Renoprotective effects of combining RAS blockade drugs with spironolactone in patients with diabetic nephropathy and overt albuminuria

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Introduction

Several studies have demonstrated that spironolactone has an anti-albuminuric property in diabetic nephropathy. As an adverse event, spironolactone often induces the elevation of creatinine levels with hypotension and hyperkalemia.

Aim

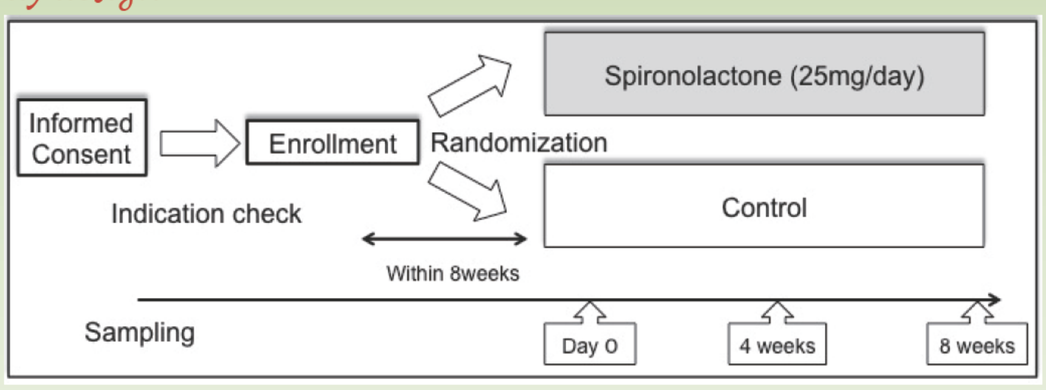
To evaluate the efficacy and safety of spironolactone in Japanese patients with type 2 diabetes treated with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Subject

- We enrolled 52 Japanese patients with type 2 diabetes and diabetic nephropathy from August 2012 to May 2013.
- Despite antihypertensive treatment with a RAS-blocker (either ARB or ACEi), the enrolled patients had persistent albuminuria (100 mg/gCr-2000 mg/gCr).
- inclusion criteria

(1) aged 30 to 70 years (2) eGFR >30 mL/min/1.73m2 calculated by serum creatinine

Study design



The primary endpoint; change in albuminuria indicated by urine albumin-to-creatinine ratio (uACR) after 8 treated weeks relative to the baseline values

The secondary endpoints; change in serum potassium, eGFR calculated by serum creatinine and cystatin C, and high-sensitive C-reactive protein (hs-CRP), in serum aldosterone, urinary angiotensinogen (AGT) and N-acetyl-beta-D-glucosaminidase (NAG), beta2-microglobulin (β2MG), L-type fatty acid binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (N-GAL), and monocyte chemoattractant protein-1 (MCP-1).

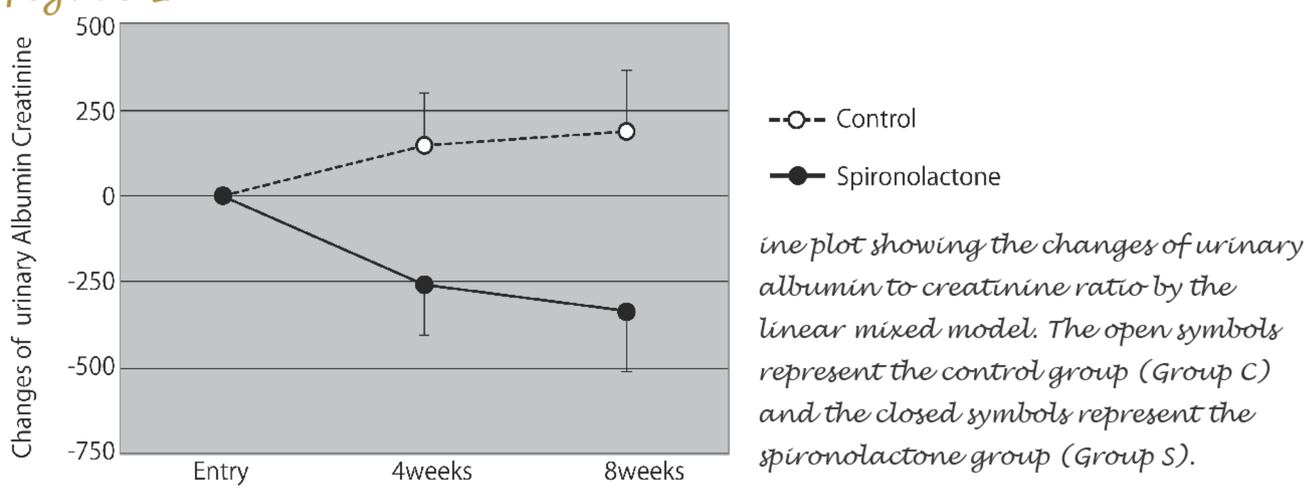
Table1 . Baseline characteristics in this study

