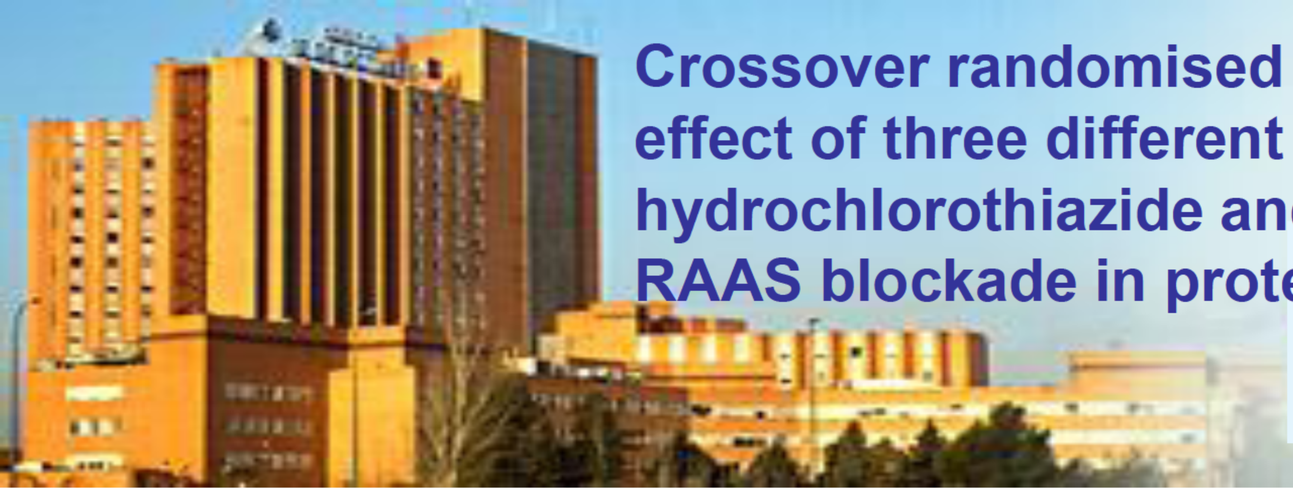

Crossover randomised clinical trial to evaluate the antialbuminuric effect of three different types of diuretics (spironolactone, hydrochlorothiazide and hydrochlorothiazide + amiloride) on top of RAAS blockade in proteinuric nephropathies

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Background

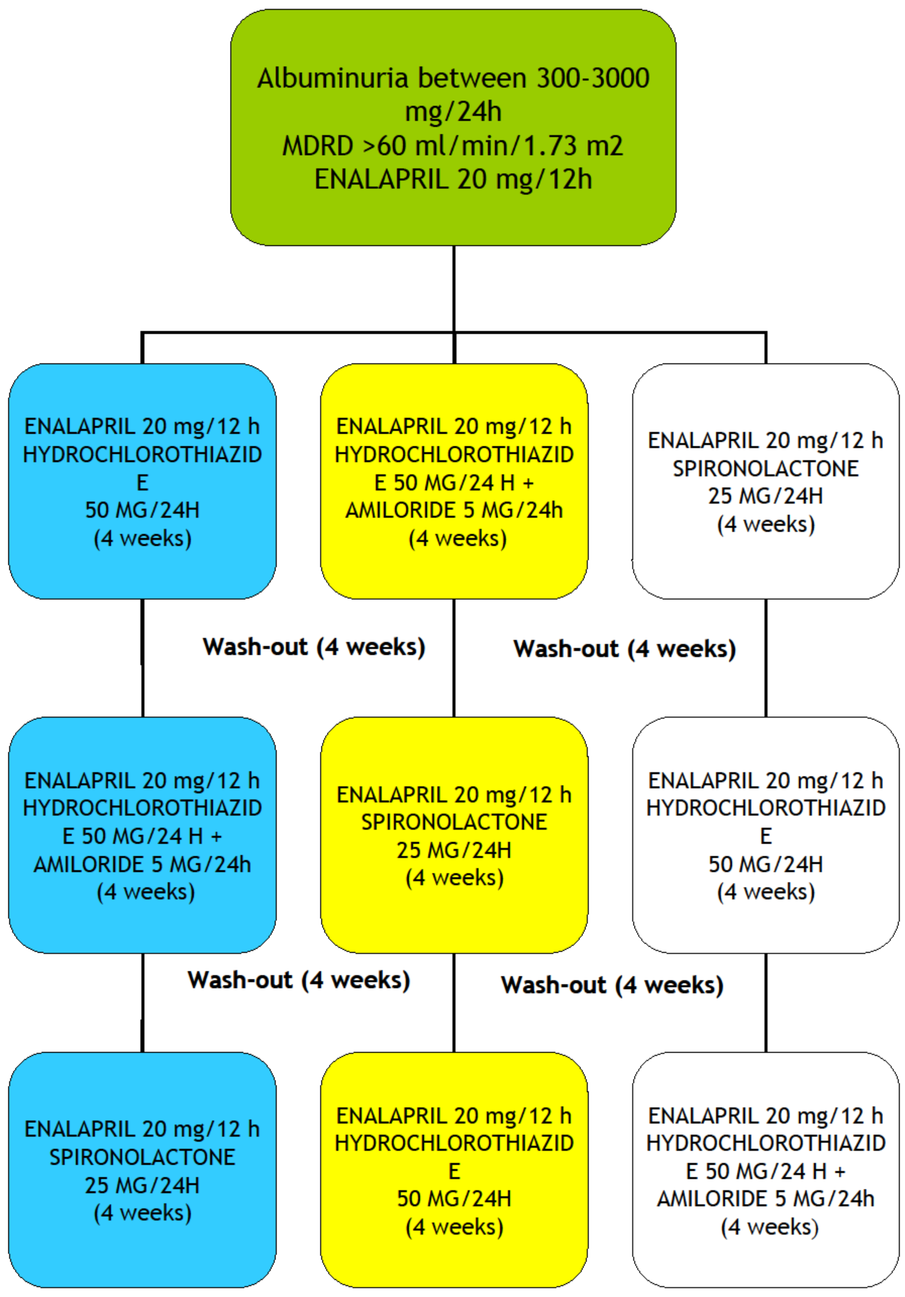
Not all patients with proteinuric nephropathies treated with renin-angiotensin-aldosterone system (RAAS) blockers show a decrease in proteinuria enough to be associated with a favorable effect on the progression of renal damage. Addition of diuretics enhances the effects of RAAS blockade on residual albuminuria in patients with chronic proteinuric nephropathies. However, comparative studies to evaluate the antialbuminuric effect of different diuretics are lacking.

