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Chronic stress and calcium oxalate stone disease: is it a potential recurrence risk factor?

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Abstract Chronic emotional stress is associated with increased cortisol release and metabolism disorders. However, few studies have evaluated the influence of chronic stress on calcium oxalate (CaOx) stone disease and its recurrence. A total of 128 patients were enrolled in this case-control study over a period of 20 months. All patients were CaOx stone formers with a recent stone episode (<3 months); 31 were first-time stone formers (FS) and 33 recurrent stone formers (RS). Dimensions of chronic stress were evaluated with self-reported validated questionnaires measuring stressful life events, perceived stress, anxiety, depression, burnout and satisfaction with life. An ad hoc self-reporting questionnaire was designed to evaluate stress-related specifically to stone episodes. Blood and urine samples were collected to determine cortisol levels and urinary composition. In addition, epidemiological data, socioeconomic information, diet and incidences of metabolic syndrome (MS) were reported. Overall, no significant differences were observed in the scores of cases and controls on any of the questionnaires dealing with stress. The number ($p < 0.001$) and the intensity ($p < 0.001$) of perceived stressful life events were higher in RS than in FS, but there were no differences between the two groups in other dimensions of stress. RS had higher glucose ($p = 0.08$), uric acid ($p = 0.02$), blood cortisol ($p = 0.01$), and urine calcium levels ($p = 0.01$) than FS. RS also had lower economic levels ($p = 0.02$) and more frequent incidences of MS ($p = 0.07$) than FS. Although no differences were observed in cases and controls among any dimension of chronic stress, the number and intensity of stressful life events were higher in RS than in FS. These differences correlate with variations in blood and urinary levels and with metabolic disorders, indicating an association between chronic stress and risk of recurrent CaOx stone formation.

Keywords Stress · Stone formers · First-time stone formers · Recurrent stone formers · Calcium oxalate

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Introduction

Nephrolithiasis is a common disorder with multifactorial causes and a high risk of recurrence; approximately 50 % of patients will have a second episode in the 5 years following their first episode, although with proper prevention the recurrence rate can be reduced by 50 % [1]. Calcium oxalate (CaOx), the most common type of stone, has been associated with several risk factors, including psychological stress [2–6]. Stress activates the pituitary-adrenocortical axis and sympathetic-adrenal axis, inducing major variations in blood levels of cortisol, aldosterone and catecholamines [6]. Cortisol can increase urinary excretion of calcium either

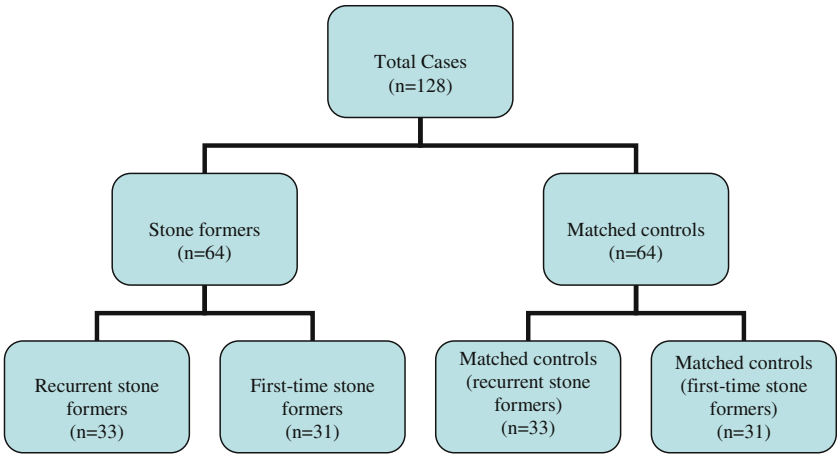

Fig. 1 Summary of patients and controls included in the study

by competing with aldosterone at the renal intracellular level or by reducing intestinal calcium absorption that affects bone metabolism [7, 8]. Moreover, animals subjected to continuous stress present metabolic alterations that promote CaOx stone formation [2].

Chronic stress is a condition caused by the interaction of several factors in addition to the stressful event itself; the individual's perception of the event and the secondary emotional impact and physiological responses are also crucial [9–11]. In fact, specific stressful conditions and the specific way an organism appraises these conditions can elicit distinct emotional and physiological responses [10]. Chronic stress can cause high blood pressure, accumulation of visceral fat secondary to chronic hypercortisolism and insulin hypersecretion, obesity, dyslipidemia and increased frequency of metabolic syndrome (MS), all of which are in turn related to CaOx stone formation [8].