	Spironolactone (25 mg)	Control	P value
Number	26	26	
Age (years)	61.0 ± 9.2	59.4 ± 10.8	0.56
Sex (male; %)	18 (69.2)	19 (73.8)	0.76
Smoking			
Current smoker*a	7 (29)	7 (32)	0.85
History of smoking*b	18 (72)	14 (55)	0.24
Blood pressure			
Systolic blood pressure	137.3 ± 16.3	131.3 ± 13.0	0.14
Diastolic blood pressure	76.8 ± 12.2	77.6 ± 8.8	0.79
Medication			
Calcium channel blockers (%)	9 (35)	11 (42)	0.57
Diuretics(thiazide/furosemide; %)	0/2 (0/7)	1/2 (4/8)	0.21
Statin (%)	22 (88)	16 (64)	0.043
Hemoglobin (g/dL)	13.6 ± 1.8	13.9 ± 1.6	0.61
White blood cell (/mm^3)	6624.0 ± 1683	6848.0 ± 2080	0.68
Platelet (×10^4/mm^3)	22.2 ± 6.0	22.7 ± 6.1	0.78
Serum creatinine (mg/dL)	0.86 ± 0.2	0.88 ± 0.2	0.66
BUN (mg/dL)	16.1 ± 4.2	16.8 ± 5.3	0.63
UA (mg/dL)	5.8 ± 1.1	6.0 ± 1.1	0.66
Serum sodium (mEq/L)	139.6 ± 2.9	140.0 ± 2.0	0.54
Serum potassium (mEq/L)	4.3 ± 0.3	4.4 ± 0.3	0.29
Serum chloride (mEq/L)	104.0 ± 3.7	100.5 ± 2.3	0.44
Triglyceride (mg/dL)	161.4 ± 74.0	165.5 ± 73.5	0.85
HDL cholesterol (mg/dL)	46.3 ± 11.0	47.5 ± 14.6	0.75
LDL cholesterol (mg/dL)	101.3 ± 33.0	91.5 ± 22.0	0.23
AST (IU/L)	22.7 ± 7.5	26.7 ± 17.6	0.30
ALT (IU/L)	27.0 ± 14.4	33.5 ± 19.8	0.18
Cystatin C	0.98 ± 0.2	1.06 ± 0.3	0.28
Proteinuria (g/gCr)	0.90 ± 0.9	0.94 ± 0.8	0.77
Albuminuria (mg/gCr)	702.1 ± 728.4	511.3 ± 450.1	0.28

Abbreviations: BUN: blood urea nitrogen, UA: uric acid, HDL: high density lipoprotein, LDL: low density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase

COI
Pfizer organized the advisory meeting about aldosterone antagonist use in patient with diabetic nephropathy and S.K., Sh.M., H.M., T.U., K.K., E.I. and Se.M. were reimbursed for travel costs and received honoraria.

Figure 1



ine plot showing the changes of urinary albumin to creatinine ratio by the linear mixed model. The open symbols represent the control group (Group C) and the closed symbols represent the spironolactone group (Group S).

