ORIGINAL ARTICLE

Safety and benefits of a tablet combining losartan and hydrochlorothiazide in Japanese diabetic patients with hypertension

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This study was conducted to determine the effects of a tablet combining losartan/hydrochlorothiazide (L/HCTZ) in comparison with losartan alone in Japanese diabetic patients with hypertension. Thirty consecutive Japanese diabetic patients with hypertension were randomly assigned to group A, receiving losartan alone for the first 3 months, then L/HCTZ for the next 3 months, or group B, receiving L/HCTZ for the first 3 months, then losartan alone for the next 3 months. Clinical and biological parameters were obtained before, and 3 and 6 months after the start of this study. The decreases in systolic and diastolic blood pressure (BP) during treatment with L/HCTZ were significantly greater than in treatment with losartan alone. Both treatments significantly and similarly decreased urinary albumin excretion, the cardio-ankle vascular index (CAVI) and augmentation index (AI). There was no significant difference in metabolic change during both the mono- and combination pharmacotherapies. The tablet combining L/HCTZ significantly reduced systolic and diastolic BP compared with the losartan monotherapy, and offered benefits similar to losartan monotherapy for albuminuria, arterial stiffness assessed by the CAVI and AI, and metabolic effects. Thus, the L/HCTZ tablet could be a useful drug for Japanese diabetic patients with hypertension.

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INTRODUCTION

Achievement of the target blood pressure (BP) is the most crucial objective of antihypertensive treatment. More than two-thirds of hypertensive patients will require two or more antihypertensive agents from different classes to control their BP.^{1,2} Patients with diabetes or renal disease will need a greater intensity of antihypertensive treatment, on an average of 2.6 to 4.3 different classes of antihypertensive agents to attain a BP goal of lower than 130/80 mm Hg.³ The angiotensin II type 1 receptor blocker (ARB) is currently one of the most widely used first-line antihypertensive drugs, especially for diabetic patients with hypertension based on the evidence that it slows the progressive deterioration of kidney function in patients with diabetic nephropathy.⁴ However, it is often difficult to achieve the target BP with dose titration of ARB alone, and other antihypertensive medications are often required to provide sufficient BP control in addition to an ARB.

Hydrochlorothiazide (HCTZ) is a diuretic that has been a standard antihypertensive drug prescribed worldwide because of its cost and efficacy in lowering BP based on the available evidence including the ALLHAT trial⁵ and NICS-EH trial.⁶ The guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection,

Evaluation, and Treatment of High Blood Pressure,⁷ the European Society of Hypertension⁸ and Japanese Society of Hypertension⁹ also recommend combination therapy comprising ARB and thiazide-type diuretics for hypertensive patients. However, add-on HCTZ may have some adverse effects on electrolyte, glucose, lipid and uric acid metabolism, especially in Japanese diabetic patients with hypertension.

The aim of this crossover study was to examine the effects of a tablet combining losartan and HCTZ (L/HCTZ) on urinary albumin excretion (UAE), arterial stiffness, and BP and its adverse effects on the metabolic changes in comparison with losartan alone in Japanese diabetic patients with hypertension. UAE was evaluated as a surrogate marker for cardiovascular morbidity and mortality,¹⁰ and arterial stiffness was assessed by the cardio-ankle vascular index (CAVI) and augmentation index (AI).

METHODS

Study population and design

The subjects of this study comprised 30 consecutive Japanese diabetic patients who had untreated hypertension or uncontrollable hypertension treated with medications except for renin–angiotensin system (RAS) inhibitors. Hypertension was defined as a clinic systolic BP of >140 mm Hg at any time and/or a

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clinic diastolic BP of >90 mm Hg at any time. Patients with serious refractory hypertension defined as more than 120 mm Hg in diastolic BP, history of acute myocardial infarction, stroke, or any other cardiovascular events within 6 months, heart failure with NYHA grade III, or grade IV, history of gout or hyperuricemia at the beginning of this study, kidney dysfunction defined as a serum creatinine (Cr) level of more than 2 mg per 100 ml, liver dysfunction defined as a serum transaminase level more than 3 times higher than normal, bilateral renal artery stenosis, secondary, or malignant hypertension, polycystic kidney disease, congenital kidney deformities, solitary kidney, pregnancy or probable pregnancy, history of allergy to the medication in this study, or those considered inappropriate were excluded from the study. The glomerular filtration rate was estimated by the MDRD equation modified by a Japanese coefficient, as follows:

$$\text{eGFR} = 0.741 \text{ if male gender (or } 0.742 \text{ if female gender)} \\ \times 175 \times \text{Age}^{-0.203} \times \text{Cr}^{-1.154}$$

