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Original Article

Proteinuria versus albuminuria in 24-hour urine collection: prevalence and clinical outcome in non-hypoxemic adult patients with congenital heart disease

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Abstract: Congenital heart disease (CHD) patients, especially cyanotic ones, usually have renal function impairment. However, little information exists in non-cyanotic CHD patients. The objective of this study is to determine renal failure in non-hypoxemic CHD patients by measuring the amount of protein and albumin released in urine over a 24-hour period and determining the glomerular filtration rate (GFR). Prospective study of consecutive outpatient non-hypoxemic CHD patients followed up in a single tertiary referral hospital. Demographic, clinical, blood test and 24-hour urine collection were recorded. 264 CHD patients, 22 (18-343) years old and 160 (61%) males, were followed up during 9.2 (5.9-11.1) years. 137 (52%), 96 (36%) and 31 (18%) CHD patients had mild, moderate, and great anatomical CHD defects. 44 (17%) and 32 (12%) CHD patients showed proteinuria (≥ 150 mg/24 hours) and albuminuria (> 30 mg/24 hours) respectively. 35 out of 44 (79%) CHD patients with proteinuria (≥ 150 mg/24 hours) showed normal to mild albuminuria levels (< 30 mg/24 hours). Variables associated with proteinuria were male sex, body mass index, auricular fibrillation/flutter, arterial hypertension, diabetes mellitus and being under angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB), loop diuretics or anti-aldosterone treatment. Major adverse cardiovascular events (MACE), defined as cardiovascular and non-cardiovascular deaths, stroke, myocardial infarction and heart failure requiring hospitalization, occurred in 16 (6%) patients during the follow up time. Multivariate Cox regression analysis showed that older patients, patients with a great CHD complexity and patients with proteinuria [6.99 (1.90-24.74), P=0.003] had a significant higher risk of MACE. Proteinuria is frequent among non-hypoxemic CHD patients and occurs mostly in those with a GFR above 60 ml/min/1.73 m^2 and normal to mild albuminuria levels. Having proteinuria, but not albuminuria, was independently associated with a worse outcome.

Keywords: Chronic kidney disease, congenital heart disease, glomerular filtration rate, cyanosis, survival

Introduction

Albuminuria, the most abundant urine protein in diabetic and hypertensive patients, occurs due to glomerular basement membrane alterations. Meanwhile, low-molecular-weight proteinuria relates to tubular reabsorption disorders frequently found in children with chronic kidney disease (CKD) [1]. Nonetheless both, albuminuria, and proteinuria, identify a group of patients with a higher cardiovascular risk and a greater propensity to CKD progression [2].

Despite the prevalence of cardiovascular risk factors, such as arterial hypertension or diabetes mellitus, is low among CHD patients due to their young age [3], nephropathy is a well-known complication [4]. In fact, current epidemiological evidence suggests that CKD occurs in them at a higher frequency than in the general population being associated with a large negative impact on health outcomes and mortality [5]. While proteinuria and renal dysfunction is a proved fact among hypoxemic CHD patients [6, 7] little information exists on

proteinuria and albuminuria levels in non-hypoxemic ones.

The purpose of the study is to determine the prevalence of 24 hour proteinuria and albuminuria in non-hypoxemic CHD patients, to evaluate the demographic and clinical variables that predispose to 24 hour proteinuria and how proteinuria may lead to a worse clinical outcome in patients with non-hypoxemic CHD.

Material and methods

Subjects

Prospective cohort study of clinically stable non-hypoxemic CHD patients recruited from a single hospital outpatient CHD unit between April 2008 and January 2010. The inclusion criteria were age over 18 years and having a structural CHD verified with imaging tests. Exclusion criteria were having associated hypoxemia (haemoglobin oxygen saturation < 90%), a malignancy that limited their life expectancy, surgery, hospitalization, or contrast administration at least four weeks before the blood test, not wanting to participate in the study or not doing the blood test despite granting permission for it. All patients, or their parents or tutors, gave written informed consent to participate in the research study and the study protocol was approved by the hospital's ethics committee.

Demographic and clinical data

Demographics [age, sex and body mass index (kg/m^2)], New York Heart Association (NYHA) functional class, CHD anatomical classification (simple, moderate or great complexity) [8], medical comorbidities [Down syndrome, Fontan procedure, cardiac surgery and auricular fibrillation/flutter], cardiovascular risk factors (systemic arterial hypertension, diabetes mellitus and dyslipidaemia) [3] and medical treatment (antiaggregation, anticoagulation, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), loop diuretics and anti-aldosterone therapy) were determined.

