

Adding thiazide to a rennin-angiotensin blocker regimen to improve left ventricular relaxation in diabetes and nondiabetes patients with hypertension

Takeshi Takami¹
Hiroshi Ito²
Katsuhisa Ishii³
Kenei Shimada⁴
Katsuomi Iwakura⁵
Hiroyuki Watanabe⁶
Shota Fukuda⁷
Junichi Yoshikawa⁸

¹Department of Internal Medicine, Clinic Jingumae, Kashihara, Japan;

²Department of Cardiovascular Medicine, Okayama University, Graduate School of Medicine, Okayama, Japan; ³Department of Cardiology, Kansai Electric Power Hospital, Osaka, Japan; ⁴Department of Internal Medicine and Cardiology, Osaka City University of Medicine, Osaka, Japan; ⁵Cardiovascular Center, Sakurabashi Watanabe Hospital, Osaka, Japan; ⁶Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan; ⁷Department of Medicine, Osaka Ekisaikai Hospital, Osaka, Japan; ⁸Nishinomiya Watanabe Cardiovascular Center, Nishinomiya, Japan

Abstract: The urinary albumin to creatinine ratio (UACR) is an independent predictor of outcomes in patients with diastolic dysfunction. Thus, we investigated the relationship between diastolic dysfunction, UACR, and diabetes mellitus (DM) in the EDEN study. We investigated the effect of switching from an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) to a combination of losartan and hydrochlorothiazide on left ventricular (LV) relaxation in patients with hypertension and diastolic dysfunction. We enrolled 106 patients with and 265 patients without DM. All patients had diastolic dysfunction and had not achieved their treatment goals with an ACEi or ARB. The measurements of e' velocity and E/e' ratio was performed with echocardiography as markers of LV diastolic function. We switched the ACEi or ARB to losartan/hydrochlorothiazide and followed these patients for 24 weeks. UACR was decreased in patients with DM (123.4 ± 288.4 to 66.5 ± 169.2 mg/g creatinine; $P = 0.0024$), but not in patients without DM (51.2 ± 181.8 to 39.2 ± 247.9 mg/g creatinine; $P = 0.1051$). Among DM patients, there was a significant relationship between changes in UACR and changes in e' velocity ($r = -0.144$; $P = 0.0257$) and between changes in estimated glomerular filtration rate and changes in the E/e' ratio ($r = -0.130$; $P = 0.0436$). Among patients without DM, there was a significant relationship between changes in high-sensitivity C-reactive protein (hs-CRP) and changes in E/e' ($r = 0.205$; $P = 0.0010$). Multivariate analysis demonstrated changes in hemoglobin A_{1c} levels as one of the determinants of change of e' and E/e' in patients with DM, whereas hs-CRP was the determinant of change of e' among patients without DM. These data suggest that improvement in LV diastolic function is associated with an improvement of DM and a concomitant reduction in UACR among DM patients, and with a reduction of hs-CRP in patients without DM when thiazide is added to a renin-angiotensin blocker treatment regimen.

Keywords: diastolic dysfunction, diabetes, urinary albumin to creatinine ratio, losartan, HCTZ

Introduction

Increased excretion of albumin into urine is an established risk factor for mortality, cardiovascular events, and adverse renal outcomes in the general population,^{1,2} as well as in patients with diabetes mellitus (DM)^{3,4} and those with hypertension.^{5,6} Increased albumin excretion may be a marker of diffuse vascular injury, systemic inflammation, activation of the renin-angiotensin system, altered glomerular hemodynamics, or abnormal tubular function.⁷⁻⁹ Many, if not all, of these pathophysiological abnormalities also occur during heart failure.^{10,11} The prevalence of microalbuminuria in hypertensive and DM patients (10%–15% and 15%–20%, respectively) is higher than

Correspondence: Takeshi Takami
Department of Internal Medicine,
Clinic Jingumae, Confort Yagi
5-4-41 Naizencho, Kashihara,
Nara 634-0804, Japan
Tel +81 744 238 568
Fax +81 744 236 818
Email takami66@m5.kcn.ne.jp

that in the general population (6%–8%).¹² Microalbuminuria is more frequent among patients with diastolic heart failure than in those with systolic heart failure (40% versus 24%).¹³ Recent data suggest that in the context of severe abnormalities of endothelial function, as in heart failure, albuminuria is a strong predictor of endothelial dysfunction^{14,15} and of high levels of circulating inflammatory mediators.^{14,16,17} The level of albumin in the urine is a predictor of heart failure in the general population and in patients with cardiovascular risk, such as those with DM.

In this study, we analyzed a subset of the data from the EDEN study.¹⁸ In the EDEN study, switching from an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) to losartan/hydrochlorothiazide (HCTZ) was associated with a reduction in blood pressure (BP), improvement in left ventricular (LV) relaxation, amelioration of heart failure, and attenuation of systemic inflammation in patients with hypertension and diastolic dysfunction. There were no changes in fasting glucose levels, hemoglobin A_{1c} (HbA_{1c}), fasting insulin levels, or homeostasis model assessment insulin resistance (HOMA-R) after switching to losartan/HCTZ. However, the urinary albumin to creatinine ratio (UACR), systolic BP, and high-sensitivity C-reactive protein (hs-CRP) levels were lower at final follow-up than at prior to losartan/HCTZ treatment. UACR is elevated in DM patients, as compared to non-DM patients.¹² In the original EDEN study, changes in diastolic dysfunction (e' and E/e') were associated with changes in hs-CRP. However, the association between UACR and DM was not examined in the original study.

