing with aldosterone at the renal intracellular level or by reducing intestinal calcium absorption, which affects bone metabolism.[8,9] Moreover, animals subjected to continuous stress present metabolic alterations that promote CaOx stone formation.[2]

Chronic stress (CS) is a condition caused by the interaction of several factors in addition to the stressful life event itself; the individual's perception of the event and the secondary emotional effect and physiologic responses are also crucial.[10-12] In fact, specific stressful conditions and the specific way an organism appraises these conditions can elicit distinct emotional and physiologic responses.[10] CS can cause high blood pressure, accumulation of visceral fat secondary to chronic hypercortisolism and insulin hypersecretion, obesity, dyslipidemia, and increased risk of metabolic syndrome, all of which are in turn related to CaOx stone formation.[8] In a previous study,[13] however, we found no significant differences in parameters of CS between CaOx stone formers and controls.

Alterations in urine composition have been related to acute stress, but few studies have evaluated their potential relation to CS.[14] The present study examined the relation between CS and urinary composition and the effect of

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blood cortisol in the population of stone formers and controls included in our previous study.[13]

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Hospital Germans Trias i Pujol, Badalona, Spain. All participants provided their signed informed consent.

Participants

From May 2008 to February 2010, 64 documented CaOx stone formers and 64 healthy subjects, matched for age and sex, were consecutively enrolled in this case-control study. All CaOx stone formers were outpatients in the Hospital Germans Trias i Pujol Department of Urology who had had a stone episode between 1 and 3 months before inclusion in the study. Controls were individuals with no history of stone formation who accompanied other patients (also with no history of stone formation) to the urology department.

CaOx stone composition was confirmed by visual inspection, optic crystallography, and infrared spectrography (Spectrum Bx, Perkin Elmer, Waltham, MA). The absence of stones in controls was confirmed by clinical history and by ultrasound examination of the kidneys using a 2-MHz Sonolines Antares CH4-1 abdominal transducer (Siemens, Erlangen, Germany). Data on medical history, family history, demographic characteristics, and socioeconomic status were collected for all subjects.

Exclusion criteria for cases and controls included age <18 years, pregnancy, history of serious illness, history of duodenal ulcer, osteoporosis or its treatment, morbid obesity (body mass index >40 kg/m^2), bariatric surgery, previous urinary pathology, history of psychiatric disorders, and treatment with drugs that had a lithogenic potential.

Evaluation of CS

Given the need to assess CS from a multidimensional perspective, we used 5 validated self-reporting questionnaires selected by the Research Group on Stress and Health from the Autonomous University of Barcelona School of Psychology and 1 questionnaire created specifically for this study.[13] The questionnaires were completed by cases and controls during their first visit to the Department of Urology.

The Escala General de Apreciación del Estrés (General Scale of Stress Perception)[15] was used to evaluate the number and the perceived intensity of stressful life events. Perceived stress was evaluated using the short Spanish version of the Perceived Stress Scale.[16,17] Anxiety and depression were measured with the Spanish version of the Hospital Anxiety and Depression Scale,[18,19] a screening tool of affective disorders in a hospital environment. Burnout was measured with the Spanish adaptation of the Burnout Measure.[20,21] Overall satisfaction with life was measured with the Spanish adaptation of Satisfaction with Life Scales.[22,23] The questionnaire created specifically for this study measured stress related to a stone episode. Participants were asked to evaluate the perceived threat of the episode and the resources available to them for dealing with the threat.

Furthermore, to estimate those subjects with high stress (HS) and those with a low burden of stress (LS), we create the variable "total stress" from the scores of all questionnaires used.