Blood and 24-hour urine test

After an overnight fasting period of at least 10 hours, blood samples were collected to measure serum glucose, creatinine, ions and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels. In addition, a 24-hour urine test was carried out the same day with the patients on their usual diet, except that they had to avoid alcohol intake and strenuous exercise. Blood and 24-hour urine tests were obtained by spectrophotometry using an Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany) and NT-pro-BNP levels were measured by immunoassay with the Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics, Inc, Newark, DE, USA).

Glomerular filtration rate (GFR) was estimated in all patients with the Modification of Diet in Renal Disease formulae (186 × [creatinine (mg/dl)] -1.154 × [age (years)] -0.203 × [0.724 if female]) [9]. Renal function was classified into GFR categories (G) as stated in Table 4. Proteinuria category (P) was defined as normal to mildly increased (P1) (< 150 mg/24 hours), moderately increased (P2) (150-500 mg/24 hours) and severely increased (P3) (> 500 mg/24 hours) [10, 11]. Similarly, albuminuria was classified as normal to mildly increased (A1) (< 30 mg/24 hours), (A2) moderately increased (30-300 mg/24 hours) and (A3) severely increased (> 300 mg/24 hours). Chronic Kidney Disease (CKD) was defined as a GFR < 60 ml/min/1.73 m^2 or proteinuria ≥ 150 mg/24 hours.

Clinical outcome

After enrollment, CHD patients were followed prospectively. MACE (major adverse cardiovascular event) was defined as cardiovascular and non-cardiovascular deaths, arterial thrombotic events (stroke or myocardial infarction) and heart failure requiring hospital admission. CHD patients were followed up by reviewing the International Classification of Diseases diagnostic coding system of the medico-administrative data from our institution, the clinical history and/or telephone calls.

Statistical analysis

Continuous variables are presented as mean and standard deviation (±) if normally distributed or median (interquartile range [25-75]) if not normally distributed. The χ^2 test or Fisher exact was used to compare proportions for categori-

Table 1. Demographic and clinical data in CHD patients with and without 24-hour proteinuria

	24-hour proteinuria		P
	< 150 mg/24 h	≥ 150 mg/24 h	
CHD patients, n	220	44	
Age, years	20 (18-32)	25 (18-38)	0.245
Sex (male), n	127 (58)	33 (75)	0.032
BMI, kg/m^2	24 (21-27)	25 (22-31)	0.038
NYHA functional class (≥II), n	21 (10)	9 (20)	0.087
CHD complexity (great), n	27 (12)	4 (9)	0.550
Fontan procedure, n	5 (2)	0 (0)	0.312
Down syndrome, n	18 (8)	2 (5)	0.424
Previous cardiac surgery, n	115 (52)	30 (68)	0.053
Auricular fibrillation/flutter, n	7 (3)	6 (14)	0.003
Arterial hypertension, n	29 (13)	12 (27)	0.018
Diabetes mellitus, n	8 (4)	5 (11)	0.031
Dyslipidemia, n	4 (19)	7 (16)	0.669
Treatment, n			
Aspirin	11 (5)	4 (9)	0.285
Oral anticoagulation	19 (9)	10 (23)	0.039
Beta blockers	20 (9)	8 (18)	0.074
ACE inhibitors & ARBs	33 (15)	13 (29)	0.020
Loop diuretics	18 (8)	10 (23)	0.004
Anti-aldosterone	7 (3)	5 (11)	0.016
MACE, n	9 (4)	7 (16)	0.013
Blood test			
Glucose, mg/dL	94 (88-100)	96 (91-105)	0.041
Hemoglobin, mg/dL	15 (14-16)	15 (14-16)	0.505
Creatinine, mg/dL	0.9 ± 1.9	0.9 ± 1.4	0.366
Urea, mg/dL	29 (23-35)	31 (25-36)	0.183
GFR, ml/min/1.73 m^2	89 (80-103)	93 (79-101)	0.955
GFR (<60 ml/min/1.73 m^2)	5 (0)	0 (0)	0.315
Sodium, mM/L	140 (138-141)	140 (138-141)	0.851
Potassium, mM/L	4,3 (4,1-4,5)	4,3 (4,2-4,6)	0.253
C*hloride,* mM/L	104 (103-106)	104 (102-106)	0.702
P*hosphorus,* mg/dL	3.8 ± 0.6	3.7 ± 0.7	0.725
Calcium, mg/dL	9,9 (9,6-10,2)	9,8 (9,5-10)	0.196
NT-pro-BNP, pg/mL	49 (13-118)	69 (25-179)	0.085
24 hours urine test			
Glucose, mg/24 h	39 (20-60)	65 (29-41)	0.005
Creatinine, g/24 h	1.2 (0.9-1.7)	1.7 (1.3-2.2)	< 0.001
Urea, g/24 h	17 (13-22)	23 (17-32)	< 0.001
Albumin, mg/24	9.0 (0.0-18.9)	0 (0-246)	0.865
Sodium, mM/24 h	130 ± 61	174 ± 74	< 0.001
Potassium, mM/24 h	54 (40-69)	67 (49-99)	0.002
Chloride, mM/24 h	125 (91-171)	176 (120-220)	0.001
Phosphorus, mM/24 h	673 (457-925)	915 (679-1273)	< 0.001
Calcium, mM/24 h	126 (73-187)	157 (97-273)	0.055

