Clin Exp Nephrol (2015) 19:247–253
DOI 10.1007/s10157-014-0981-2

ORIGINAL ARTICLE

Renoprotective effects of thiazides combined with loop diuretics in patients with type 2 diabetic kidney disease

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Received: 4 December 2013 / Accepted: 26 April 2014 / Published online: 13 May 2014

Abstract
Background/aims Type 2 diabetic kidney disease (DKD) is frequently accompanied by uncontrollable hypertension due to the sodium sensitivity inherent in DKD and to diuretic-resistant edema. In general, diuretics are effective in treating this condition, but thiazide diuretics are thought to be innocuous in advanced chronic kidney disease (CKD). We examined the renoprotective effects of combination therapy with thiazides and loop diuretics in type 2 DKD patients with CKD stage G4 or G5.
Methods This study included 11 patients with type 2 DKD and an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 who were suffering from severe edema even with loop diuretics. Each patient received additional hydrochlorothiazide (HCTZ) therapy, which was continued for more than 12 months. We examined clinical parameters including blood pressure (BP), proteinuria, and eGFR before and after the addition of HCTZ.
Results Patients received a 13.6 ± 3.8 mg/day dose of HCTZ in addition to loop diuretics (azosemide: 120 mg/day in 6 cases, 60 mg/day in 3 cases and furosemide: 80 mg/day in 1 case, 120 mg/day in 1 case). Side effects of HCTZ were not observed in all patients. After the addition of HCTZ therapy, systolic and diastolic blood pressures (S-BP, D-BP) as well as proteinuria significantly decreased (S-BP: at 6 months, $p < 0.05$ and 12 months, $p < 0.01$ vs. 0 month, D-BP: at 12 months, $p < 0.05$ vs. 0 month, proteinuria: at 6 months, $p < 0.05$ and 12 months, $p < 0.01$ vs. 0 month). The annual decline in eGFR was not significantly different before and after HCTZ therapy (−7.7 ± 8.5 and −8.4 ± 4.8 mL/min/1.73 m^2/year, respectively).
Conclusion Our findings suggest that the combination of HCTZ and loop diuretics improves BP levels, and decreases proteinuria even in advanced stage type 2 DKD patients with severe edema. The addition of HCTZ therapy was not found to negatively affect the change in eGFR in the present study.

Keywords Type 2 diabetic kidney disease · Thiazides · Loop diuretics · Proteinuria · Hypertension · Chronic kidney disease

Introduction

Type 2 diabetic kidney disease (DKD) is one of the most important and common causes of end-stage renal disease, and is also characterized by proteinuria, elevated blood pressure (BP), and rapid progression of renal dysfunction [1, 2]. Diabetes mellitus (DM) itself is known to be a sodium-sensitive condition, and sodium intake directly induces elevation of BP [3]. In addition to sodium sensitivity, there would be a decreased sodium excretion ability in DKD, and finally an expansion of extracellular fluid, which frequently causes the induction of hemodialysis (HD). Hypertension has recently been demonstrated as one of the major independent risk factors for DKD progression [4–7]. Thus, the management of hypertension in DKD patients is important for the mitigation of DKD progression. Many kinds of antihypertensive medications are available in current clinical practice, including calcium

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channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), thiazide and loop diuretics, and more. In particular, thiazide diuretics were found to be effective as first-step antihypertensive therapy in the ALLHAT study, as were CCBs and ACEIs [8]. Recently, it was also reported that thiazide diuretics would be effective in natriuretic diuresis even in the presence of a low glomerular filtration rate (GFR) [9, 10]. However, thus far, studies examining the renoprotective effects of thiazides combined with loop diuretics in type 2 DKD patients with advanced renal failure have been scarce. Therefore, in the present study, we aimed to examine whether renoprotective effects, such as an improvement of hypertension and/or proteinuria and preservation of eGFR, can be achieved by the addition of thiazides to loop diuretics in type 2 DKD patients with chronic kidney disease (CKD) stage G4 or G5.