The participants also completed a semiquantitative questionnaire on food frequency,[24] which recorded the diet for each subject for 1 month, and a questionnaire on exercise patterns. Food composition was calculated using the food composition tables of the Centre d'Ensenyament Superior de Nutrició I Dietética (CESNID) and the CESNID 1.0 computer program to calculate the nutritional composition of the diet.[25]

Biochemical and Clinical Analyses

Blood and nocturnal urine samples were collected once at the start of the study to determine cortisol levels and urinary composition. Fasting blood samples were collected in the morning. Nocturnal urine, which is easy to collect and represents the period of greatest lithogenic risk during any 24-hour period, was collected by the patients the night before the blood extraction and handed in at the time of blood extraction. Two 10-mL aliquots, composed of 7 mL chlorhydric acid (0.05 M) and 3 mL urine, were frozen at −4 to −10°C for further processing. The aliquots were processed within 15 days at the Grupo de Técnicas de Separación (Group of Separation Techniques) at the Autonomous University of Barcelona. Blood cortisol levels were determined with an automated multichannel analyzer. Urine pH was measured with a digital pH meter. Urinary oxalate was determined with ion chromatography. An autoanalyzer was used to determine the urine concentration of calcium, magnesium, creatinine, phosphate, uric acid, and citrate. The concentrations of phytate and pyrophosphate were determined using inductively coupled plasma mass spectrometry (ICP-MS) with a Thermo Elemental PQ-Excel ICP-MS. All concentrations were adjusted for the nocturnal creatinine excretion to avoid the effect of nocturnal urine volume.

Statistical Analyses

Proportions were used for categoric variables and median and range for quantitative variables. The McNemar test was used to explore group differences in categoric variables between CaOx stone formers and matched controls and between HS and LS subjects. Differences in continuous were examined with the Wilcoxon signed rank test and the paired sample t test, as appropriate. A univariate generalized mixed model with random intercepts for each matched set was used to identify the variables associated with case/control status.[26] The dependent variable was defined as the status of the participant, and the independent variable was the level of stress. Odds ratios with their 95% confidence intervals were estimated for each variable potentially related to disease, using the corresponding mixed model. Multivariate linear mixed models were used to estimate the association between stress and lithiasis after adjustment for the multiple confounding variables.[27] Effect modification was assessed by including an interaction term between the stress variable and the covariate of interest. A simple linear regression analysis was used to analyze the potential correlation of cortisol and urine chemistry values with the results of the questionnaires evaluating CS. All P values were 2-sided, and statistical significance was set at $P \leq .05$. All analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC).

RESULTS

From May 2008 to February 2010, 128 subjects (64 documented CaOx stone formers and 64 healthy subjects, matched for age and sex) were consecutively enrolled in this case-control study. Of the 128 subjects, 88 (68.7%) were men, and the median age was 44.5 years (range,

Table 1. Clinical and demographic characteristics of calcium oxalate stone formers compared with matched controls