The aims of this study were: (1) to determine the impact of the change in UACR in DM and non-DM patients; (2) to determine the impact of the relationship between diastolic dysfunction (e' or E/e') and UACR in DM and non-DM patients; and (3) to determine the impact of the relationship between diastolic dysfunction (e' or E/e') and hs-CRP in DM and non-DM patients using the EDEN study dataset.

Methods

Study population

To determine their eligibility for inclusion in this study, we used echocardiography to assess the systolic and diastolic function of men and women who were 20 to 80 years of age, had a history of stage 1 or 2 essential hypertension (mean BP measurement, >140 mmHg systolic or >90 mmHg diastolic), and were receiving treatment with an ACEi or ARB. Diastolic dysfunction was defined as a mitral annular relaxation velocity of ≤ 8 cm/second. Exclusion criteria

were an LV ejection fraction of <50%, septal mitral annular relaxation velocity of >8 cm/s, treatment with diuretics, and atrial fibrillation at baseline. The study protocol was approved by the ethics committees of the Osaka Foundation for the Prevention of Cancer and Cardiovascular Diseases, and written informed consent was obtained from all patients before any study procedures were conducted. In the present study, we compared data from participating patients with and without type 2 DM.

Study protocol

The patients were followed for at least 4 weeks to confirm that the target BP (systolic BP of <130/80 mmHg) was not achieved by treatment with an ACEi or ARB. All patients underwent echocardiographic screening for systolic and diastolic function before altering their treatment regimen. ACEi or ARB administration was discontinued, and the treatment regimen was switched to losartan 50 mg/HCTZ 12.5 mg. No other medications were changed during the study period. BP and heart rate were measured at each study visit while patients were in a seated position. The adequacy of antihypertensive therapy was determined based on measured BP. The use of any concomitant antihypertensive medication was recorded at each study visit. If BP was not adequately controlled, treatment in addition to diuretics was considered. Patients who received such additional treatment were excluded from this study.

Patients were assessed at 4-week to 8-week intervals for at least 24 weeks. At the end of the study, patients underwent echocardiographic assessment. Blood and urine tests were performed at baseline and at completion of the study. We collected blood samples from fasted patients for measurement of brain natriuretic peptide (BNP), hs-CRP, and additional exploratory blood analyses. Urine was collected for measurement of spot UACR. We used the following formula to calculate estimated glomerular filtration rate (eGFR):

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine} \\ (-1.094) \times \text{age} (-0.287)$$

The resulting eGFR value was adjusted for female patients by multiplying it by 0.739.¹⁹

Echocardiographic data analysis

Measurement of echocardiographic data was performed as described previously.¹⁸ Doppler tissue interrogation of longitudinal mitral annular velocity was recorded at the septal annulus in the apical four-chamber view throughout

the cardiac cycle. The peaks of apically directed systolic (s') and early diastolic (e') myocardial velocities were measured. In the original study,¹⁸ primary endpoints were changes in e' velocity and the ratio of mitral inflow velocity to e' velocity (E/e' ratio) between baseline and follow-up. Secondary measures included changes in BP, heart rate, wall thickness, LV mass index, and the left atrial volume index between baseline and follow-up.

Statistical analysis

All results are expressed as the mean \pm SD or as proportions (%) unless otherwise specified. Baseline group differences were compared using the unpaired t test for parametric data and the Wilcoxon rank sum tests for nonparametric data, respectively. The paired t test was used to compare parametric data, while the Wilcoxon signed rank test was used to

compare nonparametric data before and after treatment within groups. Chi-square tests were used for categorical variables. Paired t -tests were used to compare continuous variables before and after treatment within groups.

After adjusting for baseline values, the comparison between DM and non-DM patients was performed using analysis of covariance for parametric data, and the van Elteren test for nonparametric data. Correlations between continuous variables were assessed using bivariate analysis, and Pearson's coefficient was estimated. Multivariate linear regression analysis was used to determine the independent factors of changes in e' velocity and E/e' in patients with and without DM, respectively. The following factors were included in the analysis: age, body mass index (BMI), and changes in systolic blood pressure, eGFR, HbA_{1c}, and UACR. Differences were considered statistically significant at P -values < 0.05 .