Although several studies have linked stressful life events to stone disease in general [2–6], in the present study, in addition to stressful life events, we have studied other factors involved in chronic stress. Moreover, to the best of our knowledge, no study has examined the role of chronic stress as a risk factor for recurrence of CaOx stones. In light of the dearth of studies in this area, we have evaluated the influence of chronic stress on CaOx stone incidence and recurrence.

Materials and methods

Participants

From May 2008 to February 2010, 64 documented CaOx stone formers and 64 controls, matched for age and gender, were consecutively enrolled in this case-control study. All CaOx stone formers were out-patients in the Urology Department at Hospital Germans Trias i Pujol, Badalona, Spain who had had a stone episode less than 3 months before inclusion in the study. Thirty-one patients were first-time stone formers (FS), and 33 were recurrent stone formers (RS) (Fig. 1). Controls were persons with no history of stones who accompanied patients to visits in the Urology Department for causes not related to stone disease to avoid that they were case relatives.

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

Exclusion criteria for both 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 (BMI) >40], bariatric surgery, previous urinary pathology, history of psychiatric disorders, and treatment with drugs having a lithogenic potential.

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

Evaluation of chronic stress

Given the need to assess chronic stress from a multidimensional perspective, we used five validated self-reporting questionnaires selected by the Research Group on Stress and Health from the School of Psychology at the Autonomous University of Barcelona and one questionnaire created specifically for this study (Table 1). The questionnaires were completed by subjects and controls during their first visit to the Urology Department.

The Escala General de Apreciación del Estrés (EAE-G; general scale of stress perception) [12] was used to evaluate the number and the perceived intensity of stressful life

Table 1 Questionnaires used to measure chronic stress in 64 stone formers and 64 matched controls

Dimension measured	Questionnaire	Reliability A	No. of items	Scale	Range of final score	Created by	Adapted for a Spanish population by
Stress							
Number of stressful life events	Escala general de apreciación del estrés (EAE-G)	0.74	54	0–3	0–54	Fernández-Seara et al. [12]	Fernández-Seara et al. [12]
Intensity of stressful life events					0–162		
Perceived stress	Perceived stress scale (PSS)	0.81	14	0–4	0–56	Cohen et al. [13]	Remor et al. [14]
Stress related to stone episode[a]	Stress related to stone episode	–	5	1–4	5–20	–	–
Emotional status							
Anxiety	Hospital anxiety and depression scale (HADS)	0.86	14	0–3	0–21	Zigmond and Snaith [15]	Tejero et al. [16]
Depression					0–21		
Burnout	Burnout measure (BM)	0.8	21	1–7	21–147	Pines and Aronson [17]	Fernández Castro et al. [18]
Satisfaction with life							
Satisfaction with life	Satisfaction with life scales (SWLS)	0.84	5	1–7	5–35	Diener et al. [19]	Atienza et al. [20]

[a] Designed specifically for the present study (see Supplement)

events. Perceived stress was evaluated using the short Spanish version of the perceived stress scale (PSS) [13, 14]. Anxiety and depression were measured with the Spanish version of the hospital anxiety and depression scale (HADS) [15, 16], a screening tool of affective disorders in a hospital environment. Burnout was measured with the Spanish adaptation of Burnout measure (BM) [17, 18]. Overall satisfaction with life was measured with the Spanish adaptation of satisfaction with life scales (SWLS) [19, 20]. 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 (Supplement 1).

In addition, the participants also completed a questionnaire on physical exercise (Supplement 2) and one on food frequency created and validated by Willet et al. [21] that recorded the diet for each subject over a period of 1 month.

Biochemical and clinical analyses

Blood and eight 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, as it is easy to collect and represents the period of greater lithogen risk during 24 h, was collected by the patients the night before the blood extraction and handed in at the time of blood extraction.

Serum chemistry studies (glucose, protein, creatine, sodium, potassium, chloride, uric acid, calcium, magnesium, phosphorous, cortisol, parathormone, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) were performed using 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 concentration of calcium, magnesium, creatinine, phosphate, uric acid, and citrate. All concentrations were adjusted for the nocturnal creatinine ratio.

Metabolic syndrome was defined according to the criteria of the American Heart Association and the National Heart, Lung and Blood Institute [22].

Statistical analysis

Proportions were used for categorical variables and median and range for quantitative variables.

Differences between cases and control subjects on the continuous variables were examined with the Wilcoxon signed rank test and the paired sample *t* test, as appropriate univariate generalized mixed model with random intercepts for each matched set used to identify the variables associated with case/control status [24]. The dependent variable was defined as the status of the participant (case vs. control), and the independent variable was the level of stress. Odds ratios (OR) with their 95 % confidence intervals (CIs) were estimated for each variable potentially related to disease, using the corresponding mixed model. Multivariate lineal

mixed models were used to estimate the association between stress and lithiasis after adjustment for the multiple confounding variables [25]. Effect modification was assessed by including an interaction term between the stress variable and the covariate of interest in the model.