Variable*	Cases (n = 64)	Controls (n = 64)	*P*
Age (y)	42.5 (19-71)	46.5 (20-74)	.88
Sex			>.99
Male	44 (68.7)	44 (68.7)	
Female	20 (31.3)	20 (31.3)	
Number of life stones events	2.3 (1-20)		
Number of prior surgical procedures			
0	9 (16.6)		
1	27 (50)		
2	8 (14.8)		
3	4 (7.4)		
4	4 (7.4)		
5	1 (1.9)		
6	1 (1.9)		
Age at urolithiasis onset (y)	36 (6-74)		
Family history of urolithiasis			.02
Yes	31 (48.4)	18 (28.1)	
No	33 (51.6)	46 (71.9)	
Body mass index (kg/m^2)	26.1 (17.9-38.3)	26.7 (19.3-36.6)	.77
Hypertension			1
Yes	11 (17.2)	12 (18.3)	
No	53 (82.8)	52 (81.2)	
Hypercholesterolemia			1
Yes	11 (17.2)	11 (17.2)	
No	53 (82.8)	53 (82.8)	
Hyperuricemia			1
Yes	2 (3.1)	2 (3.1)	
No	62 (96.9)	62 (96.9)	
Diabetes			1
Yes	3 (4.7)	3 (4.7)	
No	61 (95.3)	61 (95.3)	
Coronary disease			1
Yes	3 (4.7)	4 (6.2)	
No	61 (95.3)	60 (93.8)	
Metabolic syndrome			.47
Yes	4 (6.2)	4 (6.2)	
No	60 (93.8)	60 (93.8)	
Marital status			.48
Single	12 (18.8)	12 (18.8)	
Married	48 (75)	45 (70.3)	
Divorced	2 (3.1)	6 (9.4)	
Widowed	2 (3.1)	1 (1.6)	
Highest level of education completed			.28
Illiterate			
Literate but no formal education	7 (10.9)	4 (6.3)	
Primary school	20 (31.3)	30 (46.9)	
Technical school	16 (25)	13 (20.3)	
High school graduate	6 (9.4)	10 (15.6)	
University degree	8 (12.5)	4 (6.3)	
Postgraduate studies	6 (9.4)	2 (3.1)	
Other	1 (15.6)	1 (2)	
Employment status			.59
Employed	47 (53.6)	41 (46.4)	
Unemployed	12 (44.4)	15 (55.6)	
Others	5 (0)	8 (100)	
Type of employment contract			.26
Employed	63 (98.4)	62 (96.9)	
Unemployed	0 (0)	2 (3.1)	
Others	1 (1.6)	0 (0)	
Monthly income (€)			.02
<1000	12 (18.8)	5 (7.8)	
1000-2500	32 (50)	49 (76.6)	
>2500	20 (31.2)	10 (15.6)	

* Quantitative variables are presented as median (range) and categoric data as number (%).

Table 2. Scores of controls and calcium oxalate stone formers on questionnaires measuring chronic stress

Questionnaire	Dimension measured	Cases (n = 64) Median (Range)	Controls (n = 64) Median (Range)	Odds Ratio (95% CI)	*P*
EAE-G[14]	Number of stressful life events	18.5 (2-40)	20 (2-45)	0.9 (0.94-1.01)	.21
	Intensity of stressful life events	27 (2-73)	29.5 (3-107)	0.9 (0.96-1)	.29
PSS[15,16]	Perceived stress	23 (6-37)	21 (4-49)	1 (0.97-1.06)	.33
Stress related to stone episode	Stress related to stone episode	11 (6-16)			
HADS[17,18]	Anxiety	7.5 (0-17)	7 (1-21)	1 (0.95-1.12)	.38
	Depression	3 (0-13)	3 (0-14)	0.9 (0.88-1.11)	.97
BM[19,20]	Burnout	52.5 (21-123)	48 (21-119)	0.9 (0.98-1.02)	.66
SWLS[21,22]	Satisfaction with life	20.5 (6-25)	20 (10-25)	1 (0.94-1.12)	.27

BM, Burnout Measure; CI, confidence interval; EAE-G, Escala General de Apreciación del Estrés; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; SWLS, Satisfaction with Life Scales.

19-74 years). Table 1 reports the clinical and demographic characteristics for all subjects. Cases had more family history of lithiasis ($P = .02$) and lower economic levels ($P = .02$) than controls, but no other differences between the 2 groups were observed. Overall, no significant differences between cases and controls were observed in any of the questionnaire scores measuring CS (Table 2). Diet, computed as nutrient intake during the last month, was not significantly different between CaOx stone formers and matched controls.[13]