Materials and methods

Patients and study design

We retrospectively included patients treated between January 2009 and December 2010 who met the following criteria: (1) type 2 DKD outpatients at the divisions of nephrology of the Saitama Medical Center in Jichi Medical University with eGFR <30 mL/min/1.73 m^2, which is categorized as CKD stage G4 or G5 according to the CKD guidelines edited by the Japanese Society of Nephrology [11]; (2) more than 12 months of treatment with loop diuretics, and more than 12 months of follow-up after adding hydrochlorothiazide (HCTZ) for the management of overhydrated status such as hypertension and severe edema. Severe edema was defined as a >5 % increase in body weight with edema as compared to the previous medical examination. Patients who initiated HD during this study period were excluded.

During these periods, 20 potential patients were screened and 9 patients were excluded. The reasons for exclusion were HD initiation in 3 patients, loss to medical follow-up in 2 patients, and lack of examination data during this study in 4 patients. Ultimately, 11 patients (5 males and 6 females, mean age 70.6 ± 12.4 years) diagnosed with type 2 DKD were included in this retrospective study. Dietary educations on management of caloric intake (1,711 ± 124 kcal/day), and protein (33.4 ± 2.4 g/day) and sodium (>6 g/day) restriction was provided to 9 out of 11 patients. Educational sessions were scheduled to take place when patients received medical examination at our division, and reached 6.7 ± 3.3 times (2–12 times) on average during the study. The study was approved by the Institutional Review Board of Saitama Medical Center (approval number 13-14), Jichi Medical University, Japan, and conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo, 2004).

We analyzed socio-demographic patient data including age, gender, and antihypertensive treatment with loop diuretics, ARBs, CCBs and others. In each patient, BP was measured in the sitting position before starting medical examinations at the hospital. Biochemical parameters including serum creatinine, uric acid, sodium, potassium, and calcium were measured before and after the addition of HCTZ. Urinary protein excretion (g/g-Cr) was calculated as the ratio between urinary protein and creatinine concentration. We calculated eGFR by using the following equation [11],

$$\begin{aligned}&\text{eGFR}\left(\text{mL/min/1.73m}^2\right)\\&\quad=194\times \text{S}-\text{Cr}^{-1.094}\times \text{age}^{-0.287}\,(\text{for men})\\&\quad=194\times \text{S}-\text{Cr}^{-1.094}\times \text{age}^{-0.287}\times 0.739\,(\text{for women})\end{aligned}$$

where S-Cr is the serum creatinine concentration (mg/dL).

Energy intake was calculated by nutritionists based on each patient's daily meal record. Furthermore, 24-h urine collection was performed in each patient for evaluating urinary urea nitrogen (UUN) excretion and urinary Na^+ excretion. The urine collection method was as follows: 24-h urine collection was started in the morning after the first morning urine was discarded in the patient's toilet. Thereafter, the entire volume of urine was collected in a disposable container with a 3-L volume. Based on the values of UUN and urinary Na^+ excretion obtained from the 24-h urine collection, we calculated the daily protein and sodium intake.

Protein intake was calculated by using Maroni's equation, described below:

Protein intake (g/kg/day) = ([body weight (kg) × 0.031] + UUN (g/day)) × 6.25 [12].

Sodium intake was calculated by using the following equation:

Sodium intake (g/day) = urinary Na^+ excretion (mEq/day)/17.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Student's *t* test for paired values was used for comparisons between the 2 groups. Differences among 3 groups (at starting points, 6, and 12 months after the initiation of HCTZ therapy) were evaluated by using one-way analysis of variance (ANOVA) and Fisher's protected least significant difference. A difference of $p < 0.05$ was considered significant.

Table 1 Patient demographics and clinical characteristics

Number of patients	11
Females/males	5/6
Age (years)	70.6 ± 12.4
Loop diuretics used	Furosemide ($n = 2$)
	Azosemide ($n = 9$)
Body weight (kg)	67.0 ± 21.8
S-BP (mmHg)	167.0 ± 27.1
D-BP (mmHg)	78.5 ± 14.6
eGFR (mL/min/1.73 m^2)	21.5 ± 8.1
HbA1c (%)	6.8 ± 1.0
Hemoglobin (g/dL)	10.4 ± 0.2
Total cholesterol (mg/dL)	196.2 ± 29.6
Serum sodium (mEq/L)	140.3 ± 2.1
Serum potassium (mEq/L)	4.4 ± 0.8
Serum uric acid (mg/dL)	7.0 ± 1.3
Proteinuria (g/g-Cr)	6.7 ± 3.9

