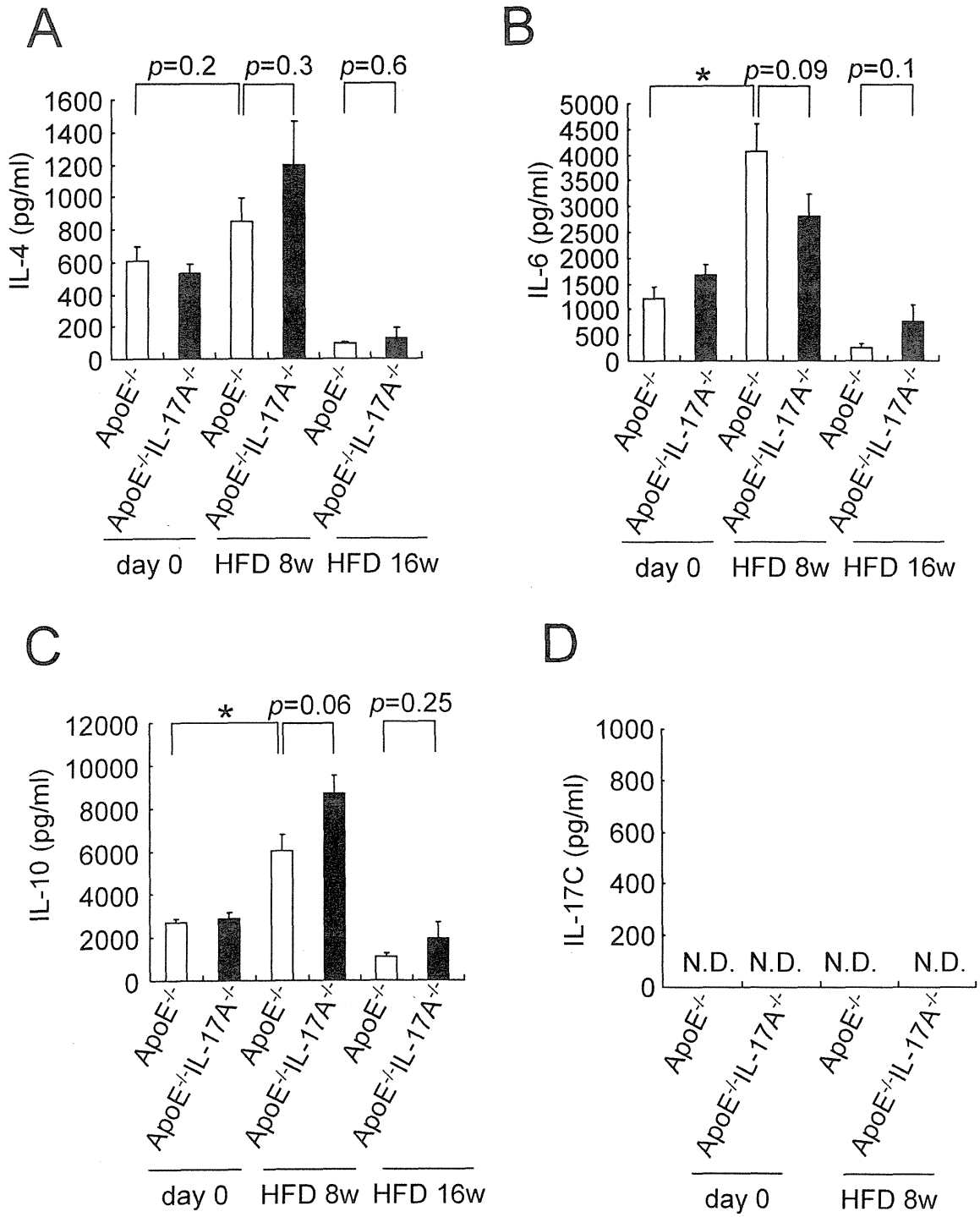
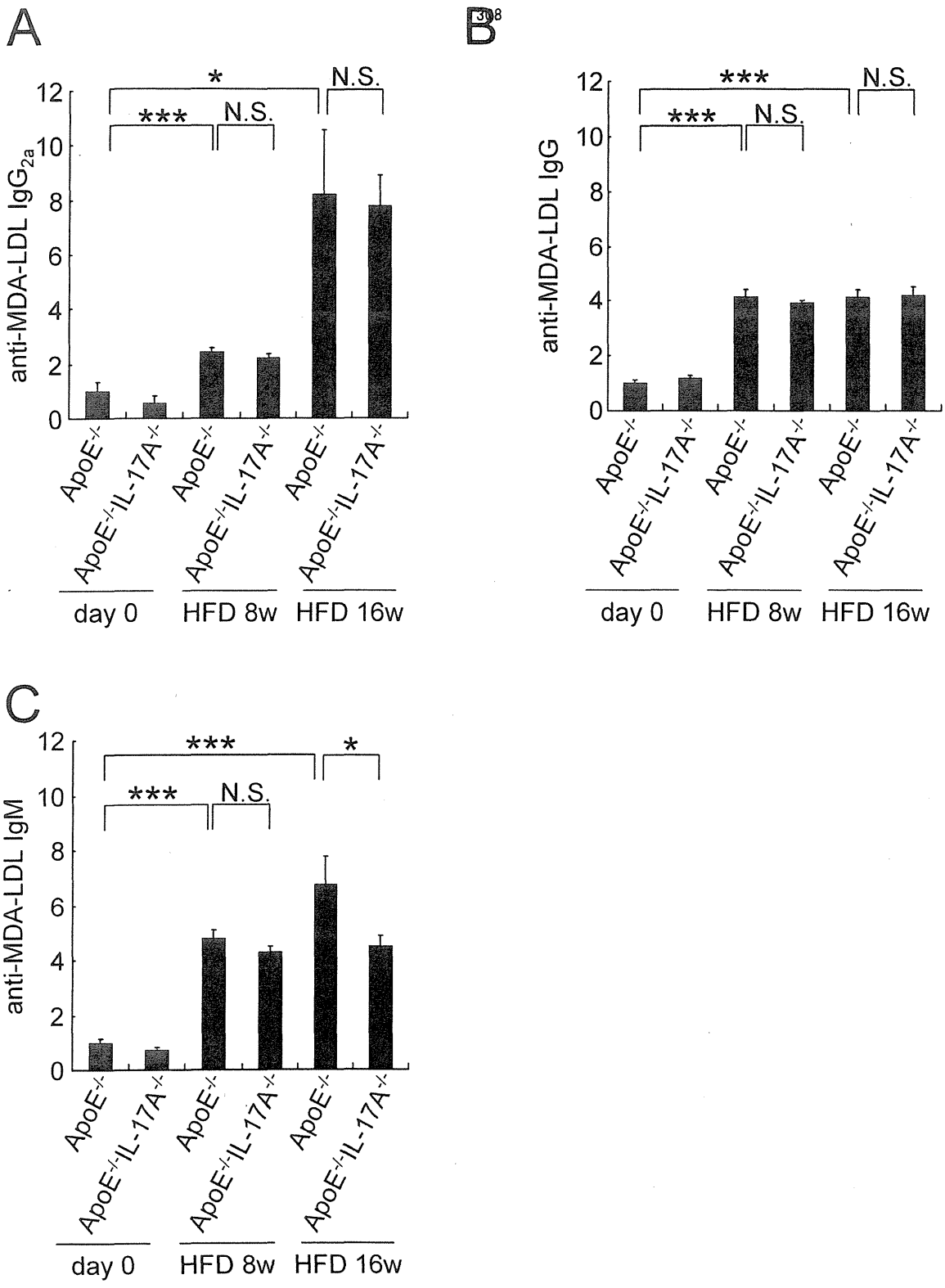


