Antihypertensive and metabolic effects of hydrochlorothiazide versus amlodipine when added to losartan in patients with type 2 diabetes

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Abstract We performed a prospective, randomized, multicenter, parallel-group, per-protocol study to compare the effects of hydrochlorothiazide (HCTZ) and amlodipine as add-on to losartan treatment in hypertensive type 2 diabetic patients. A total of 49 Japanese type 2 diabetic patients with inadequate control of blood pressure while receiving losartan 50 mg were randomly allocated to receive a fixed-dose single-pill combination of HCTZ 12.5 mg plus losartan ($N = 26$) or a free combination of amlodipine 5 mg plus losartan ($N = 23$). During 8 weeks of follow-up, changes in blood pressure and laboratory data including HbA1c, uric acid, and potassium were compared between the groups using analysis of covariance. Systolic and diastolic blood pressure decreased in both groups, the reductions of which were greater in the amlodipine group. However, the least square mean (95 % CI) differences between groups were not statistically significant [2.3 (−6.8 to 11.4) mmHg, $p = 0.618$ and 2.7 (−2.4–7.9) mmHg, $p = 0.293$, respectively]. HbA1c increased in patients receiving HCTZ but not in the amlodipine group. Uric acid also increased in patients receiving HCTZ but decreased in patients receiving amlodipine, yielding a significant between-group difference of 1.0 (0.5–1.5) mg/dl ($p < 0.001$). No intra- or intergroup change was observed

in serum potassium levels. This pilot study suggests that HCTZ and amlodipine result in nonsignificant effects on systolic and diastolic blood pressure reduction when administered as add-on therapy to losartan in hypertensive patients with type 2 diabetes; however, addition of HCTZ may be associated with less favorable effects on metabolic profiles than amlodipine.

Keywords Amlodipine · Diabetes · Hydrochlorothiazide · Hypertension

Introduction

According to the domestic [1] and international guidelines [2–4], angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) have been recommended as the first-line therapy for diabetic patients with hypertension; however, reducing blood pressure to the target levels often requires two or more antihypertensive agents [5, 6]. Calcium channel blockers (CCBs) or diuretics have been recommended as second-line, add-on therapy [1]. Recently, several kinds of single-pill combinations of two or more antihypertensive agents have been introduced in the market, most of which are combinations of an ARB plus a thiazide diuretic or an ARB plus a CCB. The use of single-pill combination therapy provides improved efficacy, tolerability, and patient adherence compared to free combination therapy [7].

Several studies have demonstrated that add-on therapy with thiazide diuretics to renin-angiotensin system (RAS) blockade, compared to that with CCBs, is effective for reducing albuminuria or proteinuria in patients with CKD including diabetic kidney disease [8, 9]. However, thiazide diuretics are also known to induce unfavorable metabolic

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effects such as impaired glucose tolerance, hypokalemia, and hyperuricemia [10–12]. CCBs are associated with lower risk of both cardiovascular and kidney events when administered with ACE inhibitors [13, 14]. Despite data from these well-controlled trials, there are no comparative outcome studies and limited clinical data to support an evidence-based decision on the optimal choice of thiazide diuretics or CCBs as add-on therapy to RAS blockade in diabetic patients. We therefore performed this pilot study to compare the effects of add-on therapy with hydrochlorothiazide (HCTZ) or amlodipine on blood pressure reduction and metabolic profiles in hypertensive type 2 diabetic patients receiving losartan.

Materials and methods

Subjects

This was a prospective, multicenter, randomized, open-labeled, parallel-group, active-controlled, per protocol study. Subjects were recruited from ambulatory Japanese type 2 diabetic patients who had been seen at the Diabetes Center, Tokyo Women's Medical University Hospital, or in two affiliated clinics in Tokyo from 2008 to 2012. Inclusion criteria were (1) age ≥ 20 years, (2) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg while receiving losartan 50 mg (i.e., inadequate blood pressure control on losartan monotherapy), and (3) prior treatment with losartan for more than 6 months. Exclusion criteria were (1) HbA1c ≥ 8.0 %, (2) concomitant insulin administration, (3) myocardial infarction or stroke within 6 months from study initiation, (4) heart failure, New York Heart Association (NYHA) class III or IV, (5) prior history of hyperuricemia or serum uric acid levels ≥ 8.0 mg/dl at baseline, (6) kidney dysfunction defined as serum creatinine ≥ 2.0 mg/dl, (7) secondary or malignant hypertension, and (8) kidney diseases other than diabetic kidney disease.