Results

Patient demographics and clinical characteristics are shown in Table 1. The mean age was 70.6 ± 12.4 years. All patients had been taking loop diuretics during the study because of hypertension and severe edema induced by diuresis insufficiency. At study initiation, the eGFR value was 21.5 ± 8.1 mL/min/1.73 m^2, and systolic and diastolic blood pressures (S-BP and D-BP) were still relatively elevated in all patients. The amount of proteinuria reached 6.7 ± 3.9 g/g-Cr. Antihypertensive medications and statins at HCTZ initiation are shown in Table 2. ARBs were taken by all patients, CCBs by 10 patients, beta-adrenergic blocking agents by 5 patients, alpha-adrenergic blocking agents by 4 patients, and a direct renin inhibitor by 3 patients. Eight out of 11 patients were also taking statins and the remaining 3 patients did not take any type of statins. With the exception of 1 patient whose statin dose was reduced, no addition of statins or change of doses took place during the study period. Table 3 shows the values of biochemical parameters before and after the addition of HCTZ. A 13.6 ± 3.8 mg/day dose of HCTZ was added to loop diuretics (azosemide: 120 mg/day in 6 cases, 60 mg/day in 3 cases and furosemide: 80 mg/day in 1 case, 120 mg/day in 1 case). After the addition of HCTZ, doses of azosemide and furosemide did not change significantly during the study period. Regarding the results of dietary education, caloric intake was continuously lower and protein and sodium intakes were slightly higher than our recommendation throughout this study. Body weight had a tendency to decrease with the improvement of edema, though these changes were not statistically significant. S-BP and D-BP significantly decreased (S-BP: at 6 months, $p < 0.05$ and 12 months, $p < 0.01$ vs. 0 months, D-BP: at 12 months, $p < 0.05$ vs. 0 month). In addition to improvements of BP, there were also significant decreases in proteinuria and total cholesterol after the initiation of HCTZ (proteinuria: at 6 months, $p < 0.05$ and 12 months, $p < 0.01$ vs. 0 month, total cholesterol: $p < 0.05$ at 6 and 12 vs. 0 month, respectively). The serum Na concentration significantly decreased (at 12 months, $p < 0.05$ vs. 0 month), but this change was within a normal range in the patient's clinical course. As shown in Fig. 1, although eGFR gradually decreased during the study, the annual eGFR decline was not significantly different before and after HCTZ initiation (−7.7 ± 8.5 and −8.4 ± 4.8 mL/min/1.73 m^2/year, respectively). Thus, although the addition of HCTZ to loop diuretics could not mitigate the degree of annual eGFR decline in these type 2 DKD patients, HCTZ therapy itself, at least, had no negative impact on eGFR change.

Table 2 Antihypertensive medications and statins at HCTZ initiation

Antihypertensive medicine	Dose (mg/day)	*n*
Angiotensin II receptor blockers (total)		(11)
Irbesartan	50	1
	100	1
Olmesartan	40	2
Losartan	12.5	1
	100	1
Valsartan	80	1
	160	4
Calcium channel blockers (total)		(10)
Amlodipine	10	1
Azelnidipine	8	1
Cilnidipine	10	1
	20	7
Beta-adrenergic blocking agents (total)		(5)
Bisoprolol	2.5	1
Carbedilol	10	4
Alpha-adrenergic blocking agents (total)		(4)
Doxazosin	1	3
	2	1
Direct renin inhibitor (total)		(3)
Ariskilen	150	3
Statins		(8)
Atorvastatin	5	2
	10	1
Rosuvastatin	2.5	2
	5	2
Pravastatin	5	1

Table 3 Comparison of changes in clinical parameters from HCTZ initiation to 6 months after initiation and 12 months after initiation