Supplemental Figure IV



Supplemental Figure V

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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction

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Aims The pathophysiology of heart failure with preserved ejection fraction (HFpEF) is complex but increased left ventricular (LV) diastolic stiffness plays a key role. A load-independent, non-invasive, direct measure of diastolic stiffness is lacking. The diastolic wall strain (DWS) index is based on the linear elastic theory, which predicts that impaired diastolic wall thinning reflects resistance to deformation in diastole and thus, increased diastolic myocardial stiffness. The objectives of this community-based study were to determine the distribution of this novel index in consecutive HFpEF patients and healthy controls, define the relationship between DWS and cardiac structure and function and determine whether increased diastolic stiffness as assessed by DWS is predictive of the outcome in HFpEF.

Methods and results Consecutive HFpEF patients ($n = 327$, EF $\geq$ 50%) and controls ($n = 528$) from the same community were studied. Diastolic wall strain was lower in HFpEF (0.33 ± 0.08) than in controls (0.40 ± 0.07, $P < 0.001$). Within HFpEF, those with DWS $\leq$ median (0.33) had higher LV mass index, relative wall thickness, E/e', Doppler-estimated LV end-diastolic pressure to LV end-diastolic volume ratio, left atrial volume index, and brain natriuretic peptide (BNP) levels than those with DWS > median. Heart failure with preserved ejection fraction patients with DWS $\leq$ median had higher rate of death or HF hospitalization than those with DWS > median ($P = 0.003$) even after the adjustment for age, gender, log BNP, LV geometry, or log E/e' ($P < 0.01$).

Conclusion These data suggest that DWS, a simple index, is useful in assessing diastolic stiffness and that more advanced diastolic stiffness is associated with worse outcomes in HFpEF.

Keywords Diastolic function • Heart failure • Preserved ejection fraction • Outcomes

Introduction

Half of the patients with the clinical syndrome of heart failure (HF) in the community have preserved ejection fraction (HFpEF).[1,2] The pathophysiology of HFpEF is complex but increased left ventricular (LV) diastolic stiffness is thought to play a key role in many patients. Diastolic stiffness is inferred from Doppler indices, which reflect filling pressures and myocardial relaxation but do not directly measure diastolic stiffness.[3] Recently, indices based on laws of physics have been shown to represent a more direct measure of myocardial stiffness[4] (Supplementary material online, *Figure S1* and video). Diastolic wall strain (DWS) is based on the linear elastic theory, which predicts that in the presence of preserved EF, impaired diastolic wall thinning reflects resistance to deformation in diastole

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and thus, increased diastolic myocardial stiffness. Diastolic wall strain correlated with the diastolic stiffness constant measured invasively in an animal model.[4] However, the utility of this new index has not been tested in a large cohort of patients with HFpEF.

Several studies have shown the association of echo Doppler indices with poor outcomes in patients with reduced ejection function[5,6] or acute myocardial infarction,[7] but fewer studies have established the association of diastolic function indices with outcomes in HFpEF.[8,9] However, the association between diastolic stiffness and outcomes in a community-based cohort of HFpEF is not well established. The objectives of this community-based study were to determine the distribution of DWS in consecutive HFpEF patients and healthy controls from the same community, define the relationship between DWS and cardiac structure and function, and determine whether increased diastolic stiffness as assessed by DWS is predictive of outcomes in HFpEF.

Methods

Study population

The unique aspects of the Rochester Epidemiology Project for population-based research have been previously described.[1] The study was approved by the Mayo Clinic Institutional Review Board.

Consecutive patients with clinical HF (Framingham criteria), no significant left-sided valvular disease, hypertrophic or infiltrative cardiomyopathy or pericardial disease, and EF $\geq$50% were identified through an Olmsted County, MN, prospective population-based HF surveillance study.[10,11] Between September 2003 and August 2006, 397 HFpEF patients were identified. Control subjects ($n = 617$) without obesity, hypertension, diabetes, or known cardiovascular disease were identified from a random sample ($n = 2042$; age >45 years) of the same community who underwent echocardiography and medical record review as part of a community-based, echocardiographic survey study. Of these, 528 had two-dimensional (2D) measurement of LV wall thickness and chamber dimension.[11]

Outcome data

Mortality data were ascertained from medical records, death certificates for Olmsted County residents, obituaries, and notices of death in the local newspapers, as previously described.[12] Heart failure hospitalization was obtained through the Olmsted County Heathcare Expenditure and Utilization Database with ICD-9 codes, as previously described.[13]

Laboratory data

Plasma brain natriuretic peptide (BNP) was determined by the Biosite Triage® assay.

Echocardiography

Echocardiography was performed by registered diagnostic cardiac sonographers.[11] Ventricular dimensions and wall thickness were determined from 2D echocardiography (parasternal long-axis view) at end diastole based on the recommendation of the American Society of Echocardiography.[14,15] Systolic and diastolic blood pressure and the heart rate were obtained at echocardiography. As previously illustrated,[4] DWS was calculated using the formula: DWS = (PWs − PWd)/PWs, where PWs is the posterior wall thickness at end-systole and PWd is the posterior wall thickness at end-diastole and where end-diastolic and end-systolic measurements were made according to ASE recommendations.[14,15] Mean ± SD of intraobserver and interobserver variability of DWS was 0.003 ± 0.051 and 0.009 ± 0.072 ($n = 50$). Diastolic wall strain calculated with 2D or M-mode measurements ($n = 50$) correlated well ($r = 0.84$, $P < 0.001$), with no systematic error (mean ± SD difference: 0.007 ± 0.055, Bland–Altman analysis). Dichotomous assessments of DWS were performed with continuous values as a semi-qualitative assessment because DWS showed variability due to errors of measuring the wall thickness.

Of the 397 HFpEF patients, 327 (82%) patients had measurable DWS, with the remaining patients excluded due to posterior wall motion abnormalities ($n = 23$), significant pericardial effusion ($n = 4$), or inadequate images ($n = 43$). The LV end-diastolic volume (EDV) and EDV index adjusted by body surface area (EDVI) were calculated by Teichholz methods.[16] The LV mass index and relative wall thickness (RWT) were calculated by standard methods.[17] Based on LV hypertrophy (LVH) defined as LV mass index >95 g/m^2 (woman) or >115 g/m^2 (man) and RWT, LV geometry was classified as normal, concentric remodelling, concentric hypertrophy, or eccentric hypertrophy as previously described.[17] The septal mitral annular early diastolic velocity (e′) was determined by spectral tissue Doppler imaging using standard methods. Early transmitral flow velocity (E) was measured by pulsed-wave Doppler, and end-diastolic pressure (EDP) was estimated as follows: (EDP = 11.96 + 0.596 × E/e′), as previously determined from Doppler and invasive EDP measurements at our institution.[18] Pulmonary arterial systolic pressure (PASP) and left atrial volume index (LAVI) were calculated as previously described.[19]

Statistical methods

Categorical variables were compared by the χ^2 test. Continuous variables were compared by a one-way analysis of variance with Bonferroni correction or the Steel–Dwass test for multiple unadjusted comparisons when appropriate after the assessment of normal distribution. Bivariate regressions used the Pearson or Spearman correlation as appropriate. Regression analysis was used to adjust for age, gender, and the presence of other diseases, where the dependent variable was the normally distributed continuous (linear least-squares regression). For variables without normal distribution, log-transformed variables were confirmed to have normal distribution and were used in regression models. The Kaplan–Meier method tested for differences in the survival rate between groups by the log-rank test. Cox proportional-hazards regression was used to adjust for the effect of differences in baseline characteristics or pertinent covariates on outcomes. Statistical comparisons were performed with JMP, version 9. All analyses were two-sided, and significance was judged at $P < 0.05$.

