Comparison of spironolactone and trichlormethiazide as add-on therapy to renin–angiotensin blockade for reduction of albuminuria in diabetic patients

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ABSTRACT

To compare the efficacy of spironolactone and trichlormethiazide, as add-on therapy to renin–angiotensin system (RAS) blockade, for reduction of albuminuria in diabetic patients with chronic kidney disease (CKD), we conducted this randomized, open-labeled, parallel-group, active-controlled, per-protocol-design study. Type 2 diabetic patients receiving an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, with persistent albuminuria (≥100 mg/g creatinine) were randomly assigned to either spironolactone (25 mg/day) or trichlormethiazide (2 mg/day). The primary outcome was the change in albuminuria at 24 weeks of treatment. In patients who completed 24 weeks of treatment with spironolactone (n = 18) and trichlormethiazide (n = 15), albuminuria decreased significantly by −57.6 ± 21.3% (SD) (P < 0.001) and −48.4 ± 27.1% (P < 0.001), respectively. There was no significant difference in the change in albuminuria between groups (P = 0.270). This pilot study suggests add-on therapy with spironolactone or trichlormethiazide to RAS blockade may be comparably beneficial to reducing albuminuria in type 2 diabetic patients. This trial was registered with UMIN-CTR (no. UMIN000008914). (J Diabetes Invest doi: 10.1111/jdi.12029, 2013)

KEY WORDS: Aldosterone blockers, Diabetic kidney disease, Thiazide diuretics

INTRODUCTION

Pharmacological blockade of the renin–angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) has been repeatedly shown to delay progression of diabetic kidney disease (DKD)[1,2]. Nonetheless, many patients with DKD receiving these RAS blockers remain at a significant residual risk of further progression of DKD, due either to their insufficient antihypertensive or antiproteinuric effects, thereby necessitating add-on therapy with other antihypertensive drugs.

Aldosterone has also been implicated in the pathogenesis of chronic kidney disease (CKD)[3,4]. Since the publication of a preliminary study by Chrysostomou *et al.*[5], several subsequent clinical studies have shown that aldosterone blockade with spironolactone or eplerenine decreases albuminuria/proteinuria[6–8]. In a recent placebo-controlled cross-sectional study of 21 type 1 diabetic patients with microalbuminuria from Denmark, spironolactone in addition to standard renoprotective treatment was shown to reduce microalbuminuria[9]. Thiazide diuretics have also been found to reduce proteinuria in patients with CKD including DKD[10–12]. However, to the best of our knowledge, differences in the magnitude of albuminuria reduction between an aldosterone receptor blocker and thiazide diuretic have not been studied. We, therefore, conducted the present pilot study to compare the efficacy of an aldosterone receptor antagonist, spironolactone, versus a thiazide diuretic, trichlormethiazide, on changes in albuminuria, when either is used as add-on therapy to an ACE inhibitor or ARB in diabetic patients with CKD.

MATERIALS AND METHODS

The present study was designed as a single-center, randomized, open-labeled, parallel-group, active-controlled, per-protocol-design protocol in adherence with the Declaration of Helsinki. Japanese type 2 diabetic women and men between the ages of 40 and 79 years were recruited from the ambulatory patients presenting at the Diabetes Center, Tokyo Women's Medical University Hospital. Inclusion criteria were urinary albumin-to-creatinine ratio (ACR) from first morning urine ≥100 mg/g on consecutive two measurements within 2 months, and use of an ACE inhibitor or ARB for at least 6 months. Patients were excluded if they had clinically significant heart, liver, infectious or malignant disease, if serum creatinine was ≥2.0 mg/dL, or if serum potassium was ≥5.0 mEq/L or <3.5 mEq/L.

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Received 14 September 2012; revised 15 October 2012; accepted 17 October 2012

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Table 1 | Baseline clinical characteristics of patients allocated to spironolactone or trichlormethiazide

	Spironolactone (n = 18)	Trichlormethiazide (n = 15)
Sex (women : men)	6:12	3:12
Age (years)	65 ± 7	62 ± 9
HbA_{1c} (%)	7.3 ± 0.9	7.3 ± 1.2
Systolic blood pressure (mmHg)	149 ± 20	146 ± 10
Diastolic blood pressure (mmHg)	79 ± 14	79 ± 11
Serum creatinine (mg/dL)	1.25 ± 0.38	1.23 ± 0.31
eGFR (mL/min/1.73 m^2)	61.6 ± 23.9	63.4 ± 17.0
Serum albumin (g/dL)	3.9 ± 0.4	3.9 ± 0.5
Serum sodium (mEq/L)	140 ± 3	140 ± 1
Serum potassium (mEq/L)	4.3 ± 0.3	4.3 ± 0.3
Serum uric acid (mg/dL)	6.0 ± 1.4	5.9 ± 1.5
Plasma renin activity (ng/mL/h)	4.4 (2.5–7.8)	3.7 (2.0–6.9)
Plasma aldosterone (ng/dL)	8.3 ± 3.3	8.9 ± 2.7
Hematocrit (%)	40.9 ± 4.2	39.1 ± 3.7
Urinary albumin (mg/g Cr)	605.6 (362.2–1,012.5)	582.6 (351.8–946.9)
Antihypertensive medications		
ACE inhibitor	14	13
ARB	4	2
Calcium channel blocker	14	8
Alpha-blocker	0	1