	0 month	6 months	12 months
Dose of HCTZ (mg/day)	0	13.6 ± 3.8	13.6 ± 3.8
Dose of azosemide (mg/day, $n = 9$)	100.0 ± 30.0	83.3 ± 36.1	73.3 ± 37.1
Dose of furosemide (mg/day/person, $n = 2$)	80 and 120	80 and 120	80 and 120
Number of antihypertensive medicine	3.0 ± 1.3	2.7 ± 1.6	2.6 ± 1.5
Caloric intake (kcal/day, $n = 9$)	1356 ± 242	1318 ± 203	1396 ± 422
Protein intake (g/day, $n = 9$)	41.1 ± 11.2	47.4 ± 8.4	45.0 ± 8.9
Sodium intake (g/day, $n = 9$)	8.6 ± 4.2	6.8 ± 2.6	7.7 ± 2.2
Body weight (kg)	67.0 ± 21.8	63.7 ± 21.8	64.3 ± 21.5
S-BP (mmHg)	167 ± 27	143 ± 27*	135 ± 23**
D-BP (mmHg)	79 ± 15	69 ± 12	66 ± 9*
Proteinuria (g/g-Cr)	6.7 ± 3.9	3.2 ± 3.6*	2.4 ± 2.6**
Hemoglobin (g/dL)	10.3 ± 2.0	11.2 ± 2.0	10.0 ± 1.0
Serum albumin (g/dL)	3.3 ± 0.6	3.6 ± 0.6	3.7 ± 0.5
Total cholesterol (mg/dL)	196 ± 30	170 ± 32*	169 ± 23*
Serum Na (mEq/L)	140 ± 2.1	138 ± 2.9	137 ± 3.7*
Serum K (mEq/L)	4.4 ± 0.8	4.5 ± 0.5	4.3 ± 0.5
Serum Ca (mg/dL)	8.5 ± 0.6	9.0 ± 0.5	9.0 ± 0.9
Serum uric acid (mg/dL)	7.0 ± 1.3	7.7 ± 1.6	8.0 ± 1.9
HbA1c (%)	6.8 ± 1.0	7.0 ± 1.4	6.7 ± 0.9

* $p < 0.05$ vs. 0 month, and ** $p < 0.01$ vs. 0 month

Discussion

In the present study, even in type 2 DKD patients with CKD stage G4 or G5, the addition of HCTZ to consecutive therapy including loop diuretics resulted in improved BP and decreased proteinuria and serum total cholesterol levels with no negative impact on annual eGFR decline.

Regarding DKD progression, thus far, various factors such as age, HbA1c, insulin treatment, eGFR levels, S-BP, hypertension, serum uric acid, serum albumin, hemoglobin, albuminuria, and proteinuria, have been reported to have significant relationships with the decline of eGFR [4–7].

It is already well known that diabetes raises sodium sensitivity, that sodium intake leads to sodium-sensitive hypertension, and that BP levels are positively correlated with urinary sodium excretion in type 2 DM patients [3]. Thiazide diuretics such as HCTZ inhibit the Na^+–Cl^- co-transporter at the luminal side of the distal convoluted tubule (thiazide-sensitive NaCl transporter) and consecutively induce natriuresis. However, there is an assumption that thiazide diuretics are not effective when renal function has declined to 1/3 of normal or less [13], and this has been thought to be nearly established in clinical conditions. On the other hand, the addition of thiazide diuretics has recently been shown to attenuate systemic hypertension, glomerular hydraulic pressure, and albuminuria in rat CKD models [14, 15]. Thus, the efficacy of thiazide diuretics in advanced stage CKD patients with type 2 DKD is still controversial. In the present study, body weight tended to decrease with the improvement of severe edema after HCTZ initiation even though the change was not significant. In addition, HCTZ therapy can be considered to improve BP levels by increasing natriuresis and the ade-