Table 3 reports the levels of urine components and blood cortisol for cases and controls and for subjects with HS and LS. Cases had higher urine calcium levels than controls ($P = .005$), but no other differences in biochemical parameters were observed. Significant relations between dimensions of CS and biochemical parameters were found more frequently in cases than in controls. Blood cortisol levels in cases were related positively with the number of stressful life events ($P = .03$), intensity of stressful life events ($P = .04$), and anxiety ($P = .05$), whereas urine magnesium and pyrophosphate levels were related positively with satisfaction with life ($P = .03$) and burnout ($P = .05$), respectively. In contrast, urine magnesium levels were inversely related to perceived stress ($P = .01$), anxiety ($P = .016$), and depression ($P = .03$), and urine phosphate levels were inversely related to perceived stress ($P = .08$; Table 4). In controls, the number of stressful life events and the intensity of these events were directly related to levels of urine calcium ($P = .07$, $P = .09$) and magnesium ($P = .06$, $P = .02$) and inversely related to levels of blood cortisol ($P = .03$, $P = .004$). Also in controls, total stress was inversely related to blood cortisol ($P = .03$), whereas this estimate variable was not related with any biochemical parameters in the cases group (Table 4).

COMMENT

CS is associated with an altered hormonal balance that affects metabolism and can significantly alter urine composition. Although there is no complete consensus on how to measure CS, the existence of stressful life events is generally regarded as an objective measure. However, stress depends not only on the number of stressful life events but also on the degree to which these situations are appraised as stressful.[28] In the present study, we investigated other factors involved in CS in addition to stressful life events, such as the intensity of these events, the emotional state of the individual, perceived stress, and life satisfaction. Because no validated Spanish questionnaire exists to evaluate CS on a general level, we used 6 different psychological instruments to measure CS in stone formers and controls. Moreover, in an effort to evaluate potential differences within HS and LS subjects, we created the variable "total stress." Also, besides the standard components related to lithiasis, we evaluated pyrophosphate and phytate levels, both of which are strong inhibitors of CaOx stone formation. Furthermore, to the best of our knowledge, this is the first study to examine the relationship between blood cortisol release and CS in the context of CaOx lithiasis.

A relation between CS and lithiasis was first proposed in 1984 by Schumucki et al,[2] who analyzed the effects of a state of continuous stress in rats that were subjected to repeated electric shocks. During the first days of the experiment, the rats had decreased urinary potassium and magnesium levels. Moreover, as the study continued and the number of stressful events increased, the levels of phosphorous and uric acid also increased. Walters[3] later demonstrated that the epidemiology of CaOx lithiasis was consistent with the hypothesis that stress could be a risk factor and posited an explanation for this association based on neuroendocrine mechanisms.

Recently, Berg et al[14] used the Trier-Inventory-of-Chronic-Stress (TICS), a validated German questionnaire evaluating 9 work-related dimensions of CS, to study the relation between CS and CaOx lithiasis in 3 populations: recurrent stone formers, healthy controls, and patients with chronic inflammatory bowel disease. TICS scores were correlated with urine levels of calcium, magnesium, oxalate, uric acid, and citrate. Cases had higher urine levels of calcium, which correlated positively with "lack of social recognition"; however, no other significant differences between cases and controls in TICS scores or urine composition were observed. Interestingly, more significant correlations were found between

Table 3. Urinary composition and blood cortisol for calcium oxalate stone formers and controls and for subjects with high stress and with low stress