The protocol was approved by the institutional ethics committee and was registered with the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) under trial identification number UMIN000017820. All study participants provided written informed consent prior to participation.

Study design

As this was a pilot study to evaluate feasibility and effect size, a priori power analysis was not performed. Participants on a stable dose of losartan 50 mg were randomly allocated to a single-pill combination containing losartan 50 mg/HCTZ 12.5 mg or to continued treatment with

losartan 50 mg in free combination with amlodipine 5 mg (i.e., co-administered as separate drugs). During the follow-up period, all diabetes medications were required to be stable to allow evaluation of the effects of the therapy on glycemic control. No other antihypertensive agents were added during the study period.

Endpoints and measurements

Patients were observed at baseline, 4 weeks and for 8 weeks after the start of add-on therapy. Blood pressure was measured once or twice during each clinic visit, while patients were in a sitting position at the clinic office using an automatic oscillometric device. When blood pressure was measured twice, the lower values were used, as these values were considered to reflect a more stable measurement. Fasting blood samples were obtained for laboratory examinations at baseline, 4 and 8 weeks. Pre-specified major endpoints were changes in systolic and diastolic blood pressure and levels of HbA1c from baseline to 8 weeks after randomization. Other outcome measures included a 0.5 % points or more increase in HbA1c from baseline, changes in levels of plasma glucose, serum insulin, uric acid, electrolytes, lipid profiles, and estimated glomerular filtration rate (eGFR). As measures of insulin sensitivity and insulin secretion, homeostasis model assessment-insulin resistance (HOMA-IR) and homeostasis model assessment- β cell function (HOMA- β) [15] were calculated, respectively.

HbA1c was measured by HPLC and standardized according to National Glycohemoglobin Standardized Program (NGSP) units using the formula advocated by the Japan Diabetes Society [16]. GFR was estimated using the equation proposed by the Japanese Society of Nephrology [17].

Statistical analysis

Continuous variables were expressed as arithmetic or geometric means and 95 % confidence interval (CI); categorical data were expressed by actual frequency and percentage. To compare the clinical characteristic and laboratory data between the two groups at baseline, Student's *t* test or Fisher's exact probability test were used. To assess changes in blood pressure and laboratory data during the observation period within each group, analysis of covariance (ANCOVA) with adjustment for multiple comparisons by Dunnett-Hsu test was used. Differences of changes in these variables in the two groups were compared using ANCOVA after adjustments for each baseline value. Missing data were imputed using last observation carried forward (LOCF) analysis. To determine the effects of induced hypokalemia on glucose metabolism,

Spearman's correlational analyses were conducted between changes in serum potassium and glycemic parameters. All analyses were performed using SAS/STAT version 13.1 (SAS institute, Cary, NC, USA). Statistical significance was defined as $p = 0.05$.

Results

Clinical characteristics at baseline

A total of 49 diabetic patients receiving stable losartan therapy were enrolled between 2005 and 2008, 26 of whom were randomized to the combination product containing HCTZ and 23 were allocated to amlodipine. Baseline clinical characteristic and laboratory data are shown in Table 1. Patients randomized to amlodipine tended to be older but this difference did not reach statistical significance. There were no significant baseline differences in systolic/diastolic blood pressure or HbA1c levels between the two groups.

Major endpoints

In patients allocated to the HCTZ/losartan combination, systolic blood pressure significantly decreased from baseline at 8 weeks but not 4 weeks; diastolic blood pressure was significantly decreased at both 4 and 8 weeks (Fig. 1a, b). In patients allocated to add-on amlodipine, systolic and diastolic blood pressure significantly decreased from baseline at both 4 and 8 weeks. Although the reductions in systolic and diastolic blood pressure after adjustment for baseline values were greater in patients receiving amlodipine than in those receiving HCTZ, the between-group differences, determined using the LOCF data set by ANCOVA were not statistically significant (Table 2).

HbA1c levels increased significantly at 4 and 8 weeks from baseline in patients receiving HCTZ; however, changes from baseline for patients receiving amlodipine were not significantly different at either 4 or 8 weeks (Fig. 1c). The between-group differences in changes from baseline for HbA1c using the LOCF data set were not statistically significant (Table 2).

