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Subclinical decrease in cardiac autonomic and diastolic function in patients with metabolic disorders: HSCAA study

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ABSTRACT

Heart failure due to decreased diastolic function, HFpEF, is a growing health concern with rising prevalence. We examined subclinical cardiac autonomic and diastolic functions in 605 patients with metabolic diseases classified as pre-heart failure. Presence of glucose intolerance or diabetes, or visceral adiposity was significantly associated with reduced cardiac autonomic and diastolic functions. Higher autonomic functions were significantly associated with a parameter of better cardiac diastolic function (E/A) (SDNN: $r = 0.306$, $p < 0.01$; HF: $r = 0.341$, $p < 0.01$), with the association independent of diabetes, body mass index, visceral adiposity and insulin resistance index. Thus, reduced autonomic function may be a potential predictor for decreased cardiac diastolic functions in metabolic disorders.

1. Introduction

Chronic heart failure is a substantial epidemic burden worldwide, with approximately half of affected patients showing a normal left ventricular (LV) ejection fraction (EF), termed heart failure with preserved ejection fraction (HFpEF) [1,2]. HFpEF is a growing health care concern with rising prevalence [3], with nearly half of all patients with heart failure symptoms have HFpEF [4]. Diabetes and obesity are common comorbid conditions in patients with HFpEF patients, and its presence appears play a fundamental role in the development of HFpEF [3,5].

HFpEF is shown to be associated with increased sympathetic and decreased parasympathetic activity, and decreased heart rate variability (HRV) [6]. Decreased HRV appears to be related to progression of heart failure [7]. Even though autonomic dysfunction is a common microvascular complication in diabetes [8], it is known to be associated with obesity [9–11], which is also a well-recognized risk factor of HFpEF.

Early detection of subclinical cardiac diastolic dysfunction is apparently a clinical priority in patients with metabolic disorders for prevention of HFpEF [12]. Limited numbers of studies have shown changes in cardiac diastolic function in prediabetes [13–15] and obesity [16,17]. Although adiposity, altered glycemic abnormalities and insulin resistance may be candidate risk factors even in the pre-heart failure period, significance of autonomic nervous functions in cardiac diastolic functions is entirely obscure.

To evaluate potential presence and predictors of subclinical cardiac autonomic and diastolic dysfunction, we examined echocardiographic cardiac functions, heart rate variability (HRV), stages of glycemic abnormalities, insulin resistance, and whole or visceral adiposity in pre-heart failure patients with metabolic disorders, who were registered in the Hyogo Sleep Cardio-Autonomic Atherosclerosis (HSCAA) study.

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2. Material and methods

2.1. Design and study participants

The HSCAA study is a single center cohort study performed at Hospital of Hyogo College of Medicine for a review of cardiovascular risk factors, including quantitatively measured autonomic nervