



Crystalluria in adolescent and adult patients with congenital heart disease

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Abstract

Introduction Crystalluria is a frequent finding in normal individuals and in patients suffering from urolithiasis. As nephrolithiasis has been associated with cardiovascular risk factors and most congenital heart disease (CHD) patients reach adulthood, the objective of this study is to determine the presence of crystalluria and if it influences their cardiovascular outcome.

Methods Case–control and observational prospective study design of patients with CHD older than 14 years with a stable CHD verified with imaging tests and a control population.

Results 214 patients with CHD [median age 21 (17–35) years and 41 (19%) males] and 345 controls were studied and followed up. None of them had symptoms of renal calculi. Nine (4%) patients with CHD and 24 (7%) patients in the control group showed crystalluria ($p=0.180$), all of them composed of calcium oxalate. No significant differences were seen in age, sex, body mass index, CHD complexity, cardiovascular risk factors, NYHA functional class, cyanosis, and medical treatment between CHD patients with and without crystalluria. In relation to survival, 18 patients with CHD had a major acute cardiovascular event (MACE) (3 strokes, 2 myocardial infarction, 9 cardiovascular death and 4 non cardiovascular mortality) during the follow up time [7.3 (4.4–8.5) years] without significant differences in the Kaplan–Meier analysis ($p=0.358$) between patients with and without crystalluria.

Conclusion No significant differences were found between CHD and control patients in relation to crystalluria and it had no impact on the occurrence of cardiovascular events in the medium term follow up of patients with CHD.

Keywords Crystals · Urine · Congenital · Survival · Cardiovascular outcome

Introduction

Crystalluria may be seen in clinically healthy people causing limited symptoms unless large enough stones develop. In most instances the precipitation of crystals of calcium oxalate, uric acid triple phosphate, calcium phosphate and amorphous phosphates or urates is caused by transient supersaturation of the urine, ingestion of foods, or by changes of

urine temperature and/or pH. In a minority of cases, however, crystalluria is associated with pathological conditions [1]. Moreover, it has been suggested that nephrolithiasis is associated with subclinical atherosclerosis, arterial hypertension, diabetes mellitus, metabolic syndrome, and adverse cardiovascular events such as myocardial infarction or stroke when compared to the general population [2–4].

As the number of patients with congenital heart disease (CHD) reaching adulthood continues to increase, it is becoming clear that pathophysiological derangement occurs not only in the heart but in other organs [5, 6]. In fact, renal impairment has been recognized as a common complication in patients with CHD [7] particularly in those with cyanosis [8] as long-standing hypoxemia may affect the glomerular and tubular function leading to acidosis, crystallization, and stones formation [9]. However, there is a paucity of data on crystalluria among patients with CHD.

The purpose of this study is (a) to determine the presence of crystalluria among patients with CHD and a control

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group, (b) which variables are associated with crystalluria in patients with CHD and (c) the cardiovascular outcome of patients with CHD depending on whether crystalluria is present or not.

Methods

A case–control study was carried out in first place to compare patients with CHD (cases) and a control population (controls) and thereafter, a prospective observational study was undertaken only in patients with CHD to watch for outcomes. Patients were recruited consecutively from a single adolescent and adult CHD outpatient unit between January 2010 and December 2015. Inclusion criteria were being older than 14 years and having a stable CHD verified with imaging tests. Controls were drawn from patients older than 14 years attending the primary health care centers, of a same geographical area, between July 2017 and December 2018 due to preventive activities or minor illnesses such as anxiety, palpitations, or muscle aches. Controls were matched for age and sex to patients with CHD. Patients excluded from the study were those with hospital admission in the previous 6 months, pregnancy, clinical symptoms of urinary tract infection at the time of the urine collection, a life expectancy under 1 year or who did not give written informed consent to participate in the study. All patients or their parents/tutors gave the informed consent for participation in the study. Approval of the research protocol was carried out by our Institutional Reviewer Board.