The different subgroups of cases (FS and RS) were compared with the χ^2 test or Fisher's exact test. Medians were compared with the non-parametric Wilcoxon or Kruskal–Wallis test. OR with their 95 % CIs were estimated using the corresponding mixed model. All p-values were two-sided. Statistical significance was set at $p \leq 0.05$ All analyses were performed using the SAS statistical package version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Table 2 shows the clinical and demographic characteristics for all subjects. Of the 128 subjects, 88 (68.7 %) were males. The median age was 44.5 years (range, 19–74). Cases had more family history of lithiasis, but no other differences between cases and controls were observed. There were no differences in gender, age, family history of stones, history of metabolic disease, physical exercise or BMI between FS and RS. However, RS had a lower age at onset of urolithiasis ($p = 0.02$), more history of hypercholesterolemia ($p = 0.03$), lower economic levels ($p = 0.02$), and a higher incidence of MS ($p = 0.07$). No differences were seen in food or beverage intake between RS and FS (Table 3).

Overall, no significant differences were observed in the scores of cases and controls on any of the questionnaires dealing with stress (Table 4). However, a higher number of stressful life events ($p < 0.001$) and a greater perceived intensity of these events ($p < 0.001$) were reported by RS than by FS. No other differences were observed between RS and FS, including stress related to a stone episode (Table 4).

Higher levels of glucose ($p = 0.08$), uric acid ($p = 0.02$), blood cortisol ($p = 0.01$), and urine calcium ($p = 0.01$) were observed in RS than in FS (Table 5).

Discussion

We have used six different psychological instruments to measure chronic stress in controls and stone formers and found that RS had a higher number and greater intensity of stressful life events than FS, while overall there was no difference between patients and controls.

Although there is no complete consensus on how to measure chronic stress, 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 [23]. In the present study, in addition to stressful life events, we have studied other factors involved in chronic stress, such as the intensity of these events, the emotional state of the individual, perceived stress and life satisfaction.

To evaluate the influence of stressful life events on CaOx stone recurrence, we used the EAE-G, which measures both the number (objective measure) and the perceived intensity (subjective measure) of these events. While other studies have measured the number of stressful life events and found that stone formers have a higher number than controls [4, 5], the present study is the only work to date that has considered both the number and the intensity of these events in relation to CaOx stones. Unlike previous studies [4, 5], we found no differences between controls and stone formers. This disparity may be attributed to the inclusion of the variable of intensity of stressful events or to patient selection, type of questionnaire or the population studied. For example, our study included only patients with confirmed CaOx stones, whereas the previous studies included patients with any previous stone episode and thus may have included patients with uric acid or struvite stones, which may have skewed the results.

Although stressful life events, as measured by the social readjustment rating scale, have been associated with recurrent renal colic [24], to the best of our knowledge, no previous study has investigated chronic stress specifically as a risk factor for CaOx stone recurrence. We have found that RS had more stressful life events with greater intensity than FS. Moreover, the range of scores reported by FS was much wider than those reported by RS, leading us to speculate that FS reporting the higher scores may well be likely to have recurrent stone episodes in the near future.

These findings could lead us to conclude that chronic stress causes nephrolithiasis, but the reverse could also be true, that patients with recurrent stones experience higher levels of chronic stress, especially within 3 months of their treatment. However, there was no difference between RS and FS in reported stress related to a stone episode, leading us to rule out this second possibility.

Numerous studies have shown that the cumulative perception of stress can predict chronic health problems [25]. However, only two previous studies have examined the relationship between perceived stress and urolithiasis. The first assessed the relationship between anxiety and perceived stress secondary to an acute stress situation, but found no correlation between perceived stress and the formation of kidney stones [6]. The second measured perceived stress over a 3-month period using the trier inventory for the assessment of chronic stress (TICS) in recurrent CaOx stone formers, controls and patients with

Table 2 Clinical and demographic characteristics of 128 subjects included in the study