Data are mean ± standard deviation, geometric mean (95% confidence interval) or number of patients. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

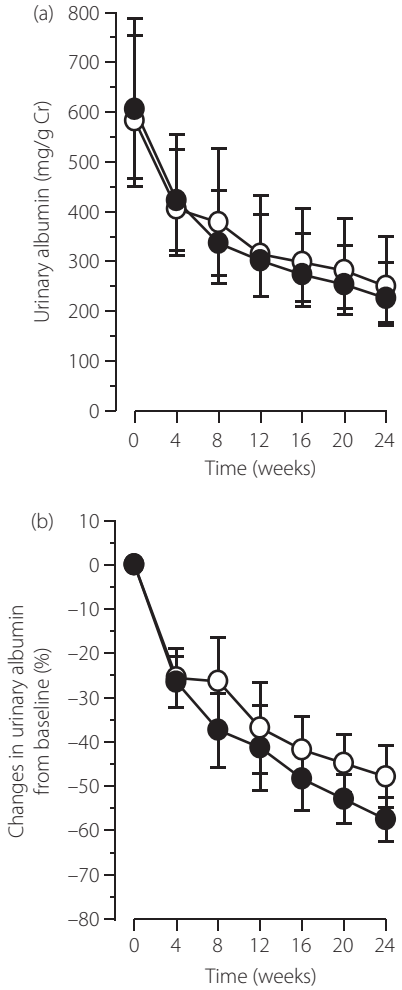

Figure 1 | Changes in (a) urinary albumin-to-creatinine ratio (ACR) and (b) percent change from baseline in ACR during 24 weeks of treatment with spironolactone (black circles, n = 18) or trichlormethiazide (white circles, n = 15). ACR was expressed as least-square geometric mean ± standard error (SE); change in ACR was expressed as least-square mean ± SE. Urinary ACR significantly decreased from baseline in both groups (P < 0.001 at all time-points). There was no significant difference in reduction of albuminuria at 24 weeks from baseline between the two groups (P = 0.270).

After informed consent was obtained, 36 patients were randomly assigned to receive a fixed dose of either spironolactone (25 mg/day, n = 19) or trichlormethiazide (2 mg/day, n = 17) without change in concomitant hypertensive medications. The prespecified primary outcome measurement was the change from baseline in urinary ACR at the end of the 24-week observational period.

Blood pressure was measured at each visit, during rest in a seated position, using an oscillometric device. A first morning voided urine sample was collected every 4 weeks for determination of ACR. Glomerular filtration rate (GFR) was estimated using the equation proposed by the Japanese Society of Nephrology[13]. Glycated hemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography and standardized to National Glycohemoglobin Standardized Program (NGSP) units using the formula advocated by the Japan Diabetes Society[14].

Continuous variables were expressed as arithmetic mean ± standard deviation (SD), and categorical data were expressed by actual frequencies and percentages. As we focused mainly on drug efficacy in the present pilot study, we used a per-protocol rather than intention-to-treat analysis. Changes from baseline in urinary ACR were analyzed using a randomized block design analysis with adjustment for multiple comparisons by Dunnett–Hsu test (SAS version 9.3; SAS Institute, Cary, NC, USA). Geometric least-square mean and standard error (SE) of urinary ACR, and percent change from baseline in ACR were calculated at each time-point. A priori power analysis was not carried out due to a preliminary study to evaluate feasibility and effect size. Other statistical analyses were carried out using appropriate methods.

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RESULTS

Two patients withdrew during trichlormethiazide treatment; one because of hyponatremia and one because of an unspecified drug intolerance; therefore, 18 patients and 15 patients successfully completed 24 weeks of treatment with spironolactone and trichlormethiazide, respectively. Sex, age, blood pressure, HbA_{1c}, and renal parameters were well matched between the treatment groups at baseline (Table 1). Baseline geometric least square mean of urinary ACR was 606 mg/g (95% CI 362–1,013) mg/g for the spironolactone group and 583 mg/g (352–965) for the trichlormethiazide group.

Urinary ACR decreased significantly from baseline in both treatment groups ($P < 0.001$ at each time point; Figure 1). The magnitude of decrease in ACR at 24 weeks was slightly greater for patients treated with spironolactone [−57.6 ± 21.3% (SD)] than those treated with trichlormethiazide (−48.4 ± 27.1%); this difference was not statistically significant (Table 2, P = 0.270).