Parameter	Cases (n = 64)	Controls (n = 64)			High Stress (n = 63)	Low Stress (n = 65)		
	Median (Range)	Median (Range)	Odds Ratio (95% CI)	*P*	Median (Range)	Median (Range)	Odds Ratio (95% CI)	*P*
Cortisol (μg/dL)	15.8 (5-37.4)	17.1 (7.6-40.1)	0.97 (0.92-1.03)	.36	16.5 (5-38.9)	17.2 (7.2-40.1)	0.98 (0.94-1.04)	.69
Calcium/creatinine (mg/mg)	0.2 (0.03-0.7)	0.1 (0.03-0.5)	2.5 (1.3-4.7)	.005	0.13 (0.03-0.43)	0.14 (0.03-0.7)	0.15 (0.005-4.64)	.27
Phosphate/creatinine (mg/mg)	0.7 (0.3-2.2)	0.69 (0.2-1.35)	5.1 (0.5-52.7)	.14	0.7 (0.21-2.2)	0.69 (0.28-2.1)	1.01 (0.95-1.06)	.77
Magnesium/creatinine (mg/mg)	67.2 (27.6-187.9)	70 (30.9-166.1)	1 (0.99-1.01)	.8	67.6 (28.2-150.87)	68.34 (27.6-187.9)	0.99 (0.98-1.01)	.39
Urate/creatinine (mg/mg)	0.3 (0-0.7)	0.3 (0.2-1.6)	1.1 (0.07-1.7)	.8	0.3 (0.2-0.7)	0.3 (0-1.6)	0.79 (0.35-1.7)	.58
Citrate/creatinine (mg/mg)	0.3 (0.03-0.9)	0.3 (0.05-1)	0.3 (0.04-2)	.3	0.3 (0.04-1)	0.29 (0.03-1)	1.2 (0.19-7.3)	.8
Oxalate/creatinine (mg/mg)	0.02 (0.002-0.05)	0.02 (0.003-0.2)	0.7 (0.4-1.4)	.7	0.02 (0.002-0.05)	0.02 (0.003-0.2)	0.6 (0.4-1)	.5
Phytate/creatinine (mg/mg)	0.001 (0.0003-0.01)	0.001 (0.0004-0.005)	1.28 (0.6-2.5)	.7	0.001 (0.0003-0.004)	0.001 (0.0004-0.01)	1.2 (0.3-2)	.36
Pyrophosphate/creatinine (mg/mg)	0.003 (0.0001-0.1)	0.003 (0.001-0.01)	0.6 (0.3-1)	.1	0.003 (0.0001-0.02)	0.003 (0.001-0.1)	0.7 (0.2-1)	.27

Abbreviation as in Table 2.

stress burden and urinary alterations in controls than in patients.

In our study, the difference between cases and controls in scores on the questionnaires measuring CS was not significant. Although urine calcium levels were no different between HS and LS subjects, they were higher in cases than in controls (Tables 2 and 3), as has been observed in previous studies.[14] In contrast to the findings by Berg et al,[14] however, significant correlations between stress burden and urinary alterations were found more frequently in cases than in controls (Table 4). In cases, the levels of blood cortisol, which can promote renal calcium excretion, were related positively with the number of stressful life events ($P = .034$) and the intensity of these events ($P = .04$), but no correlations were seen between any stress dimensions and urine calcium levels. Levels of magnesium, a strong inhibitor of CaOx lithiasis, correlated positively with life satisfaction ($P = .03$), but magnesium levels were inversely related to perceived stress ($P = .01$), anxiety ($P = .016$), and depression ($P = .03$). Although a positive association between anxiety and blood cortisol, and between burnout and pyrophosphate was seen, we could not demonstrate it with a level of evidence at $P < .05$. Burnout is a stressful event often related with depression, so we would expect an inverse relation with pyrophosphate, but in case we found a high level of evidence, we could hypothesize that burnout could activate urine pyrophosphate excretion to protect against urolithiasis.

Moreover, instead, monthly incomes, considered a CS factor in itself when located at the highest or the lowest extreme,[28] were located at the extremes in cases, whereas those of controls showed less variation and were located near the median, indicating that having a very low or a very high income may be a risk factor for CaOx formation (Table 1). We could not demonstrate any association between monthly incomes and blood cortisol or urinary parameters in cases or in controls (Table 4).

Few significant correlations were seen in controls between CS dimensions and biochemical parameters; however, the number of stressful life events, the intensity of these events, and "total stress" were inversely related with blood cortisol levels ($P = .03$, $P = .004$, $P = .03$) and the number and intensity of stressful life events were positively related with urinary magnesium levels ($P = .03$, $P = .02$), suggesting that healthy controls have opposite mechanisms of reaction against CS than patients have regarding cortisol blood levels and urinary magnesium. Although a positive relation between the number and the intensity of stressful life events was seen with urine calcium levels, we could not demonstrate it with a statistically significant level. Overall, no significant correlations were seen in cases or controls between stress dimensions and uric acid, citrate, oxalate, pyrophosphate, or phytate in urine.