Variable	Cases versus controls			FS versus RS			
	Cases $N = 64$ N (%)	Controls $N = 64$ N (%)	p	FS $N = 31$ N (%)	RS $N = 33$ N (%)	Odds ratio (95 % CI)	p
Sex							
Male	44 (68.7)	44 (68.7)	1	19 (61.3)	25 (75.8)	1.9 (0.7–5.8)	0.28
Female	20 (31.3)	20 (31.3)		12 (38.7)	8 (24.2)		
Family history of urolithiasis							
Yes	31 (48.4)	18 (28.1)	0.02	14 (45.2)	17 (51.7)	0.77 (0.3–2.1)	0.62
No	33 (51.6)	46 (71.9)		17 (54.8)	16 (48.5)		
Hypertension							
Yes	11 (17.2)	12 (18.3)	1	4 (12.9)	7 (21.2)	0.55 (0.1–2.1)	0.38
No	53 (82.8)	52 (81.2)		27 (87.1)	26 (78.8)		
Hypercholesterolemia							
Yes	11 (17.2)	11 (17.2)	1	2 (6.5)	9 (27.3)	0.19 (0.04–0.9)	0.03
No	53 (82.8)	53 (82.8)		29 (93.5)	24 (72.7)		
Hyperuricemia							
Yes	2 (3.1)	2 (3.1)	1	0 (0)	2 (6.1)		0.17
No	62 (96.9)	62 (96.9)		31 (100)	31 (93.9)		
Diabetes							
Yes	3 (4.7)	3 (4.7)	1	1 (3.2)	2 (6.1)	0.52 (0.04–6)	0.59
No	61 (95.3)	61 (95.3)		30 (96.8)	31 (93.9)		
Coronary disease							
Yes	3 (4.7)	4 (6.2)	1	1 (3.2)	2 (6.1)	0.5 (0.04–5.8)	0.57
No	61 (95.3)	60 (93.8)		30 (96.8)	31 (93.9)		
Metabolic syndrome							
Yes	4 (6.2)	4 (6.2)	0.47	0 (0)	4 (12.1)	0.28 (0.07–1)	0.07
No	60 (93.8)	60 (93.8)		31 (100)	29 (87.9)		
Marital status							
Single	12 (18.8)	12 (18.8)	0.48	8 (25.8)	4 (12.1)	0.54 (0.2–1.4)	0.3
Married	48 (75)	45 (70.3)		22 (70.9)	26 (78.8)		
Divorced	2 (3.1)	6 (9.4)		0 (0)	2 (6.1)		
Widowed	2 (3.1)	1 (1.6)		1 (3.3)	1 (3)		
Highest level of education completed							
Illiterate	–	–	0.28	–	–	1 (0.7–1.4)	0.95
Literate but no formal education	7 (10.9)	4 (6.3)		3 (9.7)	4 (12.1)		
Primary school	20 (31.3)	30 (46.9)		9 (29)	11 (33.3)		
Technical school	16 (25)	13 (20.3)		9 (29)	7 (21.3)		
High school graduate	6 (9.4)	10 (15.6)		3 (9.7)	3 (9.1)		
University degree	8 (12.5)	4 (6.3)		4 (12.9)	4 (12.1)		
Post-graduate studies	6 (9.4)	2 (3.1)		3 (9.7)	3 (9.1)		
Others	1 (15.6)	1 (2)		0 (0)	1 (3,100)		
Employment status							
Employed	47 (53.6)	41 (46.4)	0.59	23 (74.2)	23 (69.7)	0.92 (0.7–1.3)	0.68
Unemployed	12 (44.4)	15(55.6)		7 (22.6)	7 (21.2)		
Others	5 (0)	8 (100)		1 (3.2)	3 (9.1)		

Table 2 continued

Variable	Cases versus controls			FS versus RS			
	Cases $N = 64$ N (%)	Controls $N = 64$ N (%)	p	FS $N = 31$ N (%)	RS $N = 33$ N (%)	Odds ratio (95 % CI)	p
Type of employment contract							
Employed	63 (98.4)	62 (96.9)	0.26	30 (96.8)	33 (100)	1.08 (0.6–1.9)	0.12
Unemployed	0 (0)	2 (3.1)		–	0 (0)		
Others	1 (1.6)	0 (0)		1 (3.2)	–		
Monthly income (€)							
<1,000	12 (18.8)	5 (7.8)	0.02	2 (6.5)	10 (30.3)	0.84 (0.5–0.9)	0.02
1,000–2,500	32 (50)	49 (76.6)		21 (67.7)	11 (33.3)		
<2,500	20 (31.2)	10 (15.6)		8 (25.8)	12 (36.4)		
Age							
Median (range)	42.5 (19–71)	46.5 (20–74)	0.88	46 (20–74)	47 (26–70)	0.54 (0.2–1.4)	0.33
Age at onset of urolithiasis							
Median (range)	36 (6–74)	–	–	46 (20–74)	32 (6–69)	1 (0.8–1)	0.02
Exercise							
Yes	41 (64.1)	39 (60.9)	1.74	20 (64.5)	21 (63.6)	0.96 (0.35–2.67)	0.94
No	23 (35.9)	25 (39.1)		11 (35.5)	12 (36.4)		
BMI (kg/m^2)							
Median (range)	26.1 (17.9–38.3)	26.7 (19.3–36.6)	0.77	25.7 (17.9–36.3)	27.5 (18.6–38.3)	0.93 (0.8–1.04)	0.15