Results

Subject characteristics

In the 397 HFpEF patients, 327 had assessable DWS and constituted the HFpEF group. Of the 617 control subjects, 528 had a measurable DWS and constituted the control group. The distribution of DWS in HFpEF was different from that of control (*Figure 1*). The median (25th to 75th percentiles) DWS was 0.33 (0.29–0.38) in HFpEF and 0.40 (0.36–0.44) in control. *Table 1* shows the characteristics of control and selected elderly control group and of HFpEF patients with lower (≤ median) or higher (> median) DWS. When compared with control, both HFpEF groups were older, more obese, and had higher prevalence of hypertension, diabetes mellitus and coronary artery disease and higher blood pressure, heart rate, and BNP level, consistent with previous reports.[11] As there was an age

difference in the control and HFpEF patients, we selected healthy controls who were over age 70 as elderly control group. Findings were similar when comparing HFpEF patients with elderly controls. The prevalence of coronary artery disease and beta blocker use was higher than that reported in some but not all clinical trials.[20,21] Within HFpEF patients, those with low DWS had similar prevalence of comorbidities and use of angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers, beta-blocker, and diuretics, and higher BNP levels when compared with those with high DWS.

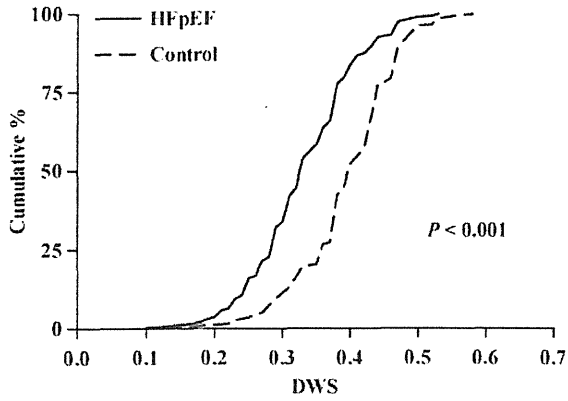

Figure 1 Cumulative frequency distribution of diastolic wall strain (DWS) in patients with heart failure and preserved ejection fraction (HFpEF, black solid) and control subjects (dashed).

Diastolic wall strain and left ventricular structure in heart failure with preserved ejection fraction

When compared with control, LV end-diastolic dimension and EDVI were not different in either HFpEF group, but HFpEF patients had greater wall thickness, LV mass index, and RWT (*Table* 2). Findings were similar when comparing HFpEF patients with elderly controls. Among HFpEF patients, those with high vs. low DWS had similar LV end-diastolic dimension, septal systolic wall thickness, and EDVI, whereas LV end-systolic dimension, PWs, PWd, septal diastolic wall thickness, LV mass index, and RWT differed with HFpEF patients with lower DWS having more abnormal geometry. Within HFpEF patients, DWS was inversely correlated with LV mass index and RWT ($r = -0.28$, $P < 0.001$, $r = -0.26$, $P < 0.001$, respectively). The association of DWS with LV mass index and RWT persisted ($P < 0.001$ for both) after the adjustment for age, gender, and comorbidities (hypertension, diabetes, and CAD).

Diastolic wall strain and left ventricular function in heart failure with preserved ejection fraction

When compared with control, EF was slightly but significantly lower in HFpEF (62.0 ± 6.2 vs. 63.7 ± 4.7%, $P < 0.001$) but among HFpEF patients, EF was similar in those with high or low DWS (*Table* 2). As expected, HFpEF patients had more indices reflective of diastolic dysfunction than control (shorter DT, lower *e'*, and higher *E/e'*, PASP and LAVI). In HFpEF patients with low DWS, mitral *E/A* ratio, *E/e'*, EDP/EDV ratio, and LAVI were significantly

Table 1 Clinical characteristics of control, elderly control, and heart failure with preserved ejection fraction subjects with high- or low-diastolic wall strain

	Control $n = 528$	Elderly control (age ≥ 70); $n = 46$	HFpEF with high DWS (>median); $n = 151$	HFpEF with low DWS (≤median); $n = 176$
Age (years)	56.7 ± 8.3	74.8 ± 4.8	76.5 ± 13.2*	77.7 ± 11.7*
Male (%)	43	39	40	47
BMI (kg/m^2)	25.3 ± 2.8	25.2 ± 2.9	29.3 ± 8.1***	29.9 ± 7.1***
Hypertension (%)	—	—	82	84
Diabetes (%)	—	—	29	32
Coronary artery disease (%)	—	—	44	51
Beta blocker (%)	—	—	60	59
ACE-I or ARBs (%)	—	—	45	48
Diuretics (%)	—	—	62	65
BNP (pg/mL)	27 ± 30	45 ± 98*	348 ± 397***	542 ± 648*****
Systolic BP (mmHg)	117 ± 12	125 ± 12*	131 ± 23*	132 ± 22*
Diastolic BP (mmHg)	70 ± 8	69 ± 8	68 ± 14	67 ± 14
Heart rate (b.p.m.)	64 ± 9	63 ± 10	70 ± 14***	70 ± 14***

Values are expressed as the mean ± SD unless otherwise noted. BMI, body mass index; ACE-I, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin receptor blockers; BNP, brain natriuretic peptide; BP, blood pressure.
*$P < 0.05$ vs. control group.
**$P < 0.05$ vs. elderly control group.
***$P < 0.05$ vs. HFpEF with the high-DWS (>median) group.

Table 2 Echocardiographic characteristics of control, elderly control, and heart failure with preserved ejection fraction subjects with high- or low-diastolic wall strain