Clinical data

Cardiovascular imaging, mainly through echocardiography, established the diagnosis of CHD and patients were classified into diagnostic groups: simple, moderate, or great complexity according to the anatomical defect [10]. The type of cardiac intervention (none, surgical or percutaneous) and the moment in which it was carried out (infancy or adulthood) were also determined. Cardiovascular risk factors were categorized as previously reported [11], the body mass index (BMI) was calculated with the formula $BMI = \text{kilograms}/\text{metres}^2$ and the Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate [12]. Medication taken by patients with CHD was determined and patients were identified as cyanotic if their hemoglobin oxygen saturation, measured using a digital oximeter (Model 512 Handheld Pulse Oximeter; Novamatrix Medical Systems Inc., Wallingford, CT, USA), was 90% or less. Information on personal history of renal colic and family history of kidney stone formation was also obtained.

Blood test, 24-h urinalysis and urine test strips

Following a 10-h overnight fast, baseline blood samples were collected. An Olympus AU 2700 (Olympus Diagnostic, Hamburg, Germany) and a Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics, Inc, Newark, DE, USA) analyzers were used for blood test. Urine test strip analyzer (AtionMax AX-430, Menarini Diagnostics, Italy) was used to measure pH, urine specific gravity, glucose, leukocytes, blood, proteins, bilirubin, urobilinogen, and ketones. Meanwhile, the urine sediment analyzer (SediMax2, Menarini Diagnostic, Italy) identified the sample, shook it, performed centrifugation and took the cuvette to the microscope to determine cells and crystals. An increased amount of glucose, leukocytes, blood, proteins, bilirubin, urobilinogen and ketones, above normal lab reference values, were considered as a “positive” chemical test result.

Follow up

Major adverse cardiac event (MACE) included cardiovascular and non-cardiovascular mortality and arterial thrombotic events (myocardial infarction or stroke) [13]. Follow-up was carried out in all patients with CHD until December 2022 and patients were censored when the first event of interest occurred. Data were obtained through the clinical terms coded with the International Classification of Diseases (ICD) system, the clinical history or telephone calls.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation or median (interquartile range), depending on the normality of distribution. Comparisons between two groups were performed using Student's *t* test for continuous variables or the Mann–Whitney *U* test for continuous non-parametric variables. Categorical values were compared using the χ^2 test. Survival analysis was estimated by the Kaplan–Meier method and the log rank test. A *p* value < 0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS 24, Chicago, IL, USA) was used for data analysis.

Results

Study population

Two hundred fourteen out of 225 (95%) Caucasian CHD patients (cases) and 345 controls were included in the study. Eleven patients in the case group were excluded: 10 did not

collect the urine sample despite having given informed consent and one due to previous hospitalization. No patient was excluded due to a reduced life expectancy or pregnancy. Table 1 shows the type of CHD and the classification according to the cardiac complexity [120 (56%) patients had simple defects, 65 (30%) patients showed moderate defects and 29 (14%) patients presented great defects], the type of intervention and the life stage in which it was done.

Demographic and blood and urine test data in patients with CHD and the control population

Table 2 shows a comparison between patients with CHD and a control population. As can be seen from the table, patients with CHD had statistically significant higher levels

of serum urea, creatinine, calcium, uric acid and haemoglobin than patients in the control group. Similarly, the urine pH was significantly higher in CHD patients than controls. Meanwhile, no significant differences were seen related to the squamous cells and the presence of crystalluria in the urinary sediment of both groups.

Clinical, blood and urine test data in patients with CHD

Nine (4%) patients showed crystalluria, all of them composed of calcium oxalate, and 20 (9%) patients presented squamous cells in the urine samples. From a clinical point of view, no significant differences were seen in age, sex, BMI, CHD complexity, NYHA functional class, cardiovascular

Table 1 Type of congenital heart disease according to complexity, type of intervention and stages of life in which it was done

Type of congenital heart disease according to complexity				
Simple complexity				120
Aortic valve disease				7
Pulmonary valve disease				28
Atrial septal defect				28
Ventricular septal defect				41
Ductus				7
Other simple defects				9
Moderate complexity				65
Subvalvular or supra valvular aortic stenosis				8
Coarctation of the aorta				20
Subvalvular or supra valvular pulmonary stenosis				1
Tetralogy of fallot				19
Ebstein anomaly				2
Atrioventricular septal defects				15
Great complexity				29
Dextro transposition of the great arteries				8
Levo transposition of the great arteries				2
Pulmonary atresia				1
Single ventricle				4
Double outlet right ventricle				1
Tricuspid atresia				1
Truncus arteriosus				1
CHD with pulmonary arterial hypertension				11
Total				214
Cardiac intervention	CHD complexity			Total
Type of CHD intervention	Simple	Moderate	Great	
None	66	12	7	85
Surgery in infancy	31	50	21	102
Surgery in adulthood	6	2	0	8
Percutaneous intervention	17	1	1	19
Total	120	65	29	214