inflammatory bowel disease. No differences were observed between RS and controls, but a significantly higher perceived stress was reported in patients with inflammatory bowel disease compared to RS [26]. In the present study, there were no differences in perceived stress between FS and RS or between stone formers and controls. Evidence to date thus indicates that despite the association between perceived stress and other chronic diseases [25], such a relation does not exist in recurrent CaOx stone formation.

Although anxiety and depression, burnout and dissatisfaction with life are common factors in many diseases [15–20], in the present study, we found no correlation between these factors and the formation of CaOx stones. Continuous stress causes tension, and if this tension is maintained, it may lead to burnout [24], or long-term exhaustion and diminished interest. In contrast to a previous study, which found differences in burnout between stone formers and controls [25], we observed no differences in the present study either between RS and FS or between stone formers and controls.

Low socioeconomic status may be a very important stressor and could be associated with chronic activation of the stress response. Despite this, an increased incidence of urinary calculi, with a higher prevalence of CaOx stones, has been reported in individuals with a higher socioeconomic level, including surgeons, pilots and company executives [23, 27]. Moreover, in animal societies where the pattern of dominance undergoes continuous change, higher cortisol levels are found in animals at the apex and at the base of the pyramid [23]. In the present study, the monthly incomes—understood as a surrogate of economic level—of RS were located at the lowest and highest extremes, while those of FS showed less variation and were located near the median, indicating that having either a very low or a very high income may be a risk factor for CaOx recurrence.

Previous studies of stress in stone formers did not correlate stress with metabolic or biochemical parameters [4, 5]. Interestingly, however, we have observed higher blood cortisol and urinary calcium levels in RS than in FS, as well as a greater number and intensity of stressful life events. The higher cortisol and calcium levels in RS may well constitute a potential biological response to these events although they may not be linked to stress alone. Chronic stress stimulates glucocorticoids and neuropeptide Y, leading to obesity and metabolic syndrome. Some mood diseases, including anxiety and depression, also lead to less exercise and metabolic syndrome [28, 29]. In order to control for these factors, we have evaluated them with questionnaires on food frequency and physical exercise; however, we found no differences between RS and FS.

RS also had a higher incidence of hypercholesterolemia and higher levels of uric acid, cholesterol and triglycerides than FS, despite the fact that no differences in diet between the groups were observed. These biochemical alterations have been associated with MS, which has in turn been