	Control, $n = 528$	Elderly control, $n = 46$	HFpEF with high-DWS (>median), $n = 151$	HFpEF with low-DWS (≤median), $n = 176$
LV structure				
LV end-diastolic dimension (mm)	48.4 ± 4.4	47.4 ± 5.1	47.5 ± 6.0	48.2 ± 6.5
LV end-systolic dimension (mm)	29.2 ± 4.2	27.6 ± 4.4*	29.3 ± 4.9	30.9 ± 5.5******
IVSd (mm)	10.0 ± 1.5	10.9 ± 1.6*	10.7 ± 2.2*	11.7 ± 2.2******
IVSs (mm)	14.8 ± 2.0	15.9 ± 1.8*	15.1 ± 2.7	14.8 ± 2.9**
PWd (mm)	9.1 ± 1.1	9.7 ± 1.2*	9.8 ± 1.6*	11.1 ± 1.7******
PWs (mm)	15.4 ± 1.9	16.2 ± 1.8*	16.4 ± 2.5*	15.4 ± 2.4***
EDVI (mL/m^2)	60.2 ± 10.9	59.5 ± 13.7	57.5 ± 14.4	58.3 ± 15.3
LV mass index (g/m^2)	88.5 ± 16.3	97.2 ± 17.6*	95.2 ± 26.7*	110.3 ± 31.2******
RWT	0.38 ± 0.06	0.41 ± 0.08*	0.44 ± 0.08*	0.48 ± 0.09******
Normal geometry (%)	67	41	31	11******
Concentric remodelling (%)	16	26	32	32
Concentric hypertrophy (%)	4	13	22	41
Eccentric hypertrophy (%)	13	20	15	16
Indices reflective of LV function				
EF (%)	63.7 ± 4.7	65.0 ± 5.1	62.7 ± 6.1	61.4 ± 6.2***
E (m/s)	0.67 ± 0.13	0.62 ± 0.15*	0.94 ± 0.33***	0.96 ± 0.31***
A (m/s)	0.54 ± 0.14	0.70 ± 0.20*	0.87 ± 0.30*	0.79 ± 0.28******
E/*A* ratio	1.30 ± 0.38	0.93 ± 0.27*	1.14 ± 0.54*	1.38 ± 0.92******
Deceleration time (ms)	219 ± 32	236 ± 46*	207 ± 56***	201 ± 53***
e′ velocity (cm/s)	9.5 ± 3.4	7.2 ± 1.9*	6.4 ± 2.2*	5.6 ± 1.9***
E/e′ ratio	7.6 ± 2.3	9.2 ± 2.8*	16.4 ± 8.2***	19.1 ± 9.5******
Estimated EDP (mmHg)	16.5 ± 1.4	17.4 ± 1.7*	21.7 ± 4.9***	23.3 ± 5.6******
EDP/EDV (mmHg/mL)	0.16 ± 0.04	0.15 ± 0.05	0.21 ± 0.08*	0.24 ± 0.12******
LAVI (mL/m^2)	21.9 ± 5.2	23.8 ± 5.2*	43.7 ± 17.0***	47.8 ± 15.5******
PASP (mmHg)	25.8 ± 3.7	27.7 ± 3.4*	47.3 ± 14.2***	49.6 ± 16.3***
DWS	0.40 ± 0.07	0.40 ± 0.06	0.40 ± 0.04	0.28 ± 0.05

Values are expressed as the mean ± SD. LV, left ventricular; IVSd, interventricular wall thickness at end-diastole; IVSs, interventricular wall thickness at end-systole; PWd, posterior wall thickness at end-diastole; PWs, posterior wall thickness at end-systole; EDVI, end-diastolic LV volume index; RWT, relative wall thickness; EF, ejection fraction; *E*, early transmitral flow velocity; *A*, late transmitral flow velocity; e′, septal mitral annular early diastolic velocity; EDP, end-diastolic LV pressure; LAVI, left atrial volume index; PASP, pulmonary arterial systolic pressure; DWS, diastolic wall strain.
*$P < 0.05$ vs. control group.
**$P < 0.05$ vs. elderly control group.
***$P < 0.05$ vs. HFpEF with the high-DWS (>median) group.

higher than those in HFpEF patients with high DWS, whereas PASP and e′ were similar (*Table 2*). Among HFpEF patients, DWS was modestly correlated with e′ ($r = 0.19$, $P = 0.001$), *E*/e′ ($r = -0.14$, $P = 0.02$), and LAVI ($r = -0.13$, $P = 0.02$). After the adjustment for age and gender, the association of DWS with these indices was still apparent ($P < 0.05$ for all).

Diastolic wall strain and outcomes

The mean follow-up in HFpEF patients who did not die or experience an HF hospitalization during follow-up was 700 ± 312 days. Death ($n = 98$, 30%) or HF hospitalization ($n = 67$, 20%) was common in HFpEF patients. Heart failure with preserved ejection fraction patients with lower DWS had a higher event (death or HF hospitalization) rate (*Figure 2*).

Univariate analysis showed that increased age, lower DWS and higher log BNP, PASP, LAVI, *E*/e′, e′, LV mass index, and RWT were all associated with higher combined event rate, whereas EF was not (*Table 3*). After adjusting for age and gender, DWS, log BNP, PASP, and LV mass index were still associated with a higher combined event rate, whereas LAVI, *E*/e′, and e′ were not (*Table 3*).

DWS was still associated with significant increases in risk of death or HF hospitalization in models adjusting for age, gender, and EF (*Table 4*, Model 1); age, gender, and Doppler-estimated EDP (Model 2); age, gender, and LV mass index (Model 3); and age, gender, EDP, and LV mass index (Model 4). The additive value of DWS to two variables potently associated with outcomes (pulmonary artery systolic blood pressure and BNP) is also shown [*Table 4* (Models 5 and 6) and Supplementary material online, *Figure S2*].

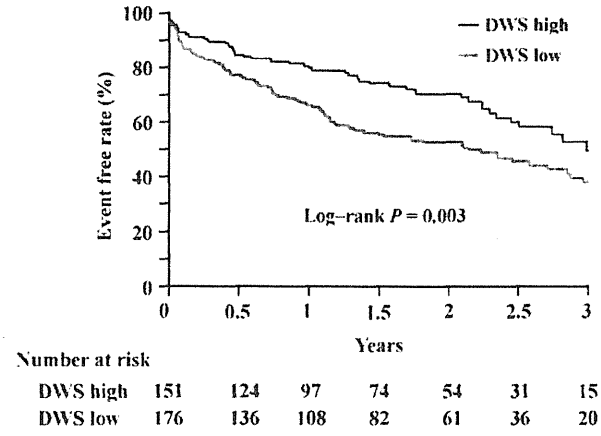

Figure 2 Event-free survival in heart failure with preserved ejection fraction patients according to diastolic wall strain (DWS). Kaplan–Meier plot of event-free (death or heart failure hospitalization) survival in patients with heart failure and preserved ejection fraction patients with diastolic wall strain above (DWS high, black) and below (DWS low, red) the median value of diastolic wall strain in heart failure with preserved ejection fraction patients.

Table 3 Factors related to events (combined outcome of death and heart failure hospitalization) among patients with heart failure and preserved ejection fraction: unadjusted and age-sex adjusted analysis

	HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age (per 1 year increase)	1.04 (1.02–1.05)	<0.001		
Male		0.13		
DWS (per 0.01 decrease)	1.04 (1.01–1.06)	<0.01	1.03 (1.01–1.06)	<0.01
Log BNP (per 1.0 log unit increase)	1.58 (1.35–1.86)	<0.001	1.50 (1.27–1.78)	<0.001
PASP (per 1 mmHg increase)	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	<0.001
LAVI (per 1 mL/m^2)	1.01 (1.00–1.02)	0.02		0.31
Log *E*/*e*′ (per 1.0 increase)	1.70 (1.19–2.43)	<0.01		0.24
e′ (per 1 cm/s decrease)	1.11 (1.02–1.22)	0.02		0.54
EF (per 1% decrease)		0.94		
LVMI (per 1 g/m^2 increase)	1.01 (1.00–1.01)	0.02	1.01 (1.00–1.01)	0.01
RWT (per 0.01 increase)	1.02 (1.00–1.04)	0.02		0.06

Abbreviations as in *Tables 1* and *2*.