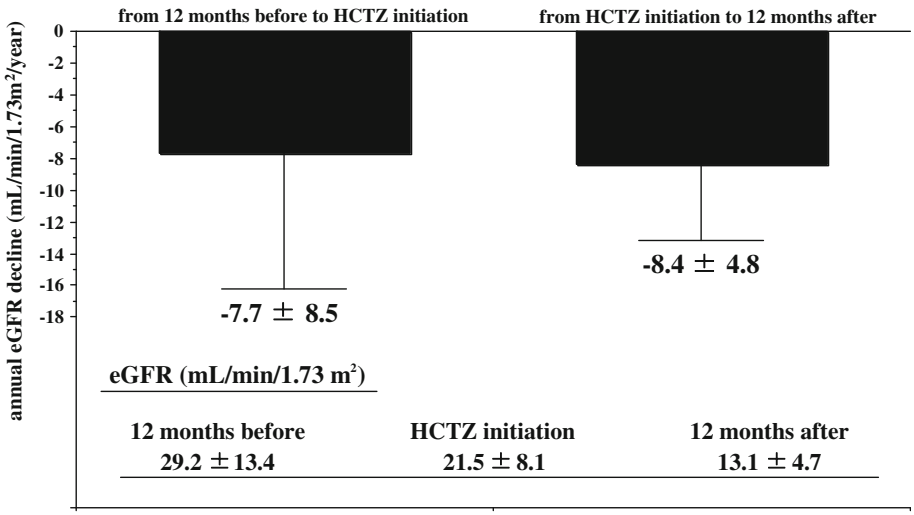

Fig. 1 Difference in annual eGFR decline before and after HCTZ therapy. Although eGFR gradually decreased during this study, annual eGFR decline was not significantly different before and after HCTZ therapy

quate management of body fluids, particularly extracellular fluid. Moreover, the improvement of systemic hemodynamics might be associated with the decrease of proteinuria through the improvement of renal hemodynamics, including glomerular hydraulic pressure, even in type 2 DKD patients with advanced stage CKD.

As to the synergistic effects between HCTZ and other medications, first, the additional effect of HCTZ initiation under the use of loop diuretics should be considered. All patients in this study had been taking loop diuretics such as furosemide and azosemide, and a relatively low dose of HCTZ (13.6 ± 3.8 mg/day) was added at the initiation of this study. Serum concentrations of HCTZ were significantly higher in patients with renal dysfunction than in normal controls taking 12.5 mg HCTZ orally [16], and the dose of HCTZ was previously recommended to be reduced to 1/2–1/4 of the normal daily dose in these patients to avoid dose-dependent side effects [17]. Therefore, in the present study, the added dose of HCTZ was lower than the normal daily dose. The Na^+ diuretic effect of loop diuretics gradually decreased under chronic administration. This is the so-called breaking phenomenon, which is due to epithelial cell hypertrophy, increased basolateral Na^+–K^+-ATPase activity, increased numbers of thiazide-sensitive NaCl transporters, and increased transcellular NaCl-transport capacity in the distal tubule [18]. All patients in this study had been taking loop diuretics for more than 12 months, and so, the breaking phenomenon might, to some extent, have been induced by their chronic administration. In that case, the addition of even low-dose HCTZ can be expected to ameliorate natriuresis, and therefore, the BP level would be decreased along with the improvement in body-fluid conditions. Indeed, it was previously reported that there were significant decreases in S-BP from 153 to 133 mmHg ($p < 0.0001$) and D-BP from 89 to 78 mmHg ($p < 0.0001$) after switching from high-dose ARBs to a combination of normal-dose telmisartan (40 mg/day) and low-dose HCTZ (12.5 mg/day) in 60 CKD patients [19]. This report, in a certain sense, shows the BP-lowering effect of adding low-dose HCTZ in CKD patients, and our results may be consistent with this report. Second, there was a concern regarding the combination of antihypertensive medications, particularly ARBs and thiazide diuretics. ARBs were previously reported to exert renoprotective effects through multiple and complex mechanisms [20]. These mechanisms includes BP reduction by systemic vasodilation, an increase in renal blood flow through renal vasodilation, reduction in intraglomerular pressure through efferent artery vasodilation, and protection of glomerular endothelium and podocyte injuries. Therefore, the use of ARBs has been recommended for the improvement of renal dysfunction and reduction of proteinuria in type 2 DKD patients [21]. In fact, all patients in this study had been taking ARBs prior to the examination. Furthermore, it was recently reported that combination therapy with losartan, categorized as an ARB, and HCTZ has a greater renoprotective effect, including BP improvement and a decrease of albuminuria, than losartan monotherapy in the chronic nephropathy rat model [15] and 5/6 nephrectomy rat model [18, 22]. These reports suggested that the renoprotective effects of combination therapy resulted from the improvement of intrarenal hemodynamics, inhibition of aldosterone production, and anti-inflammatory effects achieved through the regression of albuminuria even in advanced stage CKD. Our findings, such as the improvement of BP levels and the decrease of proteinuria, were nearly identical to these reports, and may be associated with the renoprotective mechanisms mentioned in previous reports [15, 18, 21].