CHD congenital heart disease

Table 2 Demographic and blood test data in patients with CHD and the control population

	CHD patients		<i>p</i>
	Cases	Controls	
CHD patients, <i>n</i>	214	345	
Age, years	21 (17–35)	24 (18–29)	0.686
Sex (male), <i>n</i>	111 (52)	196 (57)	0.157
BMI, kg/m ²	22 (20–25)	21 (19–23)	0.327
Blood test			
Hemoglobin, g/dL	14.6 (13.5–15.6)	13.7 (12.8–14.5)	<0.001
Hematocrit, %	42 (37–45)	41 (39–43)	<0.001
Platelets, 10 ³ /ml	226 (187–271)	249 (210–289)	<0.001
Glucose, mg/dl	94 (870–100)	92 (88–97)	0.188
Urea, md/dl	29 (24–36)	26 (22–31)	<0.001
Creatinine, mg/dl	0.9 (0.8–1.0)	0.7 (0.6–0.8)	<0.001
Calcium, mg/dl	9.8 (9.6–10.1)	9.6 (9.3–9.9)	<0.001
Uric acid, mg/dl	5.0 (4.2–6.1)	4.3 (3.5–4.9)	<0.001
Total cholesterol, mg/dl	154 (134–184)	162 (143–186)	0.093
Urine test strips			
Urine specific gravity	1.020 (1.015–1.025)	1024 (1.018–1.028)	<0.001
pH	6 (5–6)	5.5 (5–6)	0.006
Urine sediment			
Squamous cells, <i>n</i>	20 (9)	28 (8)	0.752
Crystalluria, <i>n</i>	9 (4)	24 (7)	0.180

Data are expressed as number of patients and percentages in brackets or median and interquartile range (25–75%)

CHD congenital heart disease, *n* number of patients, BMI body mass index

risk factors, medical treatment, and cyanosis between CHD patients with and without crystalluria (Table 3). On the contrary, patients with crystalluria showed lower NT-pro-BNP levels and higher 24-h calciuria than those without it. Similarly, patients with crystalluria showed in the urine test strips higher nitrites, bilirubin, and urobilinogen concentrations than patients without crystalluria.

In relation to urine pH, patients with urinary acidosis (pH ≤ 5) did not show statistically more crystalluria than patients with pH levels above 5 [2 out of 67 patients with acidosis vs. 7 out of 147 patients with a pH > 5, *p* = 0.548]. Similarly, no significant differences were found between CHD patients who had renal failure (GFR ≤ 60 ml/min/1.73 m²) and those patients who did not (GFR > 60 ml/min/1.73 m²) according to crystalluria [0 out of 13 patients with renal failure vs. 9 out of 201 patients with a GFR > 60 ml/min/1.73 m², *p* = 0.436]. No patient with CHD had a history of renal colic before or during the study enrolment and similarly no patient reported having a family history of kidney stone formation.

Cardiovascular outcome

In relation to the cardiovascular outcome, 18 patients had a MACE (3 patients had a stroke, 2 suffered a myocardial

infarction, 9 presented cardiovascular death and 4 non cardiovascular mortality) during a follow up time of 7.3 (4.4–8.5) years. As can be seen from Table 3, all the events occurred in patients without crystalluria although without reaching statistical significance (*p* = 0.368). Similarly, the Kaplan–Meier analysis showed no significant differences, in relation to the occurrence of cardiovascular events during the follow-up time, in patients with CHD regardless of the existence or not of crystalluria (*p* = 0.358).

Discussion

The pathophysiology in CHD can lead to changes in the structure and function of the kidney. Although there are a significant number of gaps in the knowledge related to renal function in patients with CHD current evidence demonstrates that chronic renal disease is increasing far beyond that of the general population [14], predicting a worse prognosis. However, little is known about crystalluria among patients with CHD despite it may induce kidney problems such as nephrolithiasis, nephrocalcinosis, kidney stone formation and renal failure [15].