Findings were consistent when analysing death or HF hospitalizations as independent outcomes. Continuous or dichotomous DWS was associated with death even after the adjustment for age, gender, and other indices (same indices as in *Table 4*). Continuous DWS tended to be associated with HF hospitalization ($P = 0.06$), and dichotomous DWS was associated even after the adjustment for age and gender ($P < 0.05$).

Discussion

In this large, prospectively and consecutively enrolled, community-based cohort of HFpEF patients, we found that, on average, DWS was lower in HFpEF patients than in control subjects, suggesting higher diastolic stiffness in HFpEF patients. However, among HFpEF patients, there was variability in DWS. Heart failure with preserved ejection fraction patients with lower DWS (higher diastolic stiffness) had more abnormal geometry, more impaired relaxation, and higher filling pressures as assessed by conventional Doppler and biochemical (BNP) indices. Further, lower DWS was associated with increased rates of the combined endpoint of death or HF hospitalization, even the after adjustment for age, gender, and other prognostic indices. Based on these data, we conclude that DWS, a simple index easily derived from standard echocardiographic data, may be useful in assessing the severity of diastolic stiffness in HFpEF patients. The association of decreased DWS and worse outcomes supports the concept that increased LV diastolic stiffness contributes to the progression of HFpEF.

Table 4 Hazard ratio of lower diastolic wall strain as continuous and dichotomous (≤ median) values for events (death or heart failure hospitalization) among patients with heart failure and preserved ejection fraction adjusting for pertinent covariates

	Continuous DWS (per 0.01 decrease)		Dichotomous DWS (≤ median)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Model 1 (age, gender, EF)	1.03 (1.01–1.06)	<0.01	1.73 (1.22–2.48)	<0.01
Model 2 (age, gender, EDP)	1.04 (1.02–1.07)	0.01	1.91 (1.31–2.84)	<0.001
Model 3 (age, gender, LVMI)	1.03 (1.01–1.05)	0.02	1.62 (1.13–2.33)	<0.01
Model 4 (age, gender, EDP, LVMI)	1.03 (1.01–1.06)	0.014	1.75 (1.19–2.62)	0.004
Model 5 (age, gender, log BNP)	1.03 (1.01–1.05)	<0.01	1.76 (1.23–2.54)	<0.01
Model 6 (age, gender, PASP)	1.03 (1.01–1.05)	0.02	1.61 (1.11–2.35)	0.01

HR, hazard ratio; CI, confidence interval. Other abbreviations as in *Tables 1* and *2*.

Diastolic wall strain as a measure of diastolic stiffness

Impaired LV relaxation and increased LV diastolic stiffness are the major components of diastolic dysfunction thought to lead to the elevation of filling pressures in HFpEF. Increased BNP, LAVI, and *E/e'* are correlated with increased filling pressure and infer the presence of increased stiffness[18,22,23] but are load dependent and do not provide specific information on intrinsic passive myocardial stiffness.[24,25] The concept of DWS is based on the linear elastic theory, which considers the physical properties of myocardial tissue in diastole, whereby distending forces exerted on the stiff myocardium in diastole produce less diastolic deformation (wall thinning) and greater translational (epicardial) wall movement than forces applied to compliant or 'compressible' myocardium (see also Supplementary material online).[4] Diastolic wall strain correlated with the diastolic stiffness constant obtained invasively, and moderate changes in filling pressure by acute volume loading did not affect DWS. Decreased DWS is theoretically associated with increased LV stiffness rather than an abnormality of active relaxation because at the heart rates observed in these resting studies, relaxation would be complete before end-diastole even if there were a marked relaxation impairment.[26] However, very severely impaired LV relaxation or atrial systolic function could influence the measurement in select cases.

In the current study, DWS was lower in HFpEF patients, suggesting increased myocardial stiffness. However, among HFpEF patients, DWS varied with significant overlap in values between control and HFpEF patients, suggesting either insensitivity of DWS to increases in diastolic stiffness in HFpEF, poor specificity of DWS with falsely low values in some control subjects, or that increased diastolic stiffness is not an invariant feature in an unselected, community cohort of HFpEF patients. The association of lower DWS values with more abnormal geometry, Doppler evidence of elevation in filling pressures, and adverse clinical outcomes provides evidence that this index reflects intrinsic myocardial properties which are related to disease severity and progression. Importantly, the association between DWS and adverse clinical outcomes persisted after the adjustment for LV geometry, Doppler evidence of filling pressure, or BNP levels. Nonetheless, limitations imposed by the accuracy of measurement of wall thickness in systole and diastole have the potential to limit the accuracy with which DWS reflects myocardial properties.

Association between diastolic stiffness as assessed by diastolic wall strain and outcomes

Diastolic function grade, PASP, BNP, *E/e'*, and LAVI were previously reported to be associated with poor outcomes.[8,19,27–29] We showed that DWS as well as BNP or PASP was associated with worse outcomes in HFpEF after the adjustment for age and gender, whereas *E/e'* and LAVI were not. *E/e'* and LAVI were correlated with age, which was strongly associated with worse outcome in this population. BNP and PASP were also strong predictors of worse outcomes, but these indices also are load sensitive and may be altered by concomitant renal dysfunction, obesity, or pulmonary disease. Importantly, DWS remained predictive of outcomes after the adjustment for these potent prognostic factors, suggesting that DWS reflects a fundamental abnormality contributing to the progression of HFpEF. Although DWS was associated with the severity of LVH, the association of DWS with poorer outcomes remained significant after adjusting for LV mass index. This observation suggests that myocardial stiffness is likely influenced by factors beyond the severity of hypertrophy, including fibrosis or alterations in myofibrillar protein expression or post-translational modification as has been described for differences in the isoform distribution and phosphorylation status of titin.[30]

Strengths and limitations

The community-based setting, consecutive and prospective enrolment of HF patients defined by diagnostic criteria validated in numerous epidemiology studies, uniform performance of echocardiography and outcome data inclusive of HF hospitalizations represent strengths of the current study. Heart failure with preserved ejection fraction patients were older than control subjects; however, the differences in LV structure and function

between control subjects and HFpEF patients were generally similar when only control subjects who were ≥70 years old ($n = 46$, mean age 74.8) were considered (*Tables 1* and *2*). Limitations include the lack of cause-specific mortality data, exclusion of the epicardial motion component when applying the linear elastic theory to the quantification of diastolic stiffness, lack of invasive gold standard measurement of diastolic stiffness, the possibility that regional assessment of LV stiffness at the posterior wall may not reflect global LV myocardial stiffness, and inherent variability in the measurement of wall thickness by 2D echocardiography. Failure to measure both diastolic and systolic wall thickness limited the calculation of DWS in some patients, although the feasibility of this index compares favourably with other diastolic indices.[18] Although echocardiographic data were used to calculate DWS, this index could potentially be derived from carefully focused M-mode imaging or magnetic resonance or computed tomographic imaging modalities, enhancing the functional data derived from such imaging techniques.