Table I Background characteristics

| | DM (-) | DM (+) | P value |
|----------------------------------|------------------------|------------------------|---------|
| N | 265 | 106 | |
| Mean age (SD), years | 67.755 (9.852) | 66.887 (9.564) | 0.4309 |
| Women, n (%) | 100 (37.7) | 35 (33.0) | 0.3936 |
| Hyperlipidemia, n (%) | 136 (51.3) | 78 (73.6) | 0.0004 |
| Renal disease, n (%) | 14 (5.3) | 17 (16.0) | 0.0023 |
| ASO, n (%) | 8 (3.0) | 6 (5.7) | 0.3282 |
| Myocardial infarction, n (%) | 11 (4.2) | 8 (7.5) | 0.3378 |
| Angina pectoris, n (%) | 41 (15.5) | 32 (30.2) | 0.0056 |
| Cerebral infarction, n (%) | 12 (4.5) | 5 (4.7) | 0.9847 |
| Cerebral hemorrhage, n (%) | 2 (0.8) | 2 (1.9) | 0.6275 |
| TIA, n (%) | 3 (1.1) | 4 (3.8) | 0.2379 |
| Smoking, n (%) | 57 (21.5) | 27 (25.5) | 0.8617 |
| Drinking (%) | 126 (47.5) | 50 (47.2) | 0.7436 |
| NYHA I, n (%) | 155 (58.5) | 61 (57.5) | 0.3019 |
| NYHA 2, n (%) | 98 (37.0) | 40 (37.7) | |
| NYHA 3, n (%) | 2 (0.8) | 3 (2.8) | |
| BMI (SD), kg/m ² | 24.856 (3.072) | 26.335 (3.768) | 0.0001 |
| SBP (SD), mmHg | 155.083 (16.435) | 156.245 (19.070) | 0.5575 |
| DBP (SD), mmHg | 88.430 (11.847) | 85.745 (13.240) | 0.0575 |
| HR (SD), bpm | 72.783 (11.204) | 72.106 (12.224) | 0.6302 |
| Serum creatinine (SD), mg/dL | 0.820 (0.222) | 0.864 (0.274) | 0.1081 |
| Uric acid (SD), mg/dL | 5.946 (1.529) | 5.958 (1.276) | 0.9453 |
| Fasting BS (SD), mg/dL | 103.640 (16.640) | 129.264 (36.747) | <0.0001 |
| HbA _{1c} (NGSP) (SD), % | 5.854 (0.428) | 6.629 (0.794) | <0.0001 |
| BNP (median, Q1–Q3), pg/dL | 28.750 (17.450–47.100) | 34.400 (19.200–54.600) | 0.1866 |
| hs-CRP (median, Q1–Q3), mg/dL | 0.200 (0.054–0.780) | 0.245 (0.056–0.900) | 0.7006 |
| UACR (median, Q1–Q3), mg/g · Cr | 17.800 (9.200–38.200) | 28.150 (16.350–65.700) | <0.0001 |
| HOMA-R (SD) | 2.897 (3.507) | 5.948 (6.992) | <0.0001 |
| e' velocity (SD), cm/s' | 5.603 (1.419) | 5.335 (1.295) | 0.0923 |
| E/e' ratio (SD) | 11.683 (3.520) | 13.240 (4.099) | 0.0003 |
| LVMI (SD), g/m ² | 99.330 (21.063) | 101.961 (22.574) | 0.2919 |
| EF (SD), % | 67.059 (9.433) | 67.599 (8.259) | 0.6065 |

Abbreviations: ASO, arteriosclerosis obliterans; TIA, transient ischemic attack; Drinking, alcohol consumption; NYHA, New York Heart Association; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BS, blood sugar; BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; UACR, urinary albumin to creatinine ratio; Cr, creatinine; HOMA-R, homeostasis model assessment insulin resistance; LVMI, left ventricular mass index; EF, ejection fraction; HbA_{1c}, hemoglobin A_{1c}; NGSP, National Glycohemoglobin Standardization Program; DM, diabetes mellitus.

Table 2 Changes in hemodynamic and laboratory data when switched from ACEi or ARB to losartan/HCTZ