Crystalluria is not rare in the general population where some series [16] have reported prevalence rates of 8% which

Table 3 Demographic, clinical and blood test data in CHD patients according to crystalluria

	CHD patients		<i>p</i>
	Non-crystalluria	Crystalluria	
CHD patients, <i>n</i>	205	9	
Age, years	21 (17–35)	20 (17–29)	0.588
Sex (male), <i>n</i>	106 (52)	5 (57)	0.821
BMI, kg/m ²	23 (20–26)	21 (20–25)	0.804
Great CHD complexity, <i>n</i>	28 (14)	1 (11)	0.827
NYHA functional class (≥ 2), <i>n</i>	10 (5)	0 (0)	0.497
Arterial hypertension, <i>n</i>	27 (13)	0 (0)	0.244
Diabetes mellitus, <i>n</i>	10 (5)	0 (0)	0.497
Dyslipidemia, <i>n</i>	36 (18)	1 (11)	0.617
Smoker, <i>n</i>	13 (6)	1 (11)	0.735
Cyanosis, <i>n</i>	12 (6)	0 (0)	0.455
Blood test			
Hemoglobin, g/dl	14.6 (13.5–15.6)	14.9 (13.4–15.6)	0.768
Glucose, mg/dl	94 (87–100)	39 (87–106)	0.745
Creatinine, mg/dl	0.9 (0.8–1.0)	0.9 (0.9–1.0)	0.833
GFR, ml/min/1.73 m ²	89 (79–102)	87 (78–115)	0.909
Proteins, g/dl	7.5 (7.2–7.8)	7.5 (7.1–7.9)	0.665
Uric acid, mg/dl	7.0 (4.2–6.1)	4.2 (3.9–6.7)	0.409
Calcium, mg/dl	9.8 (9.6–10.1)	9.7 (9.3–10.1)	0.454
Phosphorus, mg/dl	3.7 (3.4–4.3)	3.5 (3.2–4.0)	0.311
Total bilirubin, mg/dl	0.7 (0.5–1.0)	0.8 (0.6–1.1)	0.747
NT-pro-BNP, pg/ml	62 (19–174)	11 (2–81)	0.016
24-h urine test			
Glucose, mg/24 h	36 (18–58)	41 (9–60)	0.985
Creatinine, g/24 h	1.1 (0.8–1.5)	1.0 (1.2–1.7)	0.148
Proteins, g/24 h	0.08 (0.06–0.12)	0.09 (0.08–1.0)	0.238
Calcium, mg/24 h	111 (60–173)	210 (101–307)	0.040
Phosphorus, mg/24 h	648 (423–859)	856 (471–1074)	0.308
Urine test strips			
Urine specific gravity	1.020 (1.015–1.024)	1.025 (1.022–1.029)	0.006
pH	6 (5–7)	6 (5–6)	0.759
Glucose, mg/dl (positive)	99 (48)	5 (56)	0.663
Leucocytes, L/ μ l (positive)	49 (24)	1 (11)	0.897
Erythrocytes, E/ μ l (positive)	49 (24)	2 (22)	0.134
Proteins, mg/l (positive)	76 (37)	7 (78)	0.421
Nitrites (positive)	6 (3)	1 (11)	<0.001
Bilirubin, mg/dl (positive)	34 (17)	4 (44)	<0.001
Urobilinogen, mg/dl (positive)	63 (31)	7 (78)	0.012
Ketone bodies, mg/dl (positive)	6 (3)	1 (11)	0.997
Treatment			
Antiplatelet, <i>n</i>	14 (7)	0 (0)	0.417
Oral anticoagulation, <i>n</i>	20 (10)	1 (11)	0.304
Calcium channel blockers, <i>n</i>	5 (2)	0 (0)	0.635
Loop diuretics, <i>n</i>	25 (12)	0 (0)	0.265
Statins, <i>n</i>	16 (8)	1 (11)	0.720
Allopurinol, <i>n</i>	6 (3)	1 (9)	0.182
MACE	18 (8)	0 (0)	0.368

Data are expressed as number of patients and percentages in brackets or median and interquartile range (25–75%)

CHD congenital heart disease, *n* number of patients, BMI body mass index, NYHA New York Heart Association, GFR glomerular filtration rate, NT-pro-BNP NT-pro-brain natriuretic peptide, MACE major adverse cardiovascular events

is similar to ours. Likewise, the calcium oxalate, the only urine crystal seen in our patients, is the most common type of kidney stone to be generated by endogenous overproduction, increased ingestion, or excessive intestinal absorption. In fact, when a supersaturation status is reached, oxalates combine with calcium crystallize to form 80% of the urinary stones.