Table 1 Clinical characteristics and laboratory data at baseline in diabetic patients allocated to losartan/HCTZ and losartan/amlodipine

Categorical variables	Losartan/HCTZ		Losartan/amlodipine		<i>P</i> value		
	<i>N</i>	%	<i>N</i>	%			
Sex (female)	26	23.1	23	34.8	0.528		
Use of OHA	26	69.2	23	78.3	0.532		
Continuous variables	<i>N</i>	Mean	95 % CI	<i>N</i>	Mean	95 % CI	<i>P</i> value
Age (years)	26	56	51–61	23	64	58–69	0.051
BMI (kg/m ²)	26	24.9	23.5–26.3	23	25.4	24.0–26.8	0.576
SBP (mmHg)	26	141	136–146	23	147	140–155	0.148
DBP (mmHg)	26	86	80–92	23	85	80–91	0.863
Pulse rate (beats/min)	19	79	73–85	22	77	71–83	0.677
HbA1c (%)	26	7	6.7–7.2	23	7.2	6.9–7.4	0.276
FPG (mg/dl)	24	135	122–148	22	152	134–170	0.108
Insulin (mU/ml) ^a	24	6.9	6.2–8.7	23	7.1	6.3–8.9	0.893
HOMA-IR ^a	24	2.25	1.97–2.95	23	2.54	2.21–3.35	0.545
HOMA-b ^a	23	35.9	31.9–45.9	22	30.6	27.1–39.3	0.375
Serum creatinine (mg/dl)	23	0.74	0.67–0.81	23	0.75	0.69–0.81	0.858
eGFR (ml/min/1.73 m ²)	23	66.6	59.2–74.0	23	62.8	56.5–69.0	0.167
Uric acid (mg/dl)	23	5.4	4.8–6.0	23	5.3	4.7–5.8	0.667
K (mEq/l)	23	4.3	4.1–4.5	23	4.4	4.2–4.5	0.605
Na (mEq/l)	17	141	139–142	23	141	139–142	0.891
Triglycerides (mg/dl) ^a	17	140	118–198	23	140	124–179	0.999
HDL-C (mg/dl)	17	51	42–59	23	58	53–62	0.104
LDL-C (mg/dl)	17	123	108–138	23	115	102–128	0.441

^a Geometric mean. HCTZ hydrochlorothiazide, OHA oral hypoglycemic agent, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, HOMA-IR homeostasis model assessment-insulin resistance, HOMA-β homeostasis model assessment-β cell function, eGFR estimated glomerular filtration rate, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol

Fig. 1 Changes in systolic and diastolic blood pressure and HbA1c in diabetic patients treated with add-on to losartan therapy with hydrochlorothiazide and amlodipine. Changes in systolic blood pressure (SBP, **a**), diastolic blood pressure (DBP, **b**), and HbA1c (**c**) in diabetic patients treated with add-on to losartan therapy with

hydrochlorothiazide (red dots) and amlodipine (blue dots). Data are expressed as least square means and standard error. Asterisks indicate statistically significant from baseline values using analysis of covariance (ANCOVA) with adjustment for multiple comparisons by Dunnett-Hsu test

Other outcome measurements

Increase in HbA1c of more than 0.5 % points was observed in nine patients (34.6 %) treated with HCTZ and seven patients (30.4 %) treated with amlodipine, with no significant difference between groups ($P = 1.000$). Although fasting plasma glucose increased from baseline in both groups, only patients treated with amlodipine had a statistically significant increase; the difference between groups was not significant (Table 2). Uric acid levels increased significantly in the HCTZ group and decreased significantly in the amlodipine group, yielding a significant between-group difference of 1.0 mg/dl (Table 2). Within-group changes from baseline and between-group differences in least square mean changes were not statistically significant for other variables (insulin sensitivity, insulin secretion, eGFR, electrolytes, and lipid profiles).

Finally, correlational analyses were performed between 8-week changes in serum potassium and 8-week changes in glycemic parameters, which yielded no statistically significant difference in either parameter: Spearman's correlation coefficient was 0.144 ($N = 42$, $p = 0.356$) for HbA1c, -0.138 ($N = 39$, $p = 0.398$) for fasting plasma glucose, 0.068 ($N = 38$, $p = 0.686$) for HOMA-IR, and -0.020 ($N = 38$, $p = 0.903$) for HOMA- β . Similar results were obtained in the correlational analyses restricting to patients treated with HCTZ.

Discussion

This randomized control study was a pilot study designed to compare the effects of HCTZ and amlodipine on blood pressure and metabolic parameters when added to losartan

in patients with type 2 diabetes. Our results show that addition of either HCTZ or amlodipine to losartan for 8 weeks significantly decreased both systolic and diastolic blood pressure. The magnitude of the reduction in blood pressure was greater during treatment with amlodipine than HCTZ but the difference between groups was not statistically significant. HbA1c increased in the group receiving HCTZ in combination with losartan but not in patients receiving amlodipine. No intra- or intergroup difference was found in the measures of insulin sensitivity or insulin secretion or serum potassium levels. A significant increase in serum uric acid levels was observed in patients receiving HCTZ, whereas a decrease was observed in patients receiving amlodipine, yielding a significant difference between the two groups.