Conclusions

The severity of diastolic stiffness as assessed by DWS is associated with more severe abnormalities of LV structure and conventional Doppler and biochemical (BNP) indices, which imply underlying diastolic dysfunction and higher filling pressures in HFpEF patients. In this community-based cohort of HFpEF patients, lower DWS was associated with higher rates of death or HF hospitalization as a combined outcome even after adjusting for LV geometry or other potent prognostic factors such as BNP and PASP. DWS is a feasible and simple calculation which does not require complex analysis. The findings of the current study support a potential role for DWS as part of an integrated approach to the assessment of diastolic function and suggest that future studies with focused and optimized assessment of DWS should be performed to further evaluate its clinical utility.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Effects of sitagliptin beyond glycemic control: focus on quality of life

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Effects of sitagliptin beyond glycemic control: focus on quality of life

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Abstract

Background

Recently, incretin hormones, including glucagon-like peptide-1 (GLP-1) analogue and dipeptidyl peptidase-4 (DPP-4) inhibitor, have been found to regulate glucose metabolism. The aim of this study was to elucidate the efficacy and safety of the clinical usage of DPP-4 inhibitors in Japan.

Methods

This study was designed as a prospective, open-label, multi-center trial. Patients with diabetes mellitus type 2 (T2DM) with poor glycemic profiles (HbA1c $\geq$ 6.2%) in spite of receiving a medical diet, therapeutic exercise, and/or medications were eligible for this study. The participants received 50 to 100 mg of the DPP-4 inhibitor sitagliptin once daily for 12 months.

Results

One hundred and eighty-eight subjects were enrolled. After 12 months of sitagliptin treatment, HbA1c levels decreased (7.65% $\pm$ 1.32% to 7.05% $\pm$ 1.10%, $p < 0.001$) as well as fasting plasma glucose (FPG) (145 $\pm$ 52 mg/dl to 129 $\pm$ 43 mg/dl, $p = 0.005$). The rate of glycemic control achieved (in accordance with the guidelines of the Japanese Diabetes Society) significantly increased. Blood pressure and serum levels of triglycerides and total cholesterol decreased significantly. Furthermore, the Pittsburgh Sleep Quality Index (PSQI) and Diabetes Symptomatic Scores improved significantly. Adverse events such as hypoglycemia and loss of consciousness occurred in twenty three subjects (11%).

Conclusions

These results suggest that the actions of DPP-4 inhibitors improve not only glycemic control, but also blood pressure, lipid profiles, and quality of life (QOL). Sitagliptin is a sound agent for use in the comprehensive treatment of patients with T2DM.

Keywords

DPP-4 inhibitor, Diabetes type 2, HbA1c, Blood pressure, Metabolism

Introduction

In Japan, the Ministry of Health, Labour and Welfare published a report on health and nourishment in 2007 [1] that estimated that 22.1 million people have strongly suspected diabetes mellitus (DM) (HbA1c (NGSP) $\geq$ 6.5%) or potential DM (6.0% $\leq$ HbA1c (NGSP) <

6.5%). This rate has increased 1.3 times compared to that observed in the former decade, and an upward trend continues to be maintained. Additionally, the rate of diabetic treatment has increased compared to that of 10 years ago. However, it has been reported that 36.5% of affected patients have not received diabetic treatment because conventional anti-diabetic drugs are inconvenient to use and exhibit inadequate efficacy, a short duration of activity, and side effects such as hypoglycemia, weight gain, and digestive symptoms. Therefore, these drugs are associated with problems regarding safety and tolerability. In 2006, the US Food and Drug Administration approved the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin. DPP-4 inhibitors are a new class of anti-diabetic drugs that exhibit different mechanisms of action from conventional anti-diabetic drugs.

Sitagliptin binds to DPP-4 and prevents the breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [2]. Both GLP-1 and GIP are types of incretin hormones released by the intestines that stimulate insulin secretion from β cells [3] and suppress glucagon secretion [4]. GLP-1 and GIP are rapidly broken down by DPP-4 [5]. Incretin hormones depend on the level of blood glucose to stimulate insulin. DPP-4 inhibitors are associated with a lower incidence of hypoglycemia than conventional hypoglycemic drugs.

This study is a single-arm, prospective, multi-center trial conducted to evaluate the efficacy and safety of the DPP-4 inhibitor sitagliptin in clinical use. In this trial, we particularly focused on the effects of sitagliptin on quality of life (QOL).

Methods

Study design and protocol

The Institutional Review Board of Human Research at Saga University approved this study and informed consent was obtained from all participants. Patients with T2DM (age ≥ 20 years) with poor glycemic control profiles [HbA1c ≥ 6.2%, as evaluated according to the National Glycohemoglobin Standardization Program (NGSP)] in spite of receiving a medical diet, therapeutic exercise, and/or conventional anti-diabetic medications were recruited. The exclusion criteria were treatment with insulin, a history of severe diabetic ketoacidosis or coma, severe infection, perioperative state, severe trauma, pregnancy, breast-feeding, renal dysfunction (creatinine clearance < 30 ml/min or serum creatinine: male: ≥ 1.5 mg/dl, female: ≥ 1.3 mg/dl), a history of experiencing side effects to sitagliptin or other unsuitableness. For the participants, sitagliptin was given as either a new prescription, as an additional prescription to other conventional anti-diabetic agents, or replaced other anti-diabetic drugs.

The subjects received 50 mg sitagliptin, once a day for the first 3 months. After 3 months, the dose of sitagliptin was changed to between (and including) 25 mg/day and 100 mg/day, and other oral hypoglycemic drugs were added according to the discretion of each physician. The observation period was 12 months.

Clinical measurements

After 12 months of treatment with sitagliptin, changes in HbA_{1c}, fasting plasma glucose (FPG), blood pressure, body weight (BW), body mass index (BMI), total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglycerides (TG), 1.5-anhydro-D-glucitol (1.5-AG), microalbuminuria, and homeostasis model assessment analyses of beta cell

function (HOMA-β) and insulin resistance (HOMA-IR) were assessed. We also assessed changes in the subjects' quality of life (QOL) using the Euro QOL (EQ)-5 Dimensions (EQ-5D), the EQ Visual Analogue Scale (EQ-VAS), the Pittsburgh Sleep Quality Index (PSQI), and the Diabetes Symptomatic Score.

The EQ-5D is a generic instrument for measuring health-related QOL that has been developed and validated in a number of European countries [6,7]. The EQ-5D describes a patient's health status according to five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels that include no problems, some problems or severe problems. This yields 243 potential combinations of health states across the five dimensions. Dolan et al. [8] measured 42 of these health states in a representative sample of the United Kingdom general population using the Time Trade-Off method [9]. Based on these evaluations, the utility scores can be deduced by means of an additive function. The utility scores may vary between −0.59 (worst health) and 1.00 (perfect health). In addition to the five dimensions, the EuroQol consists of an EQ-VAS ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [10]. The PSQI is a self-administered questionnaire used to assess subjective sleep quality during the previous month [11]. The self-rated items of the PSQI generate seven component scores (range of subscale scores: 0 to 3) for sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. The sum of these seven component scores yields one global score of subjective sleep quality (range: 0 to 21), with higher scores representing poorer subjective sleep quality. The psychometric properties of the PSQI have been confirmed in previous studies [11,12]. We have used 5.5 points as a cut-off in the Japanese version of the PSQI global score [6]. The Diabetes Symptomatic Score is a method for assessing QOL that was originally developed for the S-DOG trial. This score is calculated as the sum of the scores, graded 1 to 5, for 10 diabetes-related symptoms (Table 1).