(where eGFR=estimated glomerular filtration rate, Age=age (years old); and

Cr = serum Cr level (mg per 100 ml)

This study was designed as a crossover study. All patients were randomly assigned either to group A (receiving losartan for the first 3 months, then L/HCTZ for the next 3 months) or group B (receiving L/HCTZ for the first 3 months, then losartan alone for the next 3 months). Five patients (three patients in group A and two patients in group B) were dropped out of the study mainly due to the concern about adverse effects of the medication such as diabetes and hyperuricemia. The doses of losartan and L/HCTZ were fixed throughout the study at 50 mg day⁻¹ and 50 mg per 12.5 mg day⁻¹, respectively, which are typical doses administered in Japanese patients. Clinical and biological parameters were obtained before the start of the study, as well as 3 and 6 months after. During the study period, previous medications and therapies except RAS blockers and diuretics were continued. To achieve the target BP of <130/80 mm Hg, amlodipine was added at a dose of 2.5 mg day⁻¹, and the dose was subsequently increased by 2.5 mg increments at intervals of 4 weeks to a maximum dose of 10 mg day⁻¹. The study was approved by the review board of Keio University Medical School Hospital, and written informed consent was obtained from every subject.

Serum levels of Cr, cystatin C, potassium, uric acid, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, and glycoalbumin, and plasma levels of active renin concentrations (ARC), and aldosterone were measured in venous blood samples drawn in the morning after an overnight fast on the same days as those in which CAVI, AI and BP measurements were taken.

Cardio-ankle vascular index

The CAVI was measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) as described previously.¹¹ Cuffs are applied to the bilateral upper arms and ankles, with the subject lying supine and the head held in the midline position. ECG electrodes are placed on both wrists, and a microphone for detecting heart sounds is placed on the sternum. Patients rested in the supine position for at least 10 min before the start of monitoring. The CAVI was calculated with the following formula:

$$\text{CAVI} = a\{(2\rho/\Delta P) \times \ln(P_s/P_d) \text{PWV}^2\} + b$$

where P_s is systolic BP, P_d is diastolic BP, ΔP is $P_s - P_d$, ρ is blood density and a and b are constants. The number of patients in this study was assumed to be statistically sufficient because the estimated required sample size for pulse wave velocity (PWV) is 15.6 in each group with an α -error of 0.05 and a power of 0.8.

Augmentation index

The AI was measured using an automated tonometric device (HEM-9000AI; Omron Healthcare, Kyoto, Japan) as described previously.¹² Peripheral pressure waveforms were recorded over 30 s from the radial artery at the wrist with the subjects in a sitting position after at least 5 min rest. The AI was calculated with

the following formula:

$$\text{AI} = (\text{late systolic BP} - \text{diastolic BP (DBP)}) / (\text{systolic BP} - \text{DBP}) \times 100 (\%)$$

Urinary albumin excretion

Urinary albumin excretion was evaluated on the basis of the mean albumin-to-creatinine ratio in three nonconsecutive overnight urine samples. Urinary concentrations of albumin and Cr were determined using a turbidimetric immunoassay with a Superior-Microalbumin kit (DPC, Tokyo, Japan) and with the Jaffé reaction using an autoanalyzer.

Statistical analyses

Analyses were performed with StatView 5.0. software (SAS Institute, Cary, NC, USA). The χ^2 -test and Fisher's exact test were used to analyze the proportion of patients who achieved target BP. The changes in biological parameters were analyzed with a one-way analysis of variance for repeated measures combined with the Dunnett and Tukey-Kramer *post hoc* tests. A P -value <0.05 was considered significant. Data are reported as means $\pm$ s.d.