Furthermore, regarding the BP improvement and decrease of proteinuria, the effect of dietary education, especially on sodium restriction, should be pointed out. Although sodium intake was 8.6 ± 4.2 g/day at HCTZ initiation and the 0.9–1.8 g/day reduction in sodium intake during the study was not statistically significant, sodium restriction would decrease sodium retention, improve the body-fluid status and lead to BP improvement in this study. Therefore, sodium restriction similarly to the combination of HCTZ and loop diuretics would have beneficial effects on BP management and proteinuria reduction in advanced stage type 2 DKD patients with severe edema. In addition, total cholesterol significantly decreased after the addition of HCTZ in this study. CKD patients with nephrotic syndrome have increased total and LDL cholesterol levels because of the increased production and decreased catabolism of LDL cholesterol [23]. In addition, plasma cholesterol concentrations were reported to significantly rise with the increase of urinary albumin excretion in type 2 DKD patients [24]. In the present study, statins were taken by 8 out of 11 patients at HCTZ initiation, and these doses remained constant during the study with the exception of 1 case of statin dose reduction. Therefore, the significant decrease of proteinuria induced by HCTZ therapy would be associated with the significant decrease of total cholesterol and the increase of serum albumin concentrations, even though the latter was not significant.

Although this study demonstrated that the addition of HCTZ to treatment with loop diuretics resulted in an improvement of BP levels, decrease of proteinuria, and lowering of total cholesterol, annual eGFR decline was not significantly changed by HCTZ therapy. In general, eGFR is determined by renal blood flow, glomerular filtration area, and glomerular hydraulic pressure. In this study, BP markedly decreased, and the glomerular hydraulic pressure would decrease without an increase in renal blood flow and glomerular filtration area by the addition of HCTZ. In such

conditions, eGFR would further decrease with a reduction in intraglomerular pressure after the addition of HCTZ. On the other hand, the addition of HCTZ in this study decreased proteinuria via marked improvement of systemic BP and the decrease of glomerular hydraulic pressure, and consecutively improved lipid metabolism disorders. Decreased proteinuria and total cholesterol are known to be potent renoprotective factors [25, 26]. Thus, the reason that annual eGFR decline did not accelerate after the addition of HCTZ in this study was that the decrease of proteinuria and improvement of lipid metabolism disorders may prevent the progression of renal dysfunction. Moreover, the mechanism of the renoprotective effects induced by HCTZ, which included marked decreases of systemic BP and glomerular hydraulic pressure, a decrease of proteinuria, and the improvement of lipid metabolism disorders, would differ from the renoprotective mechanism of ARBs and CCBs (L/T type and L/N type), which was mainly a reduction in intraglomerular pressure via vasodilation of the glomerular efferent artery [20, 27].

Regarding the limitations of this study, first of all, the sample size was very small. Furthermore, 3 out of the 20 patients screened for inclusion in this study showed no renoprotective effects during combination therapy with thiazides and loop diuretics and had to initiate HD therapy during the study. Therefore, our results cannot yet be considered justified either generally or for all type 2 DKD patients with advanced renal failure, and so, further study will be required to confirm the associations we found between HCTZ therapy combined with loop diuretics and changes in BP, proteinuria, and annual eGFR decline in type 2 DKD patients.

In conclusion, our findings suggest that the combination of HCTZ and loop diuretics improves BP levels and decreases proteinuria even in advanced stage type 2 DKD patients with severe edema. The addition of HCTZ therapy was not found to negatively affect the change in eGFR in the present study.

Conflict of interest The authors have no conflicts of interest to declare.

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