Table 1 Checklist of diabetes symptomatic score

	Checklist
1	Are you often thirsty?
2	Do you produce urine frequently?
3	Are you worried about urinary smell?
4	Do you feel numbness of your extremities?
5	Do you have edema in your legs?
6	Do you have cramps in your legs?
7	Are you insensitive to the pain of a small wound or burn?
8	Do you have a feeling of listlessness?
9	Do you feel lightheaded?
10	Is your vision blurry? Is your eyesight getting worse?

Diabetes Symptomatic Score is used to measure the grade of ten diabetic symptoms. Patients with a high score have worsening of diabetic symptoms.
None: 0 point, Rare: 1 point, Sometimes: 2 points, Frequent: 3 points, Always: 4 points. Maximum: 40 points.

Statistics

Values are expressed as the mean ± SD. To compare changes in the values of HbA1c, FPG, BW, BMI, BP, lipids, 1.5AG, and HOMA from baseline to after 12 weeks of treatment, we used the paired *t*-test. To compare changes in the values of the EQ-5D, EQ-VAS, PSQI, and

Diabetes Symptomatic Score, we used the Wilcoxon signed-rank test. Values of $p < 0.05$ were considered to be statistically significant.

Results

Baseline characteristics

A total of 221 patients agreed to participate in this study. Of the 221 patients, 14 were excluded due to protocol violation. Among the 207 enrolled subjects, seven were excluded due to discontinuing sitagliptin within the first 3 months, and 12 were excluded because data acquisition to evaluate the efficacy of the drug failed. Therefore, sitagliptin efficacy over 3 months was evaluated in 188 subjects as efficacy population. The safety of sitagliptin over 12 months was also evaluated in the 207 enrolled subjects as safety population (Figure 1).

Figure 1 Study Enrollment.

Table 2 shows the clinical characteristics of the study subjects prior to the start of treatment with sitagliptin. The average age of the evaluated subjects was 66.9 years, 91 subjects (48%) were male, the mean duration of diabetes was 6.9 years and the mean HbA1c level was 7.65% at baseline.

Table 2 Baseline characteristics

	Enrolled subjects (n = 207)	Evaluated subjects (n = 188)
Age (years)	66.5 ± 12.8	66.9 ± 12.6
Gender	Male: 50% (n = 103), Female: 50% (n = 104)	Male: 48% (n = 91), Female: 52% (n = 97)
BMI	25.0 ± 4.4 kg/m^2	25.0 ± 4.4 kg/m^2
Waist circumference	89.4 ± 12.8 cm	89.0 ± 12.8 cm
Obesity (BMI > 25)	51%	50%
Duration of DM (years)	6.8 ± 6.5	6.9 ± 6.6
Smoking status	Smoker: 24% Past smoker: 13% Never: 63%	Smoker: 23% Past smoker: 13% Never: 63%
Alcohol consumption	Yes: 30%	Yes: 29%,
Complications	HT: 67%, DL: 55%, HUA: 7%, Arrhythmia: 5%, CKD 43%	HT: 65%, DL: 55%, HUA: 6%, Arrhythmia: 5%, CKD 43%
Use of sitagliptin	New: 35% Added: 45%, Changed: 20%	New: 35% Added 45%, Changed 20%
Combined drugs	SU: 49%, BG: 20%, TZD: 28%, Glinide: 2%, α-GI: 7%	SU: 48%, BG: 22%, TZD: 28%, Glinide: 2%, α-GI: 7%

BMI, Body mass index; DM, diabetes mellitus; HT, hypertension; DL, dyslipidemia; HUA, hyperuricemia; CKD, chronic kidney disease; SU, sulfonylurea; BG, biguanide; TZD, thiazolidinedione; α-GI, α-glucosidase inhibitor.

Effects of sitagliptin on glycemic control

Overall, HbA1c levels decreased in all of the 188 evaluated subjects after 3 months (7.65% ± 1.32% to 7.06% ± 1.07%, $p < 0.001$) and 12 months (7.05% ± 1.10%, $p < 0.001$) of sitagliptin treatment (Figure 2a). The HbA1c decreases per subgroup are described here.

Figure 2 Serial HbA1c changes in (a) all subjects, (b) BMI-based groups, (c) age-based groups, (d) HbA1c-based groups, and (e) fasting plasma glucose. HbA1c, hemoglobin A1c; BMI, body mass index. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, vs. baseline by paired t-test.

For the 66 subjects who received sitagliptin alone, the decreases were 7.44% ± 1.31% to 6.72% ± 0.82%, $p < 0.001$ at 3 months and 6.61% ± 0.82%, $p < 0.001$ at 12 months. Eighty-five subjects received sitagliptin along with other anti-diabetic agents, HbA1c level decreases were 7.86% ± 1.25% to 7.22% ± 1.18%, $p < 0.001$, 3 months and 7.32% ± 1.20%, $p < 0.001$, 12 months. In subjects with a BMI < 25 kg/m^2 ($n = 81$) and those with a BMI ≥ 25 kg/m^2 ($n = 80$), a decrease in HbA1c levels was observed after 12 months of sitagliptin treatment: 7.59% ± 1.16% to 7.06% ± 1.12%, $p < 0.001$ and 7.68% ± 1.47% to 7.05% ± 1.03%, $p < 0.001$, respectively (Figure 2b). By age group, HbA1c levels decreased as follows: in subjects < 65 years of age ($n = 65$), 8.00% ± 1.59% to 7.29% ± 1.23%, $p < 0.001$; those 65 to 74 years of age ($n = 46$), 7.61% ± 1.11% to 7.05% ± 0.99%, $p < 0.001$; and in those ≥ 75 years of age ($n = 51$), 7.21% ± 0.87% to 6.75% ± 0.96%, $p < 0.001$ (Figure 2c).

In each subgroup of baseline HbA1c level [<6.9% ($n = 56$), 6.9% ≤ baseline HbA1c < 8.4% ($n = 89$), and 8.4% ≤ baseline HbA1c ($n = 43$)], the HbA1c levels were decreased at 3 months (−0.19%, -0.43%, and −1.45%, respectively) (Figure 2d). FPG was also decreased after 3 months ($n = 84$, 145 ± 52 to 129 ± 43 mg/dl, $p < 0.001$) and 12 months of sitagliptin treatment ($n = 65$, to 129 ± 42 mg/dl, $p = 0.005$). The rate of glycemic control achieved (in accordance with the guidelines of the Japanese Diabetes Society) significantly increased (Figure 2e).

Effects of sitagliptin on blood pressure, lipid profiles and insulin resistance

BW and BMI decreased after 3 months of sitagliptin treatment (BW: 62.1 ± 14.1 to 61.5 ± 13.8 kg, $p = 0.003$, BMI: 25.0 ± 4.5 to 24.8 ± 4.5 kg/m^2, $p = 0.006$). At 12 months, these values had returned to baseline levels (BW: 62.0 ± 13.7 kg, $p = 0.800$, BMI: 25.1 ± 4.4 kg/m^2, $p = 0.560$) (Figure 3a, b). Systolic (SBP) and diastolic blood pressure (DBP) also decreased after 3 months (SBP: 135 ± 18 to 131 ± 17 mmHg, $p < 0.001$, DBP: 75 ± 12 to 71 ±11 mmHg, $p < 0.001$) (Figure 3c, d) as did serum levels of TC and TG (TC: 201 ± 40 to 191 ± 37 mg/dl, $p < 0.001$; TG: 161 ± 171 to 136 ± 126 mg/dl, $p = 0.003$) (Figure 3e). However, there was no change in the levels of 1.5 AG, HOMA-β, and HOMA-IR observed (Figure 3f, g).