| | DM (-) | | DM (+) | | DM versus non-DM P value |
|----------------------------------|------------------------|--------------------------|------------------------|-------------------------|-----------------------------|
| | 0W | 24W | 0W | 24W | |
| SBP (SD), mmHg | 155.083 (16.435) | 131.860 (11.823)** | 156.245 (19.070) | 132.915 (13.785)** | |
| ΔSBP | | -23.223 (16.963) | | -23.330 (19.812) | P = 0.5592 |
| DBP (SD), mmHg | 88.430 (11.847) | 76.513 (10.219)** | 85.745 (13.240) | 75.877 (9.669)** | |
| ΔDBP | | -11.917 (10.366) | | -9.868 (13.716) | P = 0.6598 |
| HR (SD), bpm | 73.285 (11.071) | 70.711 (11.274)** | 72.645 (14.093) | 70.301 (11.833) | |
| ΔHR | | -2.574 (8.958) | | -2.344 (11.846) | P = 0.9883 |
| TC (SD), mg/dL | 204.558 (30.129) | 195.445 (29.384)** | 197.41 (33.871) | 194.562 (36.181) | |
| ΔTC | | -9.113 (23.660) | | -2.848 (27.609) | P = 0.1278 |
| HDL-C (SD), mg/dL | 56.628 (14.143) | 54.905 (13.483)* | 52.34 (14.150) | 51.509 (13.300) | |
| ΔHDL-C | | -1.723 (8.653) | | -0.831 (8.311) | P = 0.9113 |
| TG (SD), mg/dL | 150.175 (96.026) | 135.110 (58.220)* | 173.189 (132.911) | 155.792 (80.927)* | |
| ΔTG | | -15.065 (83.409) | | -17.397 (90.168) | P = 0.0439 |
| AST (SD), IU/L | 26.016 (8.835) | 25.899 (8.399) | 26.340 (8.959) | 26.010 (7.612) | |
| ΔAST | | -0.117 (6.996) | | -0.330 (7.358) | P = 0.9086 |
| ALT (SD), IU/L | 24.766 (12.495) | 24.722 (12.553) | 27.979 (20.748) | 25.866 (15.155) | |
| ΔALT | | -0.044 (8.439) | | -2.113 (18.143) | P = 0.5641 |
| γ-GTP (SD), IU/L | 50.300 (44.885) | 46.288 (39.953)* | 46.000 (38.234) | 40.383 (32.277) | |
| Δγ-GTP | | -4.012 (24.954) | | -5.617 (29.671) | P = 0.3030 |
| Total protein (SD), g/dL | 7.266 (0.480) | 7.230 (0.496) | 7.291 (0.495) | 7.265 (0.386) | |
| ΔTotal protein | | -0.036 (0.453) | | -0.026 (0.485) | P = 0.6456 |
| Serum albumin (SD), g/dL | 4.387 (0.431) | 4.297 (0.340)* | 4.373 (0.406) | 4.340 (0.354) | |
| ΔSerum albumin | | -0.090 (0.395) | | -0.033 (0.388) | P = 0.1810 |
| Total bilirubin (SD), mg/dL | 0.714 (0.301) | 0.730 (0.300) | 0.640 (0.315) | 0.648 (0.328) | |
| ΔTotal bilirubin | | 0.016 (0.203) | | 0.008 (0.178) | P = 0.3131 |
| ALP (SD), IU/L | 235.713 (68.466) | 219.910 (64.671)** | 239.418 (78.527) | 220.769 (65.363)* | |
| ΔALP | | -15.803 (36.267) | | -18.649 (56.156) | P = 0.6996 |
| LDH (SD), IU/L | 209.701 (69.758) | 201.525 (46.620)* | 219.274 (87.763) | 210.200 (58.519) | |
| ΔLDH | | -8.176 (57.202) | | -9.074 (77.837) | P = 0.3106 |
| CPK (SD), IU/L | 119.809 (70.563) | 132.178 (81.467)* | 113.948 (55.156) | 122.510 (65.095) | |
| ΔCPK | | 12.369 (65.726) | | 8.562 (45.841) | P = 0.4599 |
| BUN (SD), mg/dL | 16.875 (4.397) | 17.994 (5.496)* | 17.259 (4.866) | 18.651 (4.942)* | |
| ΔBUN | | 1.119 (4.610) | | 1.392 (4.164) | P = 0.4356 |
| Serum creatinine (SD), mg/dL | 0.820 (0.223) | 0.850 (0.238)** | 0.864 (0.274) | 0.882 (0.263) | |
| ΔSerum creatinine | | 0.030 (0.119) | | 0.018 (0.147) | P = 0.6141 |
| Uric acid (SD), mg/dL | 5.916 (1.435) | 5.966 (1.515) | 5.958 (1.276) | 5.918 (1.345) | |
| ΔUric acid | | 0.050 (1.461) | | -0.040 (1.139) | P = 0.6144 |
| Na (SD), mEq/L | 141.747 (1.900) | 141.356 (2.567)* | 141.490 (2.052) | 141.110 (2.025) | |
| ΔNa | | -0.391 (2.507) | | -0.380 (2.343) | P = 0.6431 |
| K (SD), mEq/L | 4.243 (0.377) | 4.137 (0.402)** | 4.269 (0.361) | 4.143 (0.352)* | |
| ΔK | | -0.106 (0.402) | | -0.126 (0.369) | P = 0.8829 |
| CL (SD), mEq/L | 104.004 (2.501) | 103.025 (3.242)** | 103.959 (2.182) | 102.939 (2.885)* | |
| ΔCL | | -0.979 (3.395) | | -1.020 (2.922) | P = 0.8514 |
| Fasting BS (SD), mg/dL | 103.702 (16.687) | 105.095 (21.075) | 129.264 (36.747) | 125.104 (37.483) | |
| ΔFasting BS | | 1.393 (20.190) | | -4.160 (33.422) | P = 0.0946 |
| HbA _{1c} (NGSP) (SD), % | 5.847 (0.433) | 5.802 (0.496) | 6.653 (0.814) | 6.611 (0.785) | |
| ΔHbA _{1c} | | -0.045 (0.252) | | -0.042 (0.681) | P = 0.0057 |
| hs-CRP (median, IQ-3Q), mg/dL | 0.200 (0.054-0.780) | 0.113** (0.042-0.300) | 0.245 (0.056-0.900) | 0.086* (0.040-0.300) | P = 0.1207 |
| IRI (SD), μU/mL | 10.671 (10.827) | 11.544 (13.564) | 16.245 (14.877) | 13.428 (14.937) | |
| ΔIRI | | 0.873 (14.154) | | -2.817 (19.494) | P = 0.9170 |
| HOMA-R (SD) | 2.902 (3.538) | 3.284 (4.588) | 5.763 (7.110) | 4.141 (4.636)* | |
| ΔHOMA-R | | 0.382 (4.549) | | -1.622 (7.663) | P = 0.9071 |

(Continued)

Table 2 (Continued)

| | DM (-) | | DM (+) | | DM versus non-DM P value |
|----------------------------------|---------------------------|----------------------------|---------------------------|---------------------------|-----------------------------|
| | 0W | 24W | 0W | 24W | |
| eGFR (SD) | 68.963 (16.569) | 66.647 (17.216)** | 68.165 (20.203) | 66.335 (20.968) | |
| Δ eGFR | | -2.316 (8.820) | | -1.830 (13.367) | P = 0.7421 |
| BNP (median, I Q–3Q), pg/mL | 28.750 (17.450–47.100) | 19.600* (10.500–36.900) | 34.400 (19.200–54.600) | 19.400 (10.250–46.600) | P = 0.9505 |
| UACR (median, I Q–3Q), mg/g · Cr | 17.800 (9.200–38.200) | 9.900 (5.500–16.500) | 28.150 (16.350–65.700) | 15.400* (8.200–36.500) | P = 0.9832 |