The reduction in blood pressure with thiazide diuretics and CCBs (either as monotherapy or as add-on to other antihypertensive drugs) has been shown to be equivalent in some studies [8, 13, 18–20], while in other studies, CCBs have been shown to be associated with a greater reduction in blood pressure than thiazide diuretics [21, 22]. In the current study in Japanese diabetic patients, least square mean reduction of systolic and diastolic blood pressure, after adjustment for baseline values, was 2.3 and 2.7 mmHg greater, respectively, for patients receiving amlodipine than HCTZ-treated patients. Although the difference did not reach statistical significance, this may be due to the small sample size in this study.

Effects of antihypertensive medications are expected to be dose-dependent [11], and higher doses of HCTZ may have shown a greater magnitude of blood pressure reduction than amlodipine. A recent systematic review demonstrated that HCTZ at doses of both 12.5 and 25 mg

Table 2 Changes in blood pressure, pulse rate, and laboratory data from baseline in diabetic patients allocated to losartan/HCTZ and losartan/amlodipine

	Difference from baseline				Losartan/amlodipine				Difference in LS mean between groups	95 % CI	P value
	Losartan/HCTZ										
	N	LS mean	95 % CI	P value	N	LS mean	95 % CI	P value			
SBP (mmHg) ^a	26	-7.3	-13.5 to -1.2	0.021	23	-9.6	-16.2 to -3.0	0.005	2.3	-6.8 to 11.4	0.618
DBP (mmHg) ^a	26	-4.6	-8.2 to -1.1	0.012	23	-7.3	-11.0 to -3.6	<0.001	2.7	-2.4 to 7.9	0.293
Pulse rate (beats/min) ^a	19	-0.3	-4.3 to 3.7	0.875	22	0.2	-3.5 to 3.9	0.923	-0.5	-6.0 to 5.0	0.865
HbA1c (%) ^a	26	0.26	0.03-0.48	0.028	23	0.21	-0.03 to 0.44	0.090	0.05	-0.28 to 0.38	0.769
FPG (mg/dl) ^a	24	7.1	-0.5 to 14.7	0.065	22	9.3	1.4 to 17.2	0.023	-2.2	-13.3 to 8.9	0.694
Insulin (μU/ml) ^a	23	-0.8	-2.3 to 1.0	0.412	23	-0.3	-1.7 to 1.1	0.651	-0.4	-2.5 to 1.8	0.740
HOMA-IR ^a	23	-0.20	-0.88 to 0.48	0.549	22	1.37	-0.45 to 0.72	0.637	-0.34	-1.24 to 0.56	0.448
HOMA-β ^a	22	-3.7	-12.2 to 4.8	0.385	22	-6.3	-13.3 to 0.7	0.075	2.6	-8.5 to 13.8	0.635
eGFR (ml/min/1.73 m ²)	22	-0.7	-4.2 to 2.8	0.685	23	2.1	-1.3 to 5.5	0.222	-2.8	-7.7 to 2.1	0.254
Uric acid (mg/dl)	22	0.5	0.2-0.9	0.004	23	-0.5	-0.8 to -0.1	0.013	1.0	0.5 to 1.5	<0.001
Na (mEq/l)	16	-0.3	-1.0 to 0.4	0.404	23	-0.7	-1.4 to -0.1	0.025	0.4	-0.6 to 1.4	0.402
K (mEq/l)	22	-0.1	-0.2 to 0.0	0.107	23	0.0	-0.1 to 0.1	0.777	-0.1	-0.3 to 0.1	0.177
Triglycerides (mg/dl)	16	-4.3	-40.8 to 32.0	0.808	22	-14.0	-45.1 to 17.0	0.365	9.7	-38.4 to 57.7	0.686
HDL-C (mg/dl)	16	-1.3	-4.5 to 1.8	0.388	22	2.1	-0.6 to 4.7	0.121	-3.4	-7.6 to 0.8	0.108
LDL-C (mg/dl)	16	-2.8	-9.9 to 4.3	0.425	22	1.7	-4.4 to 7.8	0.574	-4.5	-13.9 to 4.8	0.334

^a Variables were compared using the last observation carried forward data sets. Other variables were difference from baseline to 8 weeks. *LS* least square. Other abbreviations are listed in the footnote of Table 1

provided inferior 24-h blood pressure reduction than other antihypertensive classes, including CCBs [23]. Reduction of 24-h blood pressure by HCTZ at a dose of 50 mg was comparable to that of other medications. Even in a smaller dose range, a 12.5-mg dose of HCTZ produced less reduction of blood pressure than a 25-mg dose [24]. Nevertheless, any efficacy advantages of a higher dose of HCTZ need to be considered in the context of the potential for greater adverse effects of glucose metabolism and hyperuricemia, which is discussed below, when compared to the 5-mg dose of amlodipine.