In both groups, serum creatinine increased, and eGFR and systolic blood pressure decreased significantly from baseline, with no significant difference between groups (Table 2). As expected, serum potassium increased modestly, but significantly, in patients treated with spironolactone. Serum potassium did not change in patients treated with trichlormethiazide. There was no significant difference in HbA_{1c} levels during each treatment. In analysis using the combined treatment groups, there was no significant relationship between change in urinary ACR and systolic blood pressure [Spearman's correlation coefficient (rs) = 0.236, $P = 0.186$], diastolic blood pressure ($rs = 0.188$, $P = 0.295$), or eGFR ($rs = 0.120$, $P = 0.508$) during follow up. There was also no significant relationship between these parameters in a separate analysis by treatment group.

DISCUSSION

The present pilot study shows the efficacy of add-on therapy, using either spironolactone or a thiazide diuretic, to decrease albuminuria in DKD patients receiving an ACE inhibitor or ARB. The magnitude of the reduction in urinary ACR was qualitatively comparable in groups throughout the 24 weeks of treatment. The absence of a significant relationship between changes in ACR and changes in blood pressure suggests that these drugs may be acting to reduce albuminuria independently of blood pressure lowering.

Albuminuria is an established risk factor for progressive decline in GFR in DKD[15]. Albuminuria can be effectively lowered using antihypertensive drugs that inhibit the RAS; however, previous intervention studies with RAS blockade failed to arrest progression of DKD[1,2]. Although the reasons for this are not clear, a single agent might be insufficient to achieve blood pressure targets or to completely normalize albuminuria[1,2]. Reduction of residual albuminuria to the lowest achievable level is recommended as a treatment goal for renoprotection in type 2 diabetic patients with nephropathy[16]. For this purpose, either aldosterone receptor blockers or thiazide diuretics might be effective as add-on therapy in DKD patients who fail to decrease albuminuria with RAS blockade.

Aldosterone receptor blockers and thiazide diuretics are associated with several adverse effects. Spironolactone might provoke life-threatening hyperkalemia when combined with RAS blockade[17]. Hypopotassemia and glucose intolerance have long been known as thiazide-related adverse side-effects[18]. In the present study, only a modest increase in serum potassium was observed in patients treated with spironolactone; no patient experienced hypopotassemia during treatment with trichlormethiazide. HbA_{1c} did not change significantly during either treatment; however, the small sample size and limited duration of

Table 2 | Changes in blood pressure and laboratory data before and after treatment with spironolactone or trichlormethiazide

	Spironolactone (n = 18)		Trichlormethiazide (n = 15)		P-value‡
	Change	P-value†	Change	P-value†	
Systolic blood pressure (mmHg)	−12 ± 12	0.001	−10 ± 13	0.013	0.786
Diastolic blood pressure (mmHg)	−7 ± 13	0.021	−3 ± 7	0.116	0.469
HbA_{1c} (%)	0.1 ± 0.7	0.359	0.2 ± 0.5	0.076	0.744
Serum creatinine (mg/dL)	0.17 ± 0.16	<0.001	0.20 ± 0.24	0.003	0.942
eGFR (mL/min/1.73 m^2)	−9.3 ± 7.6	<0.001	−9.4 ± 12.0	0.005	0.942
Serum albumin (g/dL)	0.2 ± 0.3	0.059	0.1 ± 0.2	0.157	0.455
Serum sodium (mEq/L)	−1 ± 3	0.160	−1 ± 3	0.406	0.830
Serum potassium (mEq/L)	0.3 ± 0.6	0.027	0.0 ± 0.3	0.713	0.035
Serum uric acid (mg/dL)	1.0 ± 1.6	0.047	1.4 ± 0.5	0.002	0.049
Hematocrit (%)	−2.8 ± 2.2	<0.001	−0.8 ± 1.3	0.016	0.003
Urinary albumin excretion (% reduction from baseline)	−57.6 ± 21.3	<0.001	−48.4 ± 27.1	<0.001	0.270

Data are mean ± standard deviation.

†Wilcoxon's signed rank-sum test to determine significant difference of parameters before and after each treatment.

‡Wilcoxon's rank-sum test to compare the difference between patients treated with spironolactone and trichlormethiazide. Change in urinary albumin excretion was expressed as percent reduction from baseline. eGFR, estimated glomerular filtration fate; HbA_{1c}, glycated hemoglobin.

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follow up precludes firm conclusions about the safety of these drugs. In should be noted that a decrease in GFR was observed in both groups.

In conclusion, the present pilot study found add-on therapy with spironolactone or trichlormethiazide likely to be similarly efficacious in terms of reduction of albuminuria in type 2 diabetic patients with DKD. These findings might be useful in planning the design of a future confirmatory full-scale multicenter intention-to-treat study.

ACKNOWLEDGEMENTS

No potential conflicts of interest relevant to this article were reported.

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