Notes: *0W versus 24W $P < 0.05$; **0W versus 24W $P < 0.0001$.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GTP, gamma glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CPK, creatinine phosphokinase; BUN, blood urea nitrogen; BS, blood sugar; hs-CRP, high sensitivity C reactive protein; IRI, immunoreactive insulin; HOMA-R, homeostasis model assessment insulin resistance; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; UACA, urinary albumin to creatinine ratio; Cr, creatinine; W, weeks; SD, standard deviation; DM, diabetes mellitus.

Results

Patient characteristics

We analyzed data from 371 participants in the original EDEN study. Of these, 106 patients had DM at baseline and 265 did not. The percentage of patients using ARBs and ACE did not differ significantly between DM (89.6% and 10.4%, respectively) and non-DM (87.1% and 12.9%, respectively) patients. Table 1 summarizes the baseline characteristics of patients with and without DM. Hyperlipidemia, renal disease, angina pectoris, BMI, fasting blood sugar, HbA_{1c}, UACR, HOMA-R, and E/e' were higher in patients with DM than in those without. However, there were no significant differences in age, sex, myocardial infarction, cerebral infarction, cerebral hemorrhage, transient ischemic attacks, smoking, alcohol consumption, New York Heart Association classification, systolic BP, diastolic BP, heart rate, serum creatinine, uric acid, BNP, hs-CRP, e', LV mass index, or ejection fraction between the two groups.

Changes in hemodynamic and laboratory data

Table 2 summarizes the changes in hemodynamic and laboratory data in patients with and without DM between baseline and at least 24 weeks after losartan/HCTZ treatment. Systolic BP, diastolic BP, triglycerides, alkaline phosphatase, blood urea nitrogen, potassium, chloride, and hs-CRP levels decreased in both groups after treatment with losartan/HCTZ. B-type natriuretic peptide, eGFR, sodium, lactate dehydrogenase, serum albumin, γ -glutamyl transpeptidase, heart rate, total cholesterol, and high-density

lipoprotein-cholesterol decreased, while serum creatinine and creatinine phosphokinase increased in non-DM patients after losartan/HCTZ treatment. UACR and HOMA-R decreased in DM patients after losartan/HCTZ treatment. Baseline BP was similar between groups, and the reduction in BP after losartan/HCTZ treatment was similar for DM and non-DM patients. Although UACR and HOMA-R decreased in DM patients after losartan/HCTZ treatment, baseline UACR was higher in patients with DM than in those without DM. After adjusting for baseline data, a greater decrease in HbA_{1c} was observed in DM patients than in non-DM patients.

Changes in echocardiographic parameters

Table 3 summarizes the changes in echocardiographic parameters in patients with and without DM between baseline values and those obtained after losartan/HCTZ treatment. LV end-diastolic dimension, left atrial dimension, left atrial volume index, interventricular septal wall thickness, posterior wall thickness, isovolumetric relaxation time, E/e', and the LV mass index were lower in both groups after treatment than at baseline, while e' and s' were higher in both groups after losartan/HCTZ than at baseline. Early ventricular filling velocity was higher in non-DM patients after losartan/HCTZ treatment than at baseline; however, analysis of covariance revealed no significant difference between the DM and non-DM groups.

Relationship to UACR

Table 4 shows the relationship between changes in diastolic function and changes in renal function. Changes in UACR

Table 3 Changes in echocardiographic parameters when switched from ACEi or ARB to losartan/HCTZ