n: number of patients, CHD: congenital heart disease, BMI: body mass index, NYHA: New York Heart Association, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers, MACE: major acute cardiovascular events.

cal variables. Meanwhile, the Student's t-test and the Mann-Whitney test were used for continuous variables with or without normal distribution respectively. The Pearson's correlation was used to find a correlation between 24-hour proteinuria and albuminuria levels. Logistic regression analysis was carried out to determine demographic and clinical variables predictive of proteinuria. Crude Odds Ratio (OR) were obtained after considering the effect of only one independent variable and adjusted OR when more variables in the analysis were included. The Kaplan-Meier method was used for survival analysis and the Cox regression to investigate the effect of several variables upon the time a MACE occurred. Time to event was defined from the date of blood and urine tests to the date of the first clinical event. The 95% confidence interval (CI) was used to estimate the precision of the OR and HR. A *p* values less than 0.05 was considered statically significant. Data analysis was carried out using SPSS 24.0 (SPSS, Chicago, IL).

Results

CHD population

Two hundred and sixty four out of 304 (87%) CHD patients attending our tertiary center fulfilled inclusion criteria. 40 patients were excluded from the study: 2 patients due to hospitalization or contrast administration the four weeks before the blood test was drawn, 15 patients because blood or urine was not drawn de-

Table 2. Binary logistic regression analyses in CHD patients to predict proteinuria (≥ 150 mg/24 hours)

	OR (crude) (95% CI)	p	OR (adjusted) (95% CI)	p
Sex, male	0.45 (0.29-0.95)	0.035	0.42 (0.19-0.96)	0.041
BMI, Kg/m^2	1.07 (1.01-1.13)	0.024	1.06 (0.99-1.14)	0.080
Auricular fibrillation/flutter, yes	4.80 (1.53-15.08)	0.007	2.16 (0.39-11.83)	0.374
Arterial hypertension, yes	2.47 (1.14-5.33)	0.021	0.99 (0.32-3.14)	0.996
Diabetes mellitus, yes	3.40 (1.06-10.93)	0.040	1.18 (0.28-4.92)	0.825
Oral anticoagulation, yes	3.11 (1.33-7.26)	0.009	1.31 (0.32-5.33)	0.706
ACE inhibitors & ARBs, yes	2.38 (1.13-5.01)	0.023	1.47 (0.47-4.65)	0.506
Loop diuretics, yes	3.30 (1.40-7.75)	0.006	2.52 (0.63-10.08)	0.191
Anti-aldosterone, yes	3.98 (1.19-13.08)	0.025	1.14 (0.18-7.05)	0.884

CHD: congenital heart disease, BMI: body mass index, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers, OR: odds ratio, CI: confidence interval.

Table 3. 24-hour proteinuria and albuminuria categories in CHD patients

24-hour urine collection				
Albuminuria (A) categories (mg/24 hours)	Proteinuria (P) categories (mg/24 hours)			
	P1 (< 150)	P2 (150-500)	P3 (> 500)	Total
A1 (< 30 mg)	197 (89)	27 (75)	8 (100)	232
A2 (30-300 mg)	23 (11)	9 (25)	0 (0)	32
A3 (> 300 mg)	0 (0)	0 (0)	0 (0)	0
Total	220	36	8	264

CHD: congenital heart disease.