Thiazide diuretics were first shown to affect glucose metabolism more than 50 years ago [25]. Treatment with thiazide diuretics was associated with higher incidence of new-onset diabetes in patients with essential hypertension [26, 27] as well as elevated plasma glucose and HbA1c levels in diabetic patients [28, 29]. A recent meta-analysis demonstrated that diabetic patients treated with diuretics had HbA1c levels 0.24 % higher than placebo but this was not statistically significant [28]. Our results are in agreement with these findings. Although the mechanism(s) by which thiazide diuretics provoke glucose intolerance have been incompletely understood, the most widely accepted hypothesis is related to thiazide-induced hypokalemia [30]. Diminished insulin secretion and insulin sensitivity have been shown to be associated with hypokalemia in several studies [31, 32]. In this study, we were unable to find any significant association between changes in serum potassium levels and changes in HbA1c, fasting plasma glucose, or HOMA indices during the study period in either overall or HCTZ-treated patients. However, this may be due to the absence of significant changes in serum potassium levels. The risk of thiazide diuretic-induced hypokalemia is known to be dose-dependent, and a previous study indicated that as low as 12.5 mg of HCTZ caused no or little changes in levels of potassium [33, 34]. Therefore, the reasons for the metabolic changes observed with HCTZ in our study are unclear.

In this study, the levels of uric acid increased after the addition of HCTZ and decreased after the addition of amlodipine, resulting in a significant difference between these two treatment groups. Hyperuricemia is also a common adverse effect of thiazide diuretics, possibly provoked by increases in urate reabsorption through the urate transporter 1 [10]. A meta-analysis has confirmed a dose-dependent increase in serum uric acid in patients treated with thiazide and thiazide-like diuretics [11]. The post hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP) demonstrated that higher levels of baseline serum uric acid were predictive of increased incidence of cardiovascular events as well as that the benefit of diuretic therapy on coronary events was offset in individuals in whom serum uric acid increased after randomization [12].

In contrast, CCBs have been shown to inhibit reabsorption of uric acid in the kidney tubule, causing a decrease in serum uric acid levels [35]. The clinical significance of thiazide diuretic-induced increases in uric acid in diabetic patients needs to be an issue for the future.

Our study has several limitations. First, the number of patients was insufficient to yield definitive conclusions. Second, we were unable to use the same device for blood pressure measurement in the three clinics. Third, we adopted lower blood pressure values when measured two times on the assumption that these values were considered to reflect a more stable measurement, reducing the white coat response. According to the recent Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014), adopting the mean values of two measurements is recommended for the blood pressure values [1]. To evaluate changes in blood pressure more precisely and reliably, usage of mean values of multiple measurements will be needed. Nonetheless, to the best of our knowledge, this is the first randomized controlled study to compare the effects of HCTZ and amlodipine as an add-on to losartan treatment in hypertensive type 2 diabetic patients.

In conclusion, our pilot study suggests that HCTZ and amlodipine result in nonsignificant effects on systolic and diastolic blood pressure reduction when administered as add-on therapy to losartan in hypertensive patients with type 2 diabetes. Although not statistically significant, the numerically greater efficacy of amlodipine might become significant in a larger study. While this difference likely reflects the relatively low dose of HCTZ used in this study (12.5 mg), this dose was nevertheless associated with unfavorable metabolic effects, which might be amplified at higher doses. The clinical significance of these findings is unclear; however, small increases in HbA1c and hyperuricemia may translate into a greater incidence of unfavorable outcomes in diabetic patients. A confirmatory multicenter trial will be necessary to address this hypothesis.

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Compliance with ethical standards

Conflict of interest T. B. has received lecture fees from MSD, Pfizer, and Sumitomo Dainippon and research funding from MSD. O. T. has received lecture fees from MSD and Sumitomo Dainippon. Y. U has received lecture fees from MSD and research funding from MSD, Pfizer, and Sumitomo Dainippon. N. T., M. T., and Y. S. declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent or a substitute for it was obtained from all patients for being included in the study.

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