Objective

We designed a prospective crossover study to compare the effects of spironolactone (SR), hydrochorothiazide (HCT), or HCT plus amiloride (A) administered on top of RAAS blockade in patients with proteinuric nephropathies.

Materials & Methods

Patients with residual urine albumin-to-creatinine ratio (ACR) > 300 mg/g on top of enalapril therapy (40 mg daily) and CKD stages 1-3 were selected for the study. Patients were given SR (25 mg/day), HCT (50 mg/day) or HCT + A (50 mg+5mg /day, respectively) during three treatment periods of 4 weeks in a ramdom order. Treatment periods were separated by a washout period of one month. Enalapril (40 mg/day) was maintained throughout treatment and washout periods.



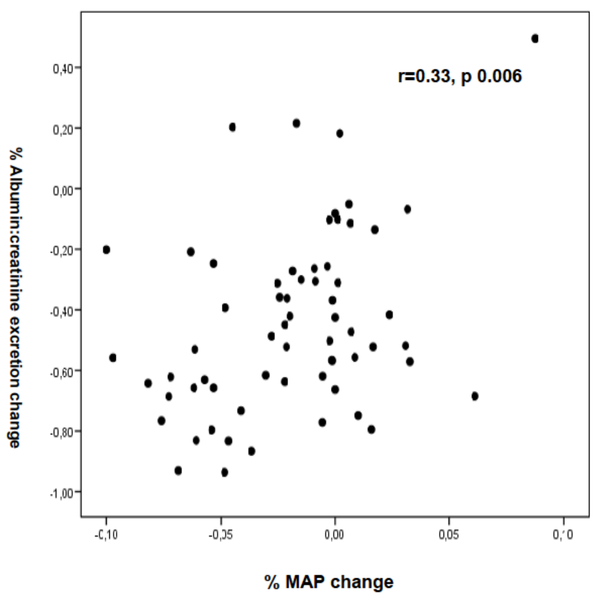
Results

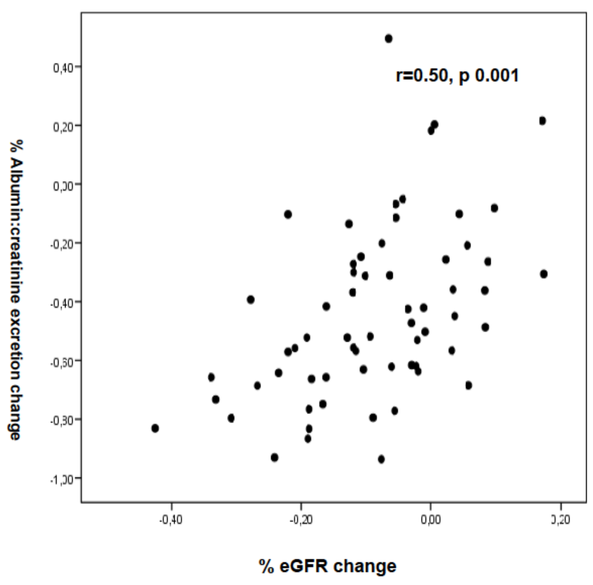
Patient characteristics

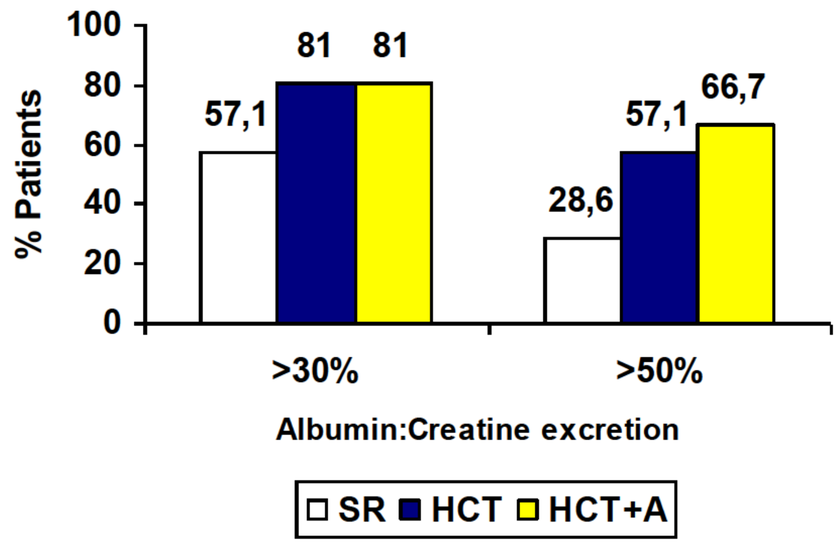
Sex female/male, n (%)	7 (33.3)/14 (66.7)
Age, years (mean, SD)	55.9±10.9 (28-73)
Causes of Nephropathy (n) (%) Diabetic nephropathy Chronic glomerulonephritis Others	 10 (47.6) 10 (47.6) 1 (4.8)
Weight (kg)	89±15.7 (58.1-121.4)
Body mass index (Kg/m2)	32.1±6.9 (22.5-51.8)
Systolic blood pressure (mmHg)	132.8±20.1 (98-168)
Diastolic blood pressure (mmHg)	75.7±10.1 (65-97)
Mean arterial pressure (mmHg)	86.6±4.5 (80-98.5)
Antyhypertensive medication (n) (%) ACEI ARB Spironolactone Calcium-chanel blockade β blockade α blockade	 14 (66.6) 6 (28.6) 5 (23.8) 3 (14.3) 2 (9.5) 2 (9.5)
Serum creatinine (mg/dl) (mean, SD)	1.1±0.3 (0.5-2)
eGFR (MDRD) (ml/min/1.73m2) (mean, SD)	68.6±27.1 (31-150.2)
Sodium (mEq/l) (mean, SD)	140.2±2.3 (134-143)
Potassium (mEq/l) (mean, SD)	4.7±0.4 (3.9-5.4)
Uric (mg/dl) (mean, SD)	6.7±1.5 (3.4-9.3)
Albumin excretion (mg/24 horas) (geometric mean, 95%CI)	1481.1 (580.6-2084,6)
Albumin:creatinine excretion (mg/g) (geometric mean, 95%CI)	1083.5 (431.3-1014.5)
Proteinuria (g/24 horas) (mean, SD)	1.8±1.0 (0.6-3.9)