Figure 3 Serial changes of (a) body weight, (b) BMI, (c) blood pressure, (d) lipid profiles including total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol, (e) 1.5 AG, and (f) HOMA-β and –IR. M, months; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; 1.5-AG, 1.5-Anhydro-D-glucitol; HOMA-β, homeostasis model assessment analyses of beta cell function; HOMA-IR, insulin resistance. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, vs. baseline by paired t-test.

Effects of sitagliptin on QOL

PSQI scores decreased after 12 months of sitagliptin treatment (4.1 ± 2.9 to 3.4 ± 2.5 points, $p = 0.007$) in all subjects (Figure 4a). In the subgroup of subjects with a PSQI score > 5.5 points, the scores significantly decreased both at 3 months (8.0 ± 1.8 to 6.5 ± 3.0 points, $p < 0.001$) and 12 months (to 6.2 ± 3.1 points, $p < 0.001$) after sitagliptin treatment. The Diabetes Symptomatic Scores also decreased at both 3 months (5.6 ± 5.71 to 4.4 ± 4.35, $p = 0.004$) and 12 months (to 3.7 ± 3.65, $p = 0.006$) (Figure 4b). Among the 10 diabetes symptomatic questions (Table 2), scores regarding urination ($p = 0.013$) and paresthesia ($p = 0.025$) were decreased at 12 months. In contrast, the EQ-5D and EQ-VAS scores did not change significantly (Figure 4c, d).

Figure 4 Effects of sitagliptin on QOL. (a) PSQI the Pittsburgh Sleep Quality Index, **(b)** the Diabetes Symptomatic Score, **(c)** Euro QOL (EQ)-5 Dimensions (EQ-5D), and **(d)** the EQ Visual Analogue Scale (EQ-VAS). *$p < 0.05$, **$p < 0.01$, **$p < 0.001$, vs. baseline by Wilcoxon signed-rank test.

Safety

Twenty-three (11%) of the 207 enrolled subjects suffered adverse events (AEs) (Table 3). Two subjects (0.96%) experienced direct sitagliptin-related AEs causing them to discontinue sitagliptin. One subject suffered from gastrointestinal (GI) symptoms, including vomiting, stomachaches, and constipation. The other subject experienced skin eruptions.

Table 3 Adverse events

Event	Number
Death (cause unknown)	1
Worsening of vomiting, stomachache, constipation	1
Loss of consciousness	1
Hypoglycemia	1
Intestinal tuberculosis, pneumonia	1
Stool abnormality	2
Acute myocardial infarction	1
Thrombocytopenia	1
Worsening of heart failure	1
New onset of dyslipidemia	3
Bleeding or ulcer of GI tract	2
Liver dysfunction	4
Elevation of CPK	2
Fever and poor physical health	1
Skin disease including eruption	2
Total number of incidents	24 in 23 subjects

GI, gastric intestinal; CPK, creatinine phosphokinase.
Liver dysfunction is defined as elevated (> 2.5 × the upper limit of normal) alanine aminotransferase or aspartate aminotransferase.
Elevation of CPK is defined as elevated > 2 × the upper limit of normal.

Three subjects (1.15%) developed AEs that were suspected to have a causal relationship with sitagliptin. Hypoglycemia and loss of consciousness occurred in two subjects (0.96%). Pneumonia/intestinal tuberculosis and stool abnormality were recognized in one subject.

Discussion

Efficacy and safety of sitagliptin

In our study, the HbA1c and FPG levels were reduced at 3 months (HbA1c: 0.59%, FPG: 15.5 mg/dl reduction) and at 12 months (HbA1c: 0.65%, FPG: 20.2 mg/dl reduction) after treatment with sitagliptin at a dose of 25 to 100 mg/day. Our results are similar to those of previous studies reported in the US [13] and Japan [14]. Nathan et al. [15] reported that the expected percentage decrease in HbA1c levels is 1.0% to 2.0% with metformin monotherapy, 1.0% to 2.0% with sulfonylureas (SUs), 0.5% to 1.0% with glinides, 0.5% to 0.8% with α-glucosidase inhibitors (α-GI), 0.5% to 1.4% with thiazolidinediones (TZD) and 0.5% to 0.8% with DPP-4 inhibitors. Monotherapy with metformin or SU exhibits a stronger reduction of HbA1c levels than a DPP-4 inhibitor alone. However, metformin is associated with side effects such as GI symptoms and is contraindicated in patients with renal insufficiency. The major side effects of SUs are hypoglycemia and weight gain. In patients receiving treatment with SUs, the incidence of hypoglycemic episodes has been reported to be 17.6% per year [16]. Side effects appear to be more frequently seen with metformin or SUs than with sitagliptin. The most common side effects of TZD are weight gain and fluid retention along with peripheral edema and an increased risk of congestive heart failure [14,17]. In our study, body weight and BMI decreased and there was no evidence of heart failure during sitagliptin treatment. While metformin, glinides, and α-GIs are required to be taken three times daily, sitagliptin is only taken once daily. Therefore, sitagliptin should be associated with higher adherence compared to metformin, glinides, and α-GIs.

In our study, AEs after sitagliptin treatment were seen in 23 (11%) of the 207 enrolled subjects. In particular, direct sitagliptin-related AEs such as hypoglycemia and loss of consciousness were observed in only two subjects (0.96%). A previous pooled analysis [18] reported that the overall incidence of AEs was similar between sitagliptin (100 mg/day) and other diabetic-comparator agents (except for other DPP-4 inhibitors), including placebos, pioglitazone, metformin, sulfonylureas, sulfonylureas + metformin, and metformin + rosiglitazone (overall side effects: 63.0% vs. 62.8%, hypoglycemia: 3.4% vs. 10.9%). Therefore, incidence of AEs in this study, including hypoglycemia, was lower than that reported in the pooled analysis. This discrepancy appears to be related to differences in dosage. In our study, subjects received doses between 50 and 100 mg/day of sitagliptin with only 24 (11.6%) receiving the highest dose of 100 mg. In the pooled analysis, all subjects received 100 mg/day. In previous studies, sitagliptin did not increase cardiovascular risk in patients with T2DM [19] and sitagliptin reduced postprandial glucose fluctuation and stabilized blood glucose levels effectively in combination with miglitol through continuous glucose monitoring (CGM) [20]. On the other hand, vildagliptin twice a day calmed down the postprandial glucose level as compared to sitagliptin by CGM [21]. The results of this study show that sitagliptin was safe and effective in this population; however, further studies are needed to evaluate the comparison of each DPP-4 inhibitor.

Effects of DPP-4 inhibitors on blood pressure and lipid profiles

Systolic and diastolic blood pressure decreased after 3 months of treatment with sitagliptin. The active isoforms of GLP-1 include GLP-1(7–36) amide and glycine-extended GLP-1(7–37) [22]. GLP-1(7–36) exhibits vascular actions via GLP-1 receptor signaling [23]. Additionally, GLP-1(9–36), a metabolite of GLP-1 (7–36), has vasodilator effects independent of the GLP-1 receptor in a nitrous oxide/cyclic guanosine monophosphate