Table 3 Nutritional intake of FS and RS

Parameter	Cases vs controls			FS vs RS			
	Cases $N = 64$ median (range)	Controls $N = 64$ median (range)	p	FS $N = 31$ median (range)	RS $N = 33$ median (range)	Odds ratio (95 % CI)	p
Energy (Kcal)	2,478.8 (721.7–7,188.9)	2,623.1 (1,356.9–4,991.3)	0.86	2,475.2 (721.7–6,266.4)	2,482.4 (396.4–7,188.9)	1 (0.99–1)	0.99
Water (g)	3,502 (1,936–8,440)	3,509 (1,266–8,547)	0.93	3,428 (2,144–5,612)	3,692 (1,936–8,440)	1 (0.99–1)	0.31
Total protein (g)	132.1 (52.6–293.3)	135.8 (54.5–229.7)	0.62	139.7 (52.6–293.3)	125.5 (74.8–221.5)	1 (0.99–1)	0.42
Vegetal protein (g)	33.7 (10.5–86.2)	32.2 (15.8–73.5)	0.98	33 (10.5–56.3)	35.2 (18.9–86.2)	1.01 (0.99–1.02)	0.64
Animal protein (g)	105.1 (42.1–247.8)	101.3 (35.1–189.4)	0.58	109.9 (42.1–247.8)	93.2 (52.9–142.1)	0.98 (0.94–1.02)	0.29
Lipids (g)	99.7 (23.9–308.3)	98.2 (38.3–207.1)	0.43	102.6 (23.9–308.3)	95.5 (49.9–217.3)	1 (0.99–1.01)	0.79
Saturated fats (g)	37 (9.5–124.2)	36.4 (13.9–99.1)	0.29	37.3 (9.5–124.2)	36.8 (15.4–78.2)	1.01 (0.9–1.03)	0.8
Monounsaturated fats (g)	39.4 (8.7–116.1)	37.9 (12.7–76.2)	0.34	39.3 (8.7–116.1)	39.48 (19.3–97.5)	1 (0.97–1.03)	0.93
Polyunsaturated fats (g)	15.4 (3.3–41.9)	15.5 (5.4–32.7)	0.29	16.2 (3.3–41.9)	14.4 (7.4–28.9)	1.03 (0.96–1.1)	0.52
Cholesterol (mg)	438.9 (187.3–1,111.1)	425.6(154.9–1,018.5)	0.37	517.9 (191.3–1,111.1)	424.5 (187.3–708.6)	1 (1–1.01)	0.06
Carbohydrates (g)	252.5 (73.9–1,068.1)	253.4 (86.1–655.1)	0.75	254.8 (73.9–569.9)	241.3 (127.8–1,068.1)	0.99 (0.99–1)	0.86
Digestible sugars (g)	125.4 (11.3–833.9)	132.4 (25.3–368.4)	0.54	121.6 (11.3–351.3)	129.7 (51.36–833.9)	0.99 (0.99–1)	0.44
Polysaccharides (g)	115.1 (40.2–238.9)	126.7 (47.4–383.8)	0.87	118.3 (40.2–238.9)	113.1 (42.5–231.1)	1.001 (0.99–1.01)	0.62
Fiber (g)	32.9 (4.9–114.3)	29.9 (12.1–70.4)	0.68	27.8 (4.9–54.1)	33.4 (12.9–114.3)	0.97 (0.94–1.01)	0.29
Ethanol (mg)	4.1 (0–26.8)	4.8 (0–51.3)	0.61	3.1 (0–25.1)	5.5 (0–26.8)	0.94 (0.9–1.02)	0.3
Sodium (mg)	3,188.1 (740.9–9,724.4)	3,187.1 (1,103.8–8,048.9)	0.84	3,527.98(740.9–9,235)	3,062 (1,481.9–9,724.4)	1 (0.99–1)	0.95
Potassium (mg)	4,481 (703.1–15,306.5)	4,869.2 (2,029.2–8,793.2)	0.76	4,289.6 (703.1–8,181.9)	4,994.5 (2,326.1–15,306.5)	1 (0.99–1)	0.83
Calcium (mg)	1,091.9 (234.9–3,388.7)	1,105.6 (365.3–2,155.6)	0.65	977.3 (234.9–2,806.1)	1,140.3 (482.7–3,388.7)	1 (0.99–1)	0.19
Magnesium (mg)	423.3 (117–1,244.9)	437.05 (198.2–908.5)	0.94	421.4 (117–698.8)	425.3 (251.1–1,224.9)	0.99 (0.99–1)	0.71
Phosphorous (mg)	1,892.5 (594.6–4,152.1)	1,892.5 (594.6–4,152.1)	0.99	1,886.6 (594.6–4,152.1)	1,900.8 (1,096.1–3,963.8)	1.01 (0.93–1.1)	0.86
Iron (mg)	17.41 (5.3–44.4)	18.6 (8.8–35.2)	0.64	18.1 (5.3–35.1)	16.6 (10.6–44.4)	1.01 (0.93–1.1)	0.43
Zinc (mg)	14.3 (4.4–30.7)	14.2 (5.5–30.6)	0.52	14.6 (4.4–30.4)	13.6 (7.3–30.7)	1.02 (0.92–1.2)	0.52
Vitamin A (mcg e.r.)	1,386.5 (100.8–4,384.2)	1,364.2 (289.5–3,745.9)	0.75	1,244.6 (100.8–4,384.2)	1,412.9 (373.9–3,659.7)	1 (0.99–1)	0.39
Retinoids (mcg)	377.9 (92.8–3,221.8)	365.5 (109.8–26,662.5)	0.43	348.6 (92.8–3,221.8)	398.3 (114.6–2,483.8)	1 (0.99–1)	0.59
Carotenoids (mcg)	4,973.1 (47.9–16,657.1)	5,043.1 (602.6–13,416.8)	0.51	4,356.3 (47.9–14,330.5)	5,522.3 (1,164.3–16,657.1)	1 (0.99–1)	0.23
Vitamin D (mcg)	7.25 (0.64–35.5)	6.76 (1.22–32.9)	0.86	7.9 (0.64–35.5)	6.73 (2.04–28.8)	1.03 (0.96–1.1)	0.51
Vitamin E (mg e.t.)	11.8 (0.6–42)	12.2 (4.8–33.6)	0.78	11.7 (0.6–25.5)	11.8 (4.3–42)	0.98 (0.9–1.06)	0.86
Vitamin B1 (mg)	2.03 (0.5–5.2)	2.12 (0.9–4.3)	0.57	2.1 (0.5–5.2)	1.98 (0.99–3.8)	1.38 (0.7–2.5)	0.3
Vitamin B2 (mg)	2.49 (0.6–6.2)	2.58 (0.2–4.7)	0.66	2.5 (0.6–6)	2.5 (1.1–6.2)	0.99 (0.6–1.6)	0.94
Niacin (mg)	32.9 (11.2–73.5)	33.1 (13.3–62.6)	0.71	33.1(11.2–73.5)	32.1 (17.7–58)	1.02 (0.97–1.01)	0.45
Vitamin B6 (mg)	3.02 (0.9–8.7)	3.1 (1.3–5.8)	0.98	2.9 (0.9–6.4)	3.2 (1.7–8.7)	1.07 (0.7–1.6)	0.5
Folic acid (mcg)	453.9 (38.7–1,343.1)	475.2 (145.9–981.6)	0.93	447.9 (38.7–915.5)	459.9 (206.5–1,343.1)	1 (0.99–1)	0.98
Vitamin B12 (mcg)	10.3 (3.2–27.7)	10.2 (3.9–30.3)	0.76	10.3 (3.2–27.7)	10.5 (4.9–24.8)	1.02 (0.95–1.1)	0.5
Vitamin C (mg)	241.8 (7.6–940.1)	244.4 (24.1–711.6)	0.43	184.3 (7.6–725.8)	248.4 (69.6–940.1)	0.99 (0.99–1)	0.31