| | DM (-) | | DM (+) | | DM versus non-DM P value |
|------------------------------|------------------|--------------------|------------------|-------------------|-----------------------------|
| | 0W | 24W | 0W | 24W | |
| LVDd (SD), cm | 4.730 (0.458) | 4.669 (0.439)* | 4.775 (0.423) | 4.689 (0.462)* | |
| Δ LVDd | | -0.061 (0.320) | | -0.086 (0.363) | <i>P</i> = 0.7056 |
| LVDs (SD), cm | 2.951 (0.453) | 2.925 (0.509) | 2.964 (0.438) | 2.903 (0.455) | |
| Δ LVDs | | -0.026 (0.426) | | -0.061 (0.320) | <i>P</i> = 0.4696 |
| LVDd/LVDs (SD) | 1.627 (0.197) | 1.627 (0.222) | 1.632 (0.177) | 1.637 (0.181) | |
| Δ LVDd/LVDs | | 0.000 (0.200) | | 0.005 (0.191) | <i>P</i> = 0.7438 |
| LAD (SD), cm | 4.066 (0.791) | 3.947 (0.677)** | 4.149 (0.855) | 4.031 (0.751)* | |
| Δ LAD | | -0.119 (0.393) | | -0.118 (0.390) | <i>P</i> = 0.5771 |
| LAVI (SD), mL/m ² | 41.598 (15.169) | 38.596 (14.124)** | 43.926 (16.240) | 40.874 (15.531)* | |
| Δ LAVI | | -3.002 (8.843) | | -3.052 (9.162) | <i>P</i> = 0.6367 |
| IVST (SD), cm | 0.990 (0.158) | 0.965 (0.157)* | 1.027 (0.163) | 0.997 (0.138)* | |
| Δ IVST | | -0.025 (0.108) | | -0.030 (0.106) | <i>P</i> = 0.6132 |
| PWTh (SD), cm | 0.979 (0.138) | 0.949 (0.137)** | 1.015 (0.142) | 0.980 (0.134)* | |
| Δ PWTh | | -0.030 (0.108) | | -0.035 (0.113) | <i>P</i> = 0.5495 |
| IVST/PWTh (SD) | 1.015 (0.116) | 1.020 (0.110) | 1.013 (0.092) | 1.021 (0.081) | |
| Δ IVST/PWTh | | 0.005 (0.131) | | 0.008 (0.114) | <i>P</i> = 0.9372 |
| E (SD), cm/s | 62.428 (14.480) | 62.604 (13.600) | 67.854 (18.067) | 67.147 (16.785) | |
| Δ E | | 0.176 (12.163) | | -0.707 (15.706) | <i>P</i> = 0.2887 |
| A (SD), cm/s | 80.926 (16.042) | 77.627 (16.195)** | 85.703 (20.875) | 83.337 (18.441) | |
| Δ A | | -3.299 (10.912) | | -2.366 (16.075) | <i>P</i> = 0.0800 |
| E/A (SD) | 0.790 (0.203) | 0.831 (0.226)* | 0.817 (0.227) | 0.824 (0.220) | |
| Δ E/A | | 0.041 (0.175) | | 0.007 (0.210) | <i>P</i> = 0.2010 |
| DT (SD), msec | 240.809 (54.843) | 231.952 (47.590)* | 232.006 (53.680) | 238.102 (48.154) | |
| Δ DT | | -8.857 (56.237) | | 6.096 (52.624) | <i>P</i> = 0.0610 |
| IRT (SD), msec | 120.108 (29.373) | 112.602 (25.911)** | 120.808 (35.329) | 112.822 (30.554)* | |
| Δ IRT | | -7.506 (21.677) | | -7.986 (27.655) | <i>P</i> = 0.9365 |
| e' (SD), cm/s' | 5.603 (1.419) | 6.518 (1.825)** | 5.335 (1.295) | 6.389 (1.778)** | |
| Δ e' | | 0.915 (1.634) | | 1.054 (1.592) | <i>P</i> = 0.7750 |
| s' (SD), cm/s' | 7.806 (2.693) | 8.269 (2.644)** | 7.517 (2.348) | 8.006 (2.491)* | |
| Δ s' | | 0.463 (1.305) | | 0.489 (1.521) | <i>P</i> = 0.9317 |
| E/e' (SD) | 11.683 (3.520) | 10.315 (3.614)** | 13.240 (4.099) | 11.216 (3.935)** | |
| Δ E/e' | | -1.368 (3.098) | | -2.024 (3.887) | <i>P</i> = 0.9450 |
| LVMl (SD), g/m ² | 99.317 (21.103) | 93.786 (21.164)** | 101.961 (22.574) | 95.071 (22.800)** | |
| Δ LVMl | | -5.531 (14.046) | | -6.890 (16.226) | <i>P</i> = 0.7181 |
| LA volume index (SD), mL | 25.312 (9.143) | 23.465 (8.535)** | 25.691 (9.638) | 23.889 (9.166)* | |
| Δ LA volume index | | -1.847 (5.317) | | -1.802 (5.477) | <i>P</i> = 0.8286 |
| EF (SD), % | 67.049 (9.450) | 66.637 (11.094) | 67.599 (8.259) | 67.724 (9.261) | |
| Δ EF | | -0.412 (11.564) | | 0.125 (9.046) | <i>P</i> = 0.4577 |

Notes: *0W versus 24W *P* < 0.05; **0W versus 24W *P* < 0.0001.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LAD, left atrial dimension; LAVI, left atrial volume index; IVST, interventricular septal wall thickness; PWTh, posterior wall thickness; DT, deceleration time; IRT, isovolumetric relaxation time; LVMl, left ventricular mass index; LA, left atrial; EF, ejection fraction; LVEF, left ventricular ejection fraction; W, weeks; DM, diabetes mellitus.

were significantly associated with changes in e', and changes in eGFR were significantly associated with changes in E/e' in patients with DM, but not in those without DM.

Relationship to hs-CRP

Table 5 shows the relationship between changes in diastolic function and changes in hs-CRP. Changes in

hs-CRP were significantly associated with changes in e' in patients with DM (*r* = -0.312, *P* = 0.0016), but there was no significant relationship between changes in hs-CRP and changes in E/e' (*r* = 0.173, *P* = 0.0853). In patients without DM, changes in hs-CRP were associated with changes in e' (*r* = -0.317, *P* < 0.0001), and changes in hs-CRP were associated with changes in E/e' (*r* = 0.205, *P* = 0.0010).

Table 4 Relationship between changes in diastolic function and changes in renal function

| | DM (-) | | DM (+) | |
|---------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| | Δ UACR estimated value | Δ eGFR estimated value | Δ UACR estimated value | Δ eGFR estimated value |
| | P value | P value | P value | P value |
| $\Delta e'$ | -0.117 P = 0.2640 | 0.014 P = 0.8947 | -0.144 P = 0.0257 | 0.111 P = 0.0856 |
| $\Delta E/e'$ | -0.148 P = 0.1564 | 0.058 P = 0.5828 | 0.079 P = 0.2219 | -0.130 P = 0.0436 |

Note: Pearson product-moment correlation coefficient.