As a history of kidney stones has been associated with an increased risk of coronary heart disease [17], systemic arterial hypertension [18] and diabetes mellitus [19] it may be hypothesized that crystalluria, which is an inexpensive and valuable tool for the detection and the monitoring of inherited and acquired diseases associated with urinary stone formation [20], may also be. However, we found no association between crystalluria and classic cardiovascular risk factors or MACE presumably due to the young age of our patients. Moreover, we found no significant differences in creatinine levels between CHD patients with and without crystalluria despite literature has linked crystalline microparticles with mechanical obstructions, local intrarenal inflammation, and tissue renal injury [21]. Moreover, no significant differences were seen in crystalluria levels between patients with CHD and the control population what implies that crystalluria must not be a key factor in the impairment of the renal function among young adult patients with CHD. Similarly, the CHD complexity, the NYHA functional class and being under loop diuretic treatment did not reach statistical significance among CHD patients with and without crystalluria probably because in both groups the NT-pro BNP level, a cardiac natriuretic peptide that is raised in heart failure, was within normal limits [22].

On the other hand, urine specific gravity, which correlates well with urine osmolality and gives important insight into hydration status and the concentrating ability of the kidneys obtained statistically significant differences between CHD patients with and without crystalluria showing patients with crystalluria higher levels. Similarly, we found a positive urine reagent strip reaction between nitrite, bilirubin, and urobilinogen and crystalluria. However, small quantities of urobilinogen may also be found in normal urine, where it contributes to the typical yellow colour of the specimen.

In relation to hypoxemia, patients with cyanotic CHD have physiological compensatory erythrocytosis associated with a shortened red blood cell lifespan. Increased red cell turnover may lead to high purine metabolism, uric acid production and stone formation as seen in the tumor lysis syndrome or in patients with leukemia. Despite of this, none of our cyanotic patients with CHD showed crystalluria and no uric acid crystals were observed in any patient of the population under study. However, relatively few patients with severe cyanotic CHD and polycythemia extreme enough to lead to hyperuricemia survive into adult life when the manifestations are most common [23].

Regarding survival, kidney stones have been associated with more morbidity than expected [3]. However, in our series no significant differences were seen in cardiovascular outcome irrespective of having or not crystalluria in the medium term follow up even though nephrolithiasis seems to be the result of crystal formation, aggregation, and retention in the kidney during crystalluria. An explanation to this lack of significance could be the young age of our patients with CHD and that crystalluria may just be an incipient state of stone formation.

There are, however, limitations in our study that may impact our findings. Firstly, the low number of patients with crystalluria and the low number of MACE observed during the follow up time, typical of young populations. Secondly, we did not determine vitamin D supplementation or medications such as amoxicillin or sulphonamides, both related to crystalluria, and used to treat some infections. Thirdly, including only Caucasian patients may have led to an underrepresentation of other minority ethnic groups. Also, we did not carry out a routine and periodic analysis of the urine to determine crystalluria as any of our patients with CHD showed findings compatible with urinary stone diseases. In such cases, the 24-h urine seems to be the most useful type of urine collection [24]. Finally, we did not use renal ultrasound, as an accurate imaging technique to diagnose stones, as none of our patients had acute renal colic or suspicion of urinary stone disease.

In conclusion, there was not significant difference in the presence of crystalluria between patients with CHD and the control group. Similarly, no significant differences were seen in cardiovascular risk factors, cyanosis, sex, age, NYHA functional class, CHD complexity or creatinine levels between patients with CHD with or without crystalluria. Likewise, crystalluria had no impact on the occurrence of cardiovascular events in the medium term follow up of patients with CHD.

Author contributions EM-Q contributed to project development, data collection, data analysis, manuscript writing; FR-G contributed to data analysis, manuscript writing.

Declarations

Conflict of interest No author has conflict of interest.

Research involving human participants and/or animals None.

Informed consent Informed consent was obtained from all participants.

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