Table 4. Chronic kidney disease by GFR and proteinuria categories in CHD patients

CKD classification				
GFR categories (ml/min/1.73 m^2)	Proteinuria categories (mg/24 hours)			
	P1 (< 150)	P2 (150-500)	P3 (> 500)	Total
G1 (≥ 90)	116 (53)	21 (58)	4 (50)	141
G2 (60-89)	99 (45)	15 (42)	4 (50)	118
G3a (45-59)	5 (2)	0 (0)	0 (0)	5
G3b (30-44)	0 (0)	0 (0)	0 (0)	0
G4 (15-29)	0 (0)	0 (0)	0 (0)	0
G5 (< 15)	0 (0)	0 (0)	0 (0)	0
Total	220	36	8	264

CHD: congenital heart disease, GFR: glomerular filtration rate.

spite granting permission for it and 23 patients due to associated hypoxemia. Median age was 22 (18-33) years old and 160 (61%) patients were males. 137 (52%), 96 (36%) and 31 (18%) CHD patients had mild, moderate, and great anatomical CHD defects.

Clinical and blood test data in CHD patients with and without proteinuria

The **Table 1** shows the demographic, clinical and blood test data in CHD patients with and without proteinuria. Variables significantly associated with proteinuria were male sex, BMI, having atrial fibrillation/flutter, systemic arterial hypertension, diabetes mellitus or being under oral anticoagulation, ACE inhibitors/ARBs, loop diuretics or anti-aldosterone treatment. However, only male gender reached statistical significance as a predictor of proteinuria in the binary logistic regression analysis (**Table 2**).

Proteinuria versus albuminuria in 24-hour urine collection

Table 3 shows 24-hour proteinuria and albuminuria categories. 44 (17%) and 32 (12%) CHD patients showed proteinuria (≥ 150 mg/24 hours) and albuminuria (≥ 30 mg/24 hours) respectively. No CHD patient had albuminuria levels above 300 mg/24 hours and 35 out

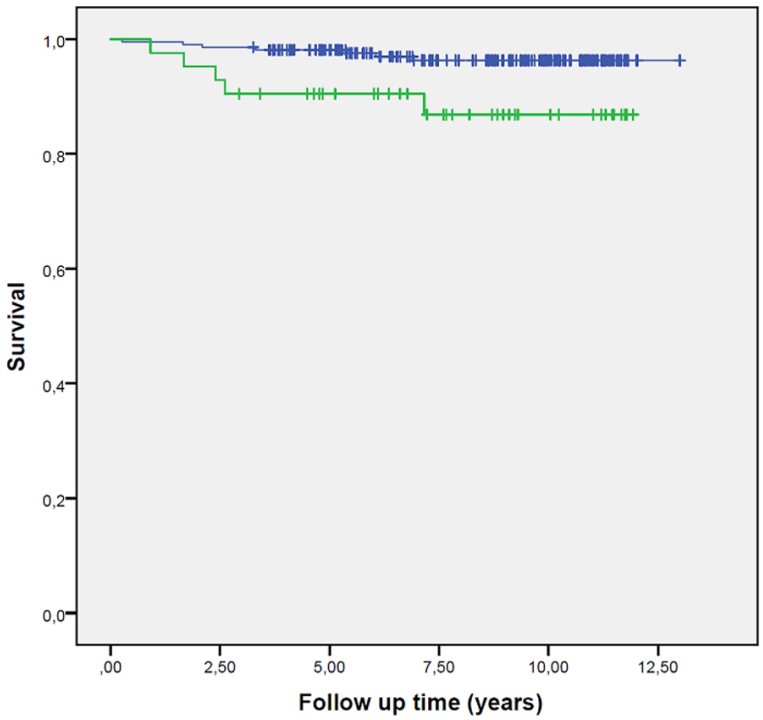

Figure 1. Kaplan-Meier survival curves showing major acute cardiovascular events (MACE) in CHD patients with (green line) and without (blue line) proteinuria (P=0.013).

of 44 (79%) CHD patients with proteinuria (≥ 150 mg/24 hours) showed normal to mild albuminuria levels (< 30 mg/24 hours). No correlation was seen between 24-hour proteinuria and albuminuria concentrations (P=0.687). Similarly, all patients with proteinuria had a GFR above 60 ml/min/1.73 m^2 (**Table 4**). CKD was seen in 49 (19%) CHD patients: 5 patients had a GFR below 60 ml/min/1.73 m^2 and 44 patients showed proteinuria ≥ 150 mg/24 hours.

Cardiovascular events during the follow-up

In relation to the outcome, MACE occurred in 16 (6%) CHD patients during a follow up time of 9.2 (5.9-11.1) years. 7 MACE occurred in CHD patients with proteinuria (2 patients had thrombotic events, 3 patients heart failure, 1 patient had a cardiac death and 1 patient presented a non-cardiac death) and 9 MACE happened in CHD patients without it (2 thrombotic events, 3 heart failure requiring hospitalization, 5 cardiac deaths and 1 non-cardiac death) (P=0.004). Kaplan Meier analysis showed a worse survival among CHD patients with proteinuria than without it (P=0.013) (**Figure 1**). However, no significant differences were seen in the survival analysis bet-ween CHD with and without 24-hour albuminuria (P=0.605). Meanwhile, Cox regression analysis showed that age, having a great CHD defect and proteinuria (≥ 150 mg/24 hours) [6.99 (1.90-24.74), P=0.003] were associated with a significant higher probability of MACE (**Table 5**).