e.r. equivalents of retinol, *e.t.* equivalents of tocopherol

Table 4 Scores of controls and stone formers and of FS and RS on questionnaires measuring chronic stress

Questionnaire	Dimension measured	Cases vs controls				FS vs RS			
		Cases $N = 64$ median (range)	Controls $N = 64$ median (range)	Odds ratio (95 % CI)	p	FS $N = 31$ median (range)	RS $N = 33$ median (range)	Odds ratio (95 % CI)	p
Stress									
EAE-G [12]	Number of stressful life events	18.5 (2–40)	20 (2–45)	0.9 (0.94–1.01)	0.21	13 (2–40)	21 (10–40)	0.89 (0.8–0.9)	<0.001
	Intensity of stressful life events	27 (2–73)	29.5 (3–107)	0.9 (0.96–1)	0.29	23 (2–64)	35 (13–73)	0.95 (0.92–0.98)	<0.001
PSS [13, 14]	Perceived stress	23 (6–37)	21 (4–49)	1 (0.97–1.06)	0.33	23 (2–64)	24 (11–35)	0.95 (0.88–1.03)	0.19
Stress related to stone episode	Stress related to stone episode	11 (6–16)	–	–	–	11 (7–15)	11 (6–16)	0.9 (0.62–1.74)	0.5
Emotional status									
HADS [15, 16]	Anxiety	7.5 (0–17)	7 (1–21)	1 (0.95–1.12)	0.38	8 (2–17)	7 (0–17)	0.05 (0.12–0.73)	0.73
	Depression	3 (0–13)	3 (0–14)	0.9 (0.88–1.11)	0.97	4 (0–13)	3 (0–12)	0.95 (0.81–1.12)	0.67
BM [17, 18]	Burnout	52.5 (21–123)	48 (21–119)	0.9 (0.98–1.02)	0.66	53 (23–123)	52.5 (21–89)	1 (0.97–1.03)	0.93
Satisfaction with life									
SWLS [19, 20]	Satisfaction with life	20.5 (6–25)	20 (10–25)	1 (0.94–1.12)	0.27	20 (9–25)	20 (6–25)	0.95 (0.85–1.07)	0.39