	SP wash-out	SP	HCT wash-out	HCT	HCT+A Wash-out	HCT+A
Diuresis (ml/24h)	2288.2 (2030.4-2545.9)	2340.5 (2005.6-2675.3)	2293.1 (2035.3-2550.9)	2395.2 (2017.1-2773.4)	2238.3 (1980.3-2496.3)	2300 (1954.2-2645.7)
Albumin excretion (mg/24h)	1600 (1047-2152.9)	1125.2* (500.1-1750.4)	1417.1 (868.4-1965.8)	935* (266.7-1603.3)	1882.9 (1325.4-2440.4)	577.9* (300.8-855.1)
% albumin excretion		44.4 (24-59.9)		54.1 (29-70)		68.4 (40-80)
Albumin:creatinine excretion (mg/g)	810.7 (601.3-1020.1)	742.9* (241.1-1244.8)	1011.3 (803.8-1218.7)	566.7*+ (205.9-927.5)	1135.4 (926.1-1344.8)	398.9*+ (212.9-584.9)
% albumin:creatinine		34.4 (21-47.9)		42.5 (28.1-56.9)		56 (44.6-67.4)
% Reduction >30%		12 (57.1)		17 (81)		17 (81)
% Reduction >50%		6 (28.6)		12 (27.1)		14 (66.7)
Proteinuria (g/24h)	1.7 (1.3-2.2)	1.5* (0.8-2.3)	1.7 (1.3-2.1)	1.3* (0.6-2)	2.4 (1.9-2.8)	0.9* (0.6-1.2)
Sodium excretion (mEq/24h)	184.3 (152.4-261)	227.6 (183.5-271.6)	216.1 (175.9-256.3)	240.2 (146.6-333.9)	194.1 (160.5-227.6)	208.9 (164.2-253.7)
Potassium excretion (mEq/24h)	73.8 (59.9-87.8)	79.6 (67.8-91.4)	77.9 (67.5-88.4)	80.9 (56.8-105.3)	80.9 (66.9-94.9)	76 (67.8-91.5)
Systolic blood pressure (mmHg)	130.9 (18.5)	125.6 (20.1)*	129.2 (18.9)	124.4 (19.4)	128.7 (20.2)	121.2 (15.3)*
Diastolic blood pressure (mmHg)	76.5 (13.3)	72.8 (10.1)*	75.1 (12.2)	71.9 (7.8)	74.8 (12.6)	70.1 (8.3)*
Mean arterial pressure (mmHg)	87.5 (5)	85.6 (5.3)*	86.1 (3.9)	85.2 (4.5)	86.7 (4.6)	84.3 (4.7)*
% MAP change		2.1 (0.6-3.6)		1 (0.6-2.6)		2.7 (0.8-4.6)
Weight (kg)	89.1 (15.6)	88.1 (15.6)*	89.1 (16.2)	88.5 (15.2)	88.6 (15.3)	87.3 (15.1)*
% Weight change		1.2 (0.2-2.1)		0.4 (0.5-1.4)		1.3 (0.5-2.1)
Sodium (mEq/L)	141.7 (2.8)	140.8 (1.8)	140.6 (3.4)	140.7 (2.3)	141.1 (1.9)	140.2 (2.7)
Potassium (mEq/L)	4.7 (0.4)	5 (0.6)*	4.6 (0.4)	4.5 (0.4)	4.6 (0.5)	5 (0.6)*
Creatinine (mg/dl)	1.17 (0.4)	1.25 (0.4)	1.15 (0.3)	1.26 (0.4)*	1.21 (0.4)	1.35 (0.4)*
eGFR (MDRD-4) ml/min/1.73m2	66.8 (26.8)	62.6 (26.8)	66.4 (25.6)	60.8 (24.7)*	64.5 (24.8)	55.5 (20.7)*
% eGFR change		6 (0.9-11.9)		8.5 (3.8-13.3)		12 (5.9-18.1)
Uric (mg/dl)	6.3 (1.4)	6.8 (1.8)*	6.5 (1.5)	7.3 (1.6)*	6.4 (1.5)	7.6 (1.7)*
Renin (pg/ml)	47.5 (28.2-66.8)	82* (37.2-126.8)	46.2 (27.2-65.2)	106.9* (50.6-163.2)	34.1 (13.7-54.4)	168.4* (95.5-241.3)
Aldosterone (pg/ml)	150.3 (110.8-198.8)	203.3* (162.4-244.3)	166.3 (127.6-205)	182.1 (142-222.2)	119.4 (80.1-158.6)	298.2* (198.2-398.3)
CRP (mg/dl)	0.3 (0.3)	0.3 (0.5)	0.3 (0.3)	0.3 (0.6)	0.4 (0.9)	0.4 (0.7)
Homocysteine (umol/l)	13.6 (3.4)	15 (3.8)*	14.3 (3.5)	16.9 (4.4)	14.5 (3.3)	17.5 (4)*

*p<.05 between intra-group; +p<.05 inter-group







Discussion

SR, HCT and the combination of HCT+A induced a significant and remarkable reduction in albuminuria. These results are important for the design of clinical trials. The possible renoprotective consequences of diuretic-induced albuminuria reduction should be evaluated by long-term prospective trials.

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