RESULTS

All patients in this study had untreated hypertension or hypertension, which had been inadequately treated for more than a month with medications other than RAS inhibitors. Patient characteristics in baseline values were as follows: age, 53 ± 11 years; the number of male gender, 20; body mass index, $25.2 \pm 4.5 \text{ kg m}^{-2}$; waist circumference, $88 \pm 13 \text{ cm}$; serum Cr, $0.82 \pm 0.16 \text{ mg per } 100 \text{ ml}$; eGFR, $75.2 \pm 14.1 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^2$; cystatin C, $0.74 \pm 0.09 \text{ mg l}^{-1}$; serum potassium, $4.31 \pm 0.24 \text{ mEq l}^{-1}$; serum uric acid, $5.9 \pm 1.4 \text{ mg per } 100 \text{ ml}$; serum total cholesterol, $211 \pm 34 \text{ mg per } 100 \text{ ml}$; serum triglyceride, $161 \pm 153 \text{ mg per } 100 \text{ ml}$; serum high-density lipoprotein cholesterol, $54 \pm 13 \text{ mg per } 100 \text{ ml}$; serum low-density lipoprotein cholesterol, $125 \pm 34 \text{ mg per } 100 \text{ ml}$; blood sugar, $109 \pm 24 \text{ mg per } 100 \text{ ml}$; glycoalbumin, $15 \pm 2.9\%$; plasma ARC, $9.4 \pm 8.5 \text{ pg ml}^{-1}$; plasma aldosterone concentration, $147 \pm 59 \text{ pg ml}^{-1}$; UAE, $25.7 \pm 42.4 \text{ mg gCr}^{-1}$; CAVI, 8.7 ± 1.1 ; AI, $87.2 \pm 11.6\%$; systolic BP, $156 \pm 16 \text{ mm Hg}$; diastolic BP, $98 \pm 16 \text{ mm Hg}$.

To achieve the target BP of <130/80 mm Hg, amlodipine was added during the losartan treatment in two patients at a dose of 5 and 10 mg day⁻¹, respectively. Figure 1 illustrated the changes in the metabolic effects with both drugs. There was no significant change in metabolic parameters with either treatment.

Figure 2 illustrated the changes in clinical parameters with both drugs. The plasma ARC significantly increased from 9.4 ± 8.5 to $70.5 \pm 72.2 \text{ pg ml}^{-1}$ during the L/HCTZ treatment. The plasma ARC after the treatment with L/HCTZ was significantly greater than that after losartan alone. UAE significantly decreased from 25.7 ± 42.4 to $11.5 \pm 17.0 \text{ mg gCr}^{-1}$ during the losartan treatment, whereas UAE significantly decreased from 25.7 ± 42.4 to $6.1 \pm 13.6 \text{ mg gCr}^{-1}$ during the L/HCTZ treatment, although there was no significant difference in UAE values between both treatment periods. The CAVI significantly decreased from 8.7 ± 1.1 to 8.0 ± 1.3 during the losartan treatment, and significantly decreased from 8.7 ± 1.1 to 7.7 ± 1.3 during the L/HCTZ treatment. There was no significant difference in the CAVI between both treatments. The AI significantly decreased from 87.2 ± 11.6 to 77.2 ± 13.9 during the losartan treatment, and significantly decreased from 87.2 ± 11.6 to 77.5 ± 9.6 during the L/HCTZ treatment. There was no significant difference in the AI values between both treatment periods. The systolic BP significantly decreased from 156 ± 16 to $137 \pm 14 \text{ mm Hg}$ during the losartan treatment, whereas the systolic BP significantly decreased from 156 ± 16 to $130 \pm 10 \text{ mm Hg}$ during the L/HCTZ treatment. The systolic BP

Figure 1 Serum creatinine (Cr), estimated glomerular filtration rate (eGFR), serum cystatin C, serum potassium, blood sugar (BS), glycoalbumin (GA), serum uric acid (UA), serum low-density lipoprotein cholesterol (LDL-C), at baseline, after 3 months of treatment with losartan alone (open circles, $n=25$) and with L/HCTZ (closed circles, $n=25$).

after the treatment with L/HCTZ was significantly lower than that after the treatment with losartan alone. The diastolic BP significantly decreased from 98 ± 16 to 87 ± 6 mm Hg during the losartan treatment, whereas the diastolic BP decreased from 98 ± 16 to 81 ± 8 mm Hg during the L/HCTZ treatment. The diastolic BP during the treatment with L/HCTZ was significantly lower than that during the treatment with losartan alone. The percentage of patients having achieved target BP of $<130/80$ mm Hg during the treatment with losartan alone and L/HCTZ was 12 and 32%, respectively, and were not statistically different between both treatment periods. There were no significant changes in other parameters during either treatment period.