Abbreviations: DM, diabetes mellitus; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Determinants of e' and E/e' in patients with and without DM

In patients with DM, multivariate analysis demonstrated that the determinants of the changes in e' were age ($P = 0.004$), changes in systolic BP ($P = 0.003$), and changes in HbA_{1c} ($P = 0.04$). Also, BMI ($P = 0.004$) and changes in HbA_{1c} ($P = 0.01$) were independent factors for changes in E/e' . In contrast, changes in systolic BP ($P = 0.0008$) and hs-CRP ($P = 0.03$) were independent factors for changes in e' in patients without DM. Finally, changes in systolic BP ($P = 0.06$) and changes in hs-CRP ($P = 0.1$) did not reach statistical significance as determinants of changes in E/e' .

Discussion

Measuring the UACR in a random urine specimen is a convenient method for detecting increased albumin excretion.^{20,21} UACR is a powerful and independent predictor of heart failure.²² In this study, UACR was decreased in patients with DM, but not in patients without DM. Recent data suggest that UACR strongly predicts endothelial dysfunction in patients with heart failure.^{14,15} In this study, changes in e' and changes in UACR were significantly correlated in the DM group, but not in the non-DM group. UACR and diastolic dysfunction are correlated in DM patients. The decrease

Table 5 Relationship between changes in diastolic function and changes in hs-CRP

| | DM (-) | | DM (+) | |
|-----------------|-----------------------------|-------------------------------|-----------------------------|-------------------------------|
| | $\Delta e'$ estimated value | $\Delta E/e'$ estimated value | $\Delta e'$ estimated value | $\Delta E/e'$ estimated value |
| | P value | P value | P value | P value |
| Δ hs-CRP | -0.317 P < 0.0001 | 0.205 P = 0.0010 | -0.312 P = 0.0016 | 0.173 P = 0.0857 |

Abbreviations: DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein.

observed in UACR levels after losartan/HCTZ treatment might be a consequence of improved patient control in their diabetes management, since better patient management of diabetes is generally associated with a decrease in HbA_{1c} . Better controlled DM and concomitant UACR reduction with losartan/HCTZ treatment seems to improve LV diastolic function in patients with DM.

In this study, changes in eGFR and changes in E/e' were significantly related in DM patients, but not in non-DM patients. A prospective study of the relationship between the echocardiographic parameters of LV diastolic function and mild-to-moderate renal function impairment in patients with type 2 DM found a significant correlation between eGFR and E/e' in patients with $e' \leq 7.1$ cm/s, but not patients with $e' > 7.1$ cm/s.²³ In our study, we found a similar significant correlation between eGFR and E/e' in DM patients with $e' < 7.1$ cm/s.

In our original study,¹⁸ hsCRP significantly decreased with changes in treatment from ACEi or ARB to losartan/HCTZ. However, the association between hsCRP and DM was not examined in the original study. CRP levels are elevated in patients with diastolic dysfunction, and they correlate with disease severity as well as LV preload.²⁴ The mechanism of CRP elevation in patients with diastolic dysfunction has not been elucidated. In this study, there was a correlation between changes in hs-CRP and changes in E/e' in non-DM patients, but this was not observed in DM patients. A reduction in LV preload with changes to losartan/HCTZ may contribute to a reduction in hs-CRP in non-DM patients.

Limitations

This study is an analysis of a subset of data from the EDEN study. The original EDEN study was a single-arm trial. However, the main objective of the present study was not to monitor clinical outcomes, but to detect changes in objective parameters that allow for the assessment of changes in LV diastolic function after switching from ACEi or ARB to losartan/HCTZ treatment.

Conclusion

In this study, UACR was decreased after switching from ACEi or ARB to losartan/HCTZ in patients with DM, but not in patients without DM. Changes in e' and changes in UACR were significantly correlated in DM patients, but not in non-DM patients. On the other hand, there was a correlation between changes in hs-CRP and changes in E/e' among non-DM patients, but this was not noted in DM patients.