This study has some limitations, including the relatively small sample size. In addition, it is difficult to define the cause-and-effect relationship between lithiasis and CS. Does CS lead to lithiasis or could a stone episode be

Table 4. Significant relations levels ($P < .1$) between chronic stress, as measured by questionnaires, and levels of urinary components and blood cortisol in cases and controls

	Stressful Life Events									
	Number	Intensity	Perceived stress	Anxiety	Depression	Burnout	Satisfaction With Life	Stress Related to Stone Episode	Monthly Incomes	Total Stress
Cases										
Blood cortisol	0.18 ($P = .03$)*	0.09 ($P = .04$)*		0.37 ($P = .05$)*						
Calcium										
Phosphate			−3.45 ($P = .08$)†							
Magnesium			−1.6 ($P = .01$)†	−2.58 ($P = .016$)†	−3.6 ($P = .03$)†		2.14 ($P = .03$)*			
Uric acid										
Citrate										
Oxalate										
Phytate										
Pyrophosphate						30.9 ($P = .05$)*				
Controls										
Blood cortisol	−0.16 ($P = .03$)†	−0.08 ($P = .004$)†								−0.1 ($P = .03$)†
Calcium	0.002 ($P = .07$)*	0.006 ($P = .09$)*								
Phosphate										
Magnesium	0.64 ($P = .06$)*	0.33 ($P = .02$)*								
Uric acid										
Citrate										
Oxalate										
Phytate										
Pyrophosphate										

Coefficient and *P* values are indicated for each relation. Blank cells indicate no significant relation.
* Indicates a positive relationship.
† Indicates a negative relationship.

the cause of stress? To minimize this we used an ad hoc self-reported questionnaire that evaluated stress related to stone episode, without finding any relation with biochemical parameters. Moreover, although we found a number of significant relations between stress dimensions and biochemical alterations, the absolute values of the linear regression coefficients are small and could be because the magnitude of association is small or because variables' units are very small. Furthermore, it is also difficult to extrapolate our findings to CaOx stone formers in general, because the relations observed in this study may simply be characteristics of our study population. Nevertheless, despite these limitations, the overall greater relation between stress burden and biochemical alterations observed in patients than in controls suggest a different biological response to CS between CaOx stone formers and controls, which in turn may promote or protect against CaOx stone formation and can pave the way for further investigation of this phenomenon.

CONCLUSIONS

Although a clear cause-and-effect relationship between CS and lithiasis cannot be concluded from this study, our findings clearly indicate a relation between stress burden and alterations in urine composition that promote CaOx lithiasis. Based on our findings, we recommend that patient stress levels should be explored during the evaluation of a patient with CaOx lithiasis.

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APPENDIX

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.urology.2013.06.077.

EDITORIAL COMMENT

Mental and emotional stress induced by external or internal stressors, or both, can exert biological effects. Some stress, such as when it is a temporary and acute reaction danger or a problem, is positive. Biological effects in this scenario would enhance one's ability to handle or avert the stressor. Continuous or chronic stress, however, is a negative reaction that may contribute variably and adversely to health. Chronic stress in susceptible individuals may contribute to, worsen, or even cause some conditions, including altered blood pressure, compromised immune status, headaches, cardiovascular problems, aberrant insulin metabolism, worsening of asthma, back pain, and arthritis, gastrointestinal problems, and mood and behavior changes.[1] A role for stress in cancer metastasis is proposed.[2] In certain individuals, stress reduction appears to attenuate disease

effects or decrease disease progression.[3,4] But does this relationship extend to kidney stone formation or to unusually aggressive or more complex stone problems?