DISCUSSION

This study demonstrated that the treatment with the L/HCTZ tablet provided a significantly great reduction in BP compared with losartan

alone, consistent with the previous studies in which ARB+HCTZ combination therapy produced more significant BP reduction than monotherapy with ARB or diuretics.¹³ This might have derived from the enhanced suppression of RAS, as we observed the significantly greater increase of ARC with L/HCTZ treatment than losartan alone. On the other hand, diuretics have been reported to have some adverse effects on the metabolism, such as insulin resistance, hyperuricemia and electrolyte disturbances.¹⁴ In this study, however, the elevation in serum levels of glucose and uric acid and the reduction in serum potassium level during the treatment with L/HCTZ were similar to those during the treatment with losartan alone. As it was expected that the use of losartan and HCTZ in combination would counteract each other's potential adverse effects, which occur when they are given as a monotherapy, most of the undesirable metabolic side effects of thiazide were minimized by the combination with losartan.

Figure 2 Plasma active renin concentration (ARC) and plasma aldosterone concentration (PAC) serum brain natriuretic peptide (BNP), urinary albumin excretion (UAE), the cardio-ankle vascular index (CAVI), augmentation index (AI) and blood pressure (BP) at baseline, after 3 months of treatment with losartan alone (open circles, $n=25$) and with L/HCTZ (closed circles, $n=25$). * $P<0.05$ vs. the baseline. * $P<0.05$ vs. the losartan alone.

Albuminuria is an important predictor of cardiovascular events and of progression to end-stage renal disease in diabetic patients with hypertension.^{15,16} In this study, the reduction in UAE with the 3-month combination therapy with 50 mg of losartan and 12.5 mg of HCTZ was similar to that with the losartan alone. This was inconsistent with a recent study showing that add-on 6-month treatment with a low sodium diet or 25 mg of HCTZ further decreased proteinuria in patients treated with 100 mg of losartan.¹⁷ As our study demonstrated that the BP reduction during the L/HCTZ tablet was significantly greater than the losartan alone, more extended observation period might have provided the significant difference in proteinuria between both treatments.

Both treatments with losartan and L/HCTZ significantly and similarly improved the CAVI, which reflects arterial stiffness with less dependency on BP compared with PWV,¹¹ and AI, which is a marker for the magnitude of arterial wave reflections. Previous studies have demonstrated that ARB improves arterial stiffness assessed by PWV independently of lowering BP in diabetic patients¹⁸ and in hypertensive patients,¹⁹ and that thiazide diuretics have a limited effect on arterial stiffness.^{20,21} In addition, angiotensin-converting enzyme inhibitors and ARBs have been reported to reduce AI in hypertensive patients,²² and monotherapy with HCTZ has been reported not to decrease AI even if it reduced BP to an extent similar to ARB.²³ On the basis of these evidences, ARB has a BP-independent benefit on vascular wall properties. Thus, the improvement of the CAVI and AI might result from the RAS blockade but not from the reduction in BP or HCTZ treatment. As arterial stiffness is a

powerful and independent risk factor for mortality in cardiovascular events,²⁴ L/HCTZ could be one of the useful antihypertensive drugs with cardiovascular protective properties. Although previous studies have demonstrated the benefits of a fixed-dose angiotensin-converting enzyme inhibitor–diuretic combination for AI compared with diuretic monotherapy,²⁵ there have not been any studies which examined the effects of a fixed-dose ARB–diuretic combination on CAVI or AI in comparison with diuretic alone. Further studies will be needed to elucidate the difference between the two treatments.

There were some other limitations in interpreting the results of this study. First, the trial population was comparatively small in number. Second, we did not compare the L/HCTZ tablet with dose-titrated ARBs. Thus, this study did not provide a definitive conclusion regarding the superiority of the L/HCTZ tablet vs. losartan alone in reducing BP. However, as no difference in adverse effects was observed during the treatment periods, the L/HCTZ tablet is a safe and useful antihypertensive drug in diabetic patients with hypertension. Finally, prognostic events were not examined. Further studies will be needed to confirm the benefits of the L/HCTZ therapy.

In conclusion, the treatment with the tablet combining L/HCTZ exerted a greater reduction in BP than losartan monotherapy, and decreased albuminuria and arterial stiffness assessed by CAVI and AI to the levels similar to losartan monotherapy. As metabolic adverse effects were similar in the L/HCTZ treatment and losartan treatment, the L/HCTZ tablet could be a safe and potent antihypertensive drug in Japanese diabetic patients with hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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