Acknowledgments

This study was supported by the Osaka Prevention Institute for Cancer and the Cardiovascular Diseases Foundation. The authors also thank the EDEN trial investigators: Hajime Kihara, MD (Kihara Cardiovascular Clinic, Asahikawa, Japan); Noriaki Kasayuki, MD (Ishikiriseiki Hospital, Higashiosaka, Japan); Fumiaki Nakamura, MD (Ibaraki Iseikai Hospital, Ibaraki, Japan); Etsuko Fushimi, MD (Hiraga General Hospital, Yokote, Japan); Lim Young-Jae, MD (Kawachi General Hospital, Higashiosaka, Japan); Shin Takiuchi, MD (Higashi Takarazuka Satoh Hospital, Takarazuka, Japan); Junichi Nakagawa, MD (Sankeikai-Nakagawa Clinic, Amagasaki, Japan); Hen Yasuki, MD (Sakakibara Heart Institute Clinic, Fuchu, Japan); Kei Tawahara, MD (Hamamatsu Red Cross Hospital, Hamamatsu, Japan); Akihiro Tani, MD (Kano General Hospital, Osaka, Japan); Hiroshi Matsuura MD (Matsuura Clinic of Medicine, Suita, Japan); Shigenori Sassa, MD (Sassa Medical Clinic, Osaka, Japan); Yasuji Doi, MD (Osaka Saiseikai Senri Hospital, Suita, Japan); Taro Minagawa, MD (Minagawa Clinic, Gifu, Japan); Yukio Abe, MD (Osaka City General Hospital, Osaka, Japan); Yoshio Kawase, MD (Izumi City General Hospital, Izumi, Japan); Toshihiko Nagano, MD (Iwasa Dai-ichi Hospital, Gifu, Japan); Naoki Gotoh, MD (Gotoh Clinic, Gifu, Japan); Kazunori Kasiwase, MD (Osaka Police Hospital, Osaka, Japan); Tsunemori Sakamoto, MD (Baba Memorial Hospital, Sakai, Japan); Keiji Ujino, MD (Tominaga Hospital, Osaka, Japan); Masahiro Yoshida, MD (Tsukushino Hospital, Fukui, Japan); Takahiko Kawarabayashi, MD (Higashisumiyoshi Morimoto Hospital, Osaka, Japan); and Yukinori Okazaki, MD (NTT West Osaka Hospital, Osaka, Japan).

Disclosure

The authors have no conflicts of interest to declare.

References

1. Arnlöv J, Evans JC, Meigs JB, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and non-diabetic individuals: the Framingham Heart Study. *Circulation*. 2005; 112(7):969–975.
2. Diercks GF, van Boven AJ, Hillege HL, et al. Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large non-diabetic population. The PREVEND (Prevention of REnal and Vascular ENdstage Disease) study. *Eur Heart J*. 2000;21(23): 1922–1927.
3. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med*. 1984;310(6): 356–360.
4. Deckert T, Yokoyama H, Mathiesen E, et al. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ*. 1996;312(7035): 871–874.
5. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol*. 1997;80(2):164–169.
6. Wachtell K, Ibsen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med*. 2003;139(11):901–906.
7. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia*. 1989;32(4):219–226.
8. Chugh A, Bakris GL. Microalbuminuria: what is it? Why is it important? What should be done about it? An update. *J Clin Hypertens (Greenwich)*. 2007;9(3):196–200.
9. Weir MR. Microalbuminuria and cardiovascular disease. *Clin J Am Soc Nephrol*. 2007;2(3):581–590.
10. van de Wal RM, Asselbergs FW, Plokker HW, et al. High prevalence of microalbuminuria in chronic heart failure patients. *J Card Fail*. 2005;11(8):602–606.
11. Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. *Curr Opin Nephrol Hypertens*. 2004;13(2):163–170.
12. Dobre D, Nimade S, de Zeeuw D. Albuminuria in heart failure: what do we really know? *Curr Opin Cardiol*. 2009;24(2):148–154.
13. Orea-Tejeda A, Colín-Ramírez E, Hernández-Gilsoul T, et al. Microalbuminuria in systolic and diastolic chronic heart failure patients. *Cardiol J*. 2008;15(2):143–149.
14. Yilmaz MI, Saglam M, Carrero JJ, et al. Serum visfatin concentration and endothelial dysfunction in chronic kidney disease. *Nephrol Dial Transplant*. 2008;23(3):959–965.
15. Yilmaz MI, Sonmez A, Saglam M, et al. ADMA levels correlate with proteinuria, secondary amyloidosis, and endothelial dysfunction. *J Am Soc Nephrol*. 2008;19(2):388–395.
16. Kshirsagar AV, Bombardier AS, Bang H, et al. Association of C-reactive protein and microalbuminuria (from the National Health and Nutrition Examination Surveys, 1999 to 2004). *Am J Cardiol*. 2008;101(3): 401–406.
17. Suliman ME, Yilmaz MI, Carrero JJ, et al. Novel links between the long pentraxin 3, endothelial dysfunction, and albuminuria in early and advanced chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3(4): 976–985.
18. Ito H, Ishii K, Kihara H, Kasayuki N, et al; for Effect of ARB/Diuretics on Diastolic Function in Patients with Hypertension (EDEN) trial investigators. Adding thiazide to a renin-angiotensin blocker improves left ventricular relaxation and improves heart failure in patients with hypertension. *Hypertens Res*. 2012;35(1):93–99.
19. Matsuo S, Imai E, Horio M; for Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53(6): 982–992.
20. Jensen JS, Clausen P, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Detecting microalbuminuria by urinary albumin/creatinine concentration ratio. *Nephrol Dial Transplant*. 1997;12 Suppl 2:6–9.
21. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis*. 1999;33(5):1004–1010.
22. Jackson CE, Solomon SD, Gerstein HC, et al; for CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet*. 2009;374(9689):543–550.
23. Pecková M, Charvat J, Schuck O, Hill M, Svab P, Horackova M. The association between left ventricular diastolic function and a mild-to-moderate decrease in glomerular filtration rate in patients with type 2 diabetes mellitus. *J Int Med Res*. 2011;39(6):2178–2186.
24. Williams ES, Shah SJ, Ali S, Na BY, Schiller NB, Whooley MA. C-reactive protein, diastolic dysfunction, and risk of heart failure in patients with coronary disease: Heart and Soul Study. *Eur J Heart Fail*. 2008;10(1):63–69.

Drug Design, Development and Therapy

Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which

has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/drug-design-development-and-therapy-journal>