A link between chronic stress and urolithiasis is suggested.[5-11] Alterations in urinary risk factors for stones are variably associated in humans and rats.[12-14] Analysis of patients' emotional and mental health factors from these studies have revealed disturbances in areas such as satisfaction with life, anxiety, and perceived stress. Stone formers are reported to have more stressful life events than non–stone formers. Derangements in the health-related quality of life of stone formers, independent of surgical intervention, are known.[15-20] Depression appears more common.[21] But current studies provide no resolution to the question of whether stress contributes to or is a result of kidney stones.

The authors describe a prospective case-control study in which a multidimensional examination of stone patients' stress was conducted, coupled with evaluation of blood and urine biomarkers of stress and calcium oxalate stone risk. Validated psychometric measures were used to measure various aspects of stress, depression, anxiety, and satisfaction with life as well as a measure the authors developed to measure total stress.

Although correlational only, some interesting associations were found, including that blood cortisol was elevated in patients, but not controls, whose number of stressful life events, anxiety, and intensity of stressful life events were high. This is clinically relevant because elevated cortisol could induce calciuria and increase calcium stone risk, although this was not observed in the present study. Urinary magnesium, an inhibitor of calcium oxalate crystals, was lower in stressed patients than in stressed controls. The authors suggest this as evidence that stone formers respond differentially (ie, pathologically) to their stress—with respect to urinary magnesium excretion at least—than do non–stone formers. Another interesting finding was that stone formers exhibited no urinary or cortisol derangements, as related to stress, from a single stone episode, as assessed by a measure the authors developed for the study. This could suggest that between-episode or chronic stress and anxiety may actually be more important for stone risk than isolated or acute stone event–related stress.

Urolithiasis is typically multifactorial in etiology, and in all its variation, rarely has a single cause. But because it is largely multifactorial, the discernment of as many individual manipulatable contributors as possible is desirable. Although not providing a definitive answer to the question, "cause or effect?," this study should stimulate discussion among providers about the effects of patients' emotional health and stress on their stone disease. Even if stress contributes only to the progression or acuity of stone disease and not its etiology, knowledge of specific risks caused or worsened by stress is valuable. Further work in this area could have high clinical relevance, because if stress does indeed play a role in causing or worsening stone disease, then stress reduction in patients at risk for recurrence would be a logical and useful tool in our medical management arsenal.

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REPLY

The Editorial Comment provides an excellent summary of our current knowledge of the relation between stress and disease. That some acute stress reactions are necessary to protect us in dangerous situations is well known. However, when this kind of reaction is maintained continuously over a long period, it can become a risk factor for a variety of chronic illnesses. The objective of our study was to examine a possible link between

chronic stress, measured from a multidimensional point of view, with one specific chronic illness: calcium oxalate (CaOx) stone disease. In addition to the points raised in the Editorial Comment, we would like to mention 2 of the most difficult aspects of our study: how to differentiate between acute and chronic stress at the time of sampling and how to define the cause-and-effect relationship between chronic stress and CaOx stones.

This was a case-control study, and at the time of sampling, there was a risk that we were measuring acute stress suffered by the patients at that moment rather than chronic stress. To minimize this risk, we used several different validated questionnaires to measure all of the areas that are known to contribute to chronic stress at different points in time. We believe that further work in the evaluation of chronic stress in stone patients should focus on the creation of a method able to evaluate all of these areas and time periods through one questionnaire.

As the writer correctly points out, we were unable to define the cause-and-effect relationship between chronic stress and CaOx stone disease. Nevertheless, we did find that CaOx stone formers had a different biochemical response to chronic stress than did matched controls, and our findings clearly indicate a relation between stress burden and alterations in urine composition that promote CaOx lithiasis. For this reason, we recommend that stress levels should be explored during the evaluation of a patient with CaOx lithiasis.

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