Drug Design, Development and Therapy

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ORIGINAL RESEARCH

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

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
11 September 2012

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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 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 ± 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 1 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 1, 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
	0W	24W	0W	24W	*P* value
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, 1Q–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
	0W	24W	0W	24W	*P* value
eGFR (SD)	68.963 (16.569)	66.647 (17.216)**	68.165 (20.203)	66.335 (20.968)	
ΔeGFR		–2.316 (8.820)		–1.830 (13.367)	$P = 0.7421$
BNP (median, 1Q–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, 1Q–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, asparate aminotranferase; ALT, alanine aminotranferase; 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
	0W	24W	0W	24W	*P* value
LVDd (SD), cm	4.730 (0.458)	4.669 (0.439)*	4.775 (0.423)	4.689 (0.462)*	
ΔLVDd		–0.061 (0.320)		–0.086 (0.363)	*P* = 0.7056
LVDs (SD), cm	2.951 (0.453)	2.925 (0.509)	2.964 (0.438)	2.903 (0.455)	
ΔLVDs		–0.026 (0.426)		–0.061 (0.320)	*P* = 0.4696
LVDd/LVDs (SD)	1.627 (0.197)	1.627 (0.222)	1.632 (0.177)	1.637 (0.181)	
ΔLVDd/LVDs		0.000 (0.200)		0.005 (0.191)	*P* = 0.7438
LAD (SD), cm	4.066 (0.791)	3.947 (0.677)**	4.149 (0.855)	4.031 (0.751)*	
ΔLAD		–0.119 (0.393)		–0.118 (0.390)	*P* = 0.5771
LAVI (SD), mL/m^2	41.598 (15.169)	38.596 (14.124)**	43.926 (16.240)	40.874 (15.531)*	
ΔLAVI		–3.002 (8.843)		–3.052 (9.162)	*P* = 0.6367
IVST (SD), cm	0.990 (0.158)	0.965 (0.157)*	1.027 (0.163)	0.997 (0.138)*	
ΔIVST		–0.025 (0.108)		–0.030 (0.106)	*P* = 0.6132
PWTh (SD), cm	0.979 (0.138)	0.949 (0.137)**	1.015 (0.142)	0.980 (0.134)*	
ΔPWTh		–0.030 (0.108)		–0.035 (0.113)	*P* = 0.5495
IVST/PWTh (SD)	1.015 (0.116)	1.020 (0.110)	1.013 (0.092)	1.021 (0.081)	
ΔIVST/PWTh		0.005 (0.131)		0.008 (0.114)	*P* = 0.9372
E (SD), cm/s	62.428 (14.480)	62.604 (13.600)	67.854 (18.067)	67.147 (16.785)	
ΔE		0.176 (12.163)		–0.707 (15.706)	*P* = 0.2887
A (SD), cm/s	80.926 (16.042)	77.627 (16.195)**	85.703 (20.875)	83.337 (18.441)	
ΔA		–3.299 (10.912)		–2.366 (16.075)	*P* = 0.0800
E/A (SD)	0.790 (0.203)	0.831 (0.226)*	0.817 (0.227)	0.824 (0.220)	
ΔE/A		0.041 (0.175)		0.007 (0.210)	*P* = 0.2010
DT (SD), msec	240.809 (54.843)	231.952 (47.590)*	232.006 (53.680)	238.102 (48.154)	
ΔDT		–8.857 (56.237)		6.096 (52.624)	*P* = 0.0610
IRT (SD), msec	120.108 (29.373)	112.602 (25.911)**	120.808 (35.329)	112.822 (30.554)*	
ΔIRT		–7.506 (21.677)		–7.986 (27.655)	*P* = 0.9365
e′ (SD), cm/s′	5.603 (1.419)	6.518 (1.825)**	5.335 (1.295)	6.389 (1.778)**	
Δe′		0.915 (1.634)		1.054 (1.592)	*P* = 0.7750
s′ (SD), cm/s′	7.806 (2.693)	8.269 (2.644)**	7.517 (2.348)	8.006 (2.491)*	
Δs′		0.463 (1.305)		0.489 (1.521)	*P* = 0.9317
E/e′ (SD)	11.683 (3.520)	10.315 (3.614)**	13.240 (4.099)	11.216 (3.935)**	
ΔE/e′		–1.368 (3.098)		–2.024 (3.887)	*P* = 0.9450
LVMI (SD), g/m^2	99.317 (21.103)	93.786 (21.164)**	101.961 (22.574)	95.071 (22.800)**	
ΔLVMI		–5.531 (14.046)		–6.890 (16.226)	*P* = 0.7181
LA volume index (SD), mL	25.312 (9.143)	23.465 (8.535)**	25.691 (9.638)	23.889 (9.166)*	
ΔLA volume index		–1.847 (5.317)		–1.802 (5.477)	*P* = 0.8286
EF (SD), %	67.049 (9.450)	66.637 (11.094)	67.599 (8.259)	67.724 (9.261)	
ΔEF		–0.412 (11.564)		0.125 (9.046)	*P* = 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; LVMI, 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 (+)	
	ΔUACR estimated value	ΔeGFR estimated value	ΔUACR estimated value	ΔeGFR estimated value
	P value	P value	P value	P value
Δe′	–0.117	0.014	–0.144	0.111
	$P = 0.2640$	$P = 0.8947$	$P = 0.0257$	$P = 0.0856$
ΔE/e′	–0.148	0.058	0.079	–0.130
	$P = 0.1564$	$P = 0.5828$	$P = 0.2219$	$P = 0.0436$

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 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.

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

	DM (–)		DM (+)	
	Δe′ estimated value	ΔE/e′ estimated value	Δe′ estimated value	ΔE/e′ estimated value
	P value	P value	P value	P value
Δhs-CRP	–0.317	0.205	–0.312	0.173
	$P < 0.0001$	$P = 0.0010$	$P = 0.0016$	$P = 0.0857$

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

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 Tawarahara, 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.

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