		4weeks		8weeks	
	N	mean±S.D.	95%CI	mean±S.D.	95%CI
Control (observation)	24	144.84±77.37	151.6	185.86±92.03	108.4
+Spironolactone	25	-256.8±75.79	148.5	-333.87±176.13	176.7

Table 2. Efficacy of spironolactone treatment adjusted by hemodynamic alterations

Variable	Estimate	SE	t	P
Intercept	-661.87	631.28	-1.05	0.3002
Spironolactone	-514.38	137.59	3.74	*0.0005
Albuminuria (at entry)	-0.42	0.09	-4.44	*<.0001
eGFR (at entry)	2.23	3.91	0.57	0.5727
eGFR [delta (8 week-0 week)]	2.4	6.13	0.39	0.6972
SBP (at entry)	3.24	4.09	0.79	0.4327
SBP [delta (8 week-0 week)]	1.87	2.57	0.73	0.4695

Table 3. Changes in serum and urinary biomarkers during 8 weeks of treatment with spironolactone

	Spironolactone (25 mg)			Control			P value
	0 week	8 week	delta (8 week-0 week)	0 week	8 week	delta (8 week-0 week)	
Serum							
Serum aldosterone (pg/mL)	84.1 ± 41.2	103.5 ± 47.6	19.4 ± 33.4	92.6 ± 39.6	94.7 ± 43.6	3.4 ± 23.8	0.0834
hs-CRP (ng/mL)	883.5 ± 1143.8	1564.8 ± 3298.9	681.4 ± 3015.6	1200.7 ± 1586.4	1025.7 ± 1099.9	-148.7 ± 1614.3	0.3254
Urine							
Angiotensinogen (μg/gCr)	90.7 ± 130.7	34.8 ± 32.2	-156.7 ± 466.0	83.9 ± 179.7	66.9 ± 85.7	17.8 ± 71.9	*0.004
NAG (U/gCr)	9.2 ± 6.5	6.9 ± 5.5	-2.3 ± 6.5	9.0 ± 6.2	10.1 ± 7.6	1.2 ± 4.4	*0.0304
β2MG (μg/gCr)	1361.0 ± 3887.6	334.1 ± 798.5	-1026.9 ± 3174.6	753.5 ± 2527.2	1113.1 ± 2978.4	307.4 ± 718.3	*0.029
L-FABP (μg/gCr)	22.7 ± 56.9	8.84 ± 13.1	-13.9 ± 49.1	7.36 ± 9.3	13.0 ± 23.2	5.6 ± 18.5	0.1637
N-GAL (μg/gCr)	35.0 ± 73	28.9 ± 77.4	-6.2 ± 37.6	22.5 ± 39.7	17.8 ± 26.0	-4.6 ± 41.2	0.8943
MCP-1 (μg/gCr)	0.18 ± 0.12	0.15 ± 0.13	-0.015 ± 0.13	0.12 ± 0.07	0.15 ± 0.11	0.03 ± 0.08	0.4485

Abbreviations: CRP: C-reactive protein, NAG: N-acetyl-beta-D-glucosaminidase, β2MG: beta2-microglobulin, L-FABP: L-type fatty acid binding protein, N-GAL: neutrophil gelatinase-associated lipocalin, MCP-1: monocyte chemoattractant protein-1

Summary of this study

- In our multicenter, prospective, randomized, open-label parallel-group comparison study, we found that the addition of spironolactone to conventional antihypertensive treatment including RAS-blockers resulted in a reduction in albuminuria in Japanese patients with type 2 diabetes, nephropathy, and albuminuria.
- The spironolactone treatment demonstrated a reduced-trend in blood pressure and a slight but significant decrease in eGFR. However, the reduction in albuminuria was independent of the changes in either blood pressure or eGFR.
- This study also demonstrated that spironolactone significantly decreased the urinary tubule-interstitial markers NAG and β2MG.
- Moreover, our study is the first to capture urinary AGT levels after spironolactone administration in the clinical setting.

limitations

- we enrolled patients who freely were treated with various RAS-blockers in the points of dose and period.
- because the range of albuminuria inclusion criteria (100 mg/gCr-2000 mg/gCr) was somewhat broad, the patients with a relatively low amount of albuminuria at baseline should be prone to underestimation.

Conclusion

- Our study suggests that spironolactone could be recommended as the second-line treatment for the patients with type 2 diabetes, nephropathy, and albuminuria and insufficient control of blood pressure using RAS-blockers

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