Discussion

The prevalence of renal failure in Europe and USA (< 60 ml/min/1.73 m^2) has been reported about one percent in individuals 35 to 44 years of age. However when CKD is determined in the general population, not only according to a GFR < 60 mL/min/1.73 m^2 but also to albuminuria/proteinuria, the prevalence of CKD, in patients 20 to 39 years old, rises to 6.3% [20]. Similarly, Dimopoulous et al. [5] found that 8% of non-hypoxemic CHD patients had a GFR < 60 mL/min/1.73 m^2. However, when the albuminuria criterion (albumin-to-creatinine (ACR) ratio >30 mg/g) was used [7] the prevalence of CKD shot up to 17% as also seen in our series. However, unlike us, the patients reported by Rajpal et al. [7] were almost twice older (median 39 years old) and 7% had associated hypoxemia. On the other hand, these same authors found that the prevalence of albuminuria was similar to that seen in the general population among patients with simple shunts without clinical sequelae and left-sided obstructive lesions. Also, having systemic arterial hypertension [10] and auricular arrhythmias [11], that implies in the majority of cases the use of anti-hypertensive agents such as ACE inhibitors/ARBs and oral anticoagulation respectively, was associated with a greater risk of 24 hour proteinuria among our CHD patients.

Despite proteinuria and albuminuria are good biomarkers predicting clinical end-points (cardiovascular events, renal events and mortality) in diabetic and non-diabetic patients, protein-

Table 5. Univariate and multivariate Cox regression analysis of variables associated with major adverse cardiovascular events in CHD patients

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.07 (1.03-1.10)	< 0.001	1.08 (1.03-1.13)	< 0.001
CHD complexity, great	4.11 (1.24-13.66)	0.021	4.61 (1.22-17.38)	0.024
NYHA class, ≥ II	6.19 (1.66-23.07)	0.007	0.51 (0.04-7.14)	0.620
GFR > 60 ml/min/1.73 m^2	0.09 (0.02-0.43)	0.002	0.25 (0.03-1.80)	0.169
Proteinuria, > 150 mg/24 hours	3.86 (1.22-12.17)	0.021	6.99 (1.90-24.74)	0.003

CHD: congenital heart disease, NYHA: New York Heart Association, GFR: glomerular filtration rate, HR: hazard ratio.

uria should be used especially in non-diabetics patients because it is cheaper than albuminuria, it is usually used as an ACE inhibitors treatment target and has been consistently associated with glomerulonephritis (which is characterized by proteinuria instead of albuminuria) and acute tubular necrosis, the most common form of renal failure following surgery both in the general population and in CHD patients [12-14]. Moreover, high levels of proteinuria associates with a faster progression of CKD and a greater risk of cardiovascular morbidity. In fact, recent findings postulate that the increased risk of proteinuria begins within normal urinary albumin excretion levels [15] as also seen in our series.

As early identification and management of CKD is highly cost-effective and may reduce the risk of kidney failure progression and cardiovascular disease by up to 50%, it is particularly important to recognize when kidneys are beginning to fail. This is especially transcendent in CHD patients with associated comorbidities and sequela who remain asymptomatic and with a normal serum creatinine concentration until advanced stages, substantial tubular injury must be caused before serum creatinine increases [16], despite their increased cardiovascular risk. Therefore, recognition of kidney damage, by determining proteinuria, becomes a key part of improving health outcomes in early stages not only in the general population [17, 18] but also in CHD.

There are, however, limitations in our study that may impact our findings. On the one hand the small number of MACE seen in our CHD patients. Nonetheless, we think that the sample size is large enough to draw a definitive link between proteinuria and cardiac events among non-hypoxemic CHD patients. On the other hand, CHD patients represent a heterogeneous population so it may be difficult to draw final conclusions in the overall prognosis.

In conclusion, the prevalence of CKD reached almost 20% of our non-hypoxemic CHD patients particularly at the expense of proteinuria. Proteinuria, in non-hypoxemic CHD patients, seems to be an important and early marker of kidney damage as well as a risk factor for cardiovascular morbidity and mortality.

Disclosure of conflict of interest

None.

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