Table 5 Blood and urinary biochemical parameters of FS vs RS

Parameter	Cases vs controls			FS vs RS			
	Cases $N = 64$ median (range)	Controls $N = 64$ median (range)	p	FS $N = 31$ median (range)	RS $N = 33$ median (range)	Odds ratio (95 % CI)	p
Glucose (mg/dl)	94 (65–213)	92 (70–150)	0.05	94 (65–213)	96 (83–153)	0.98 (0.96–1.01)	0.08
Creatinine (mg/dl)	0.9 (0.6–1.3)	0.9 (0.6–1.8)	0.52	0.93 (0.6–1.3)	0.89 (0.6–1.1)	3.2 (0.17–58.3)	0.6
Urate (mg/dl)	5.4 (2.7–7.6)	5.1 (0.7–9.4)	0.78	4.8 (2.7–7.2)	5.75 (2.9–7.6)	0.61 (0.4–0.9)	0.02
Calcium (mg/dl)	9.5 (8.3–10.8)	9.4 (8.8–10.1)	0.83	9.4 (8.3–10)	9.5 (8.6–10.8)	0.35 (0.1–1.2)	0.16
Cholesterol (mg/dl)	194(128–283)	190 (116–290)	0.95	194 (128–236)	197.5 (135–283)	0.99 (0.97–1.01)	0.65
HDL cholesterol (mg/dl)	48.95 (29–79.3)	52.3 (25.2–144.7)	0.25	52.8 (35.6–62.7)	48.3 (29–79.3)	1.02 (0.98–1.1)	0.3
LDL cholesterol (mg/dl)	110.5 (64.6–189)	111.3 (34.8–200.2)	0.98	110.5 (66.2–145.7)	109 (64.6–189)	0.99 (0.97–1.01)	0.72
Triglycerides (mg/dl)	114 (45–965)	96 (36–483)	0.37	108.5 (45–965)	127 (52–562)	1 (0.99–1)	0.46
Cortisol (μg/dl)	15.8 (5–37.4)	17.1 (7.6–40.1)	0.36	12.5 (5–37.4)	17.45 (7.2–30.8)	0.92 (0.85–1)	0.01
Parathormone (pg/ml)	40.1 (5.3–137.5)	35.8 (12.3–89.8)	0.13	39.6 (14.1–70.5)	41.3 (5.3–137.5)	0.98 (0.95–1.01)	0.49
Nocturnal urine volume (ml)	450 (50–1,700)	450 (93–1,900)	0.88	450 (50–1,250)	475 (85–1,700)	1 (0.99–1)	0.76
Nocturnal urinary creatinine (g/L)	1.15 (0.24–3.99)	1.16 (0.26–2.85)	0.95	1.26 (0.24–3.22)	1.08 (0.3–3.99)	1.28 (0.65–2.52)	0.47
Calcium/creatinine ratio (mg/mg cre)	0.16 (0.03–0.68)	0.12 (0.03–0.48)	0.005	0.12 (0.03–0.42)	0.19 (0.06–0.68)	0.002 (0.001–0.5)	0.01
Phosphate/creatinine ratio (mg/mg cre)	0.7 (0.28–2.7)	0.7 (0.21–1.35)	0.14	0.69 (0.28–2.7)	0.78 (0.43–2.51)	1 (0.95–1.1)	0.3
Magnesium/creatinine ratio (mg/mg cre)	67.2 (27.6–187.9)	70 (30.8–166.1)	0.83	66.6 (27.6–179.1)	67.69 (31.4–187.9)	0.99 (0.97–1)	0.17
Urate/creatinine ratio (mg/mg cre)	0.34 (0–0.7)	0.34 (0.17–1.6)	0.8	0.33 (0–0.63)	0.36 (0.24–0.7)	0.07 (0.001–4.7)	0.36
pH (mg/mg cre)	6 (5–7)	6 (5–7.5)	0.48	6 (5–7)	6 (5–7.5)	0.57 (0.22–1.5)	0.29
Citrate/creatinine ratio (mg/mg cre)	0.31 (0.03–0.94)	0.29 (0.05–1.04)	0.34	0.24 (0.03–0.55)	0.34 (0.06–0.94)	0.14 (0.006–2.9)	0.37
Oxalate/creatinine ratio (mg/mg cre)	0.016 (0.0004–0.05)	0.17 (0.003–0.2)	0.72	0.016 (0.0004–0.05)	0.018 (0.002–0.036)	0.12 (0.10–1)	0.27

linked to kidney stones [30, 31]. MS has also been directly linked to stress, since stress stimulates glucocorticoids, which leads to obesity and other symptoms of MS [28]. Along these lines, we have observed a trend towards a higher frequency of MS among the RS patients in the present study.

Conclusions

Although we did not find differences in any of chronic stress dimensions evaluated among cases and controls, an increased number and perceived intensity of stressful life events were observed in RS in comparison to FS. These differences were associated with an increased biological response to stress as evidenced by higher blood cortisol and urinary calcium levels, by a greater number of metabolic abnormalities and by a higher frequency of MS. Taken together, our findings suggest that there is a link between CaOx recurrence, chronic stress and MS. Future prospective studies are warranted to compare FS patients who recur with those who do not to further refine the impact of chronic stress as a risk factor for CaOx recurrence.

Conflict of interest The author declare that they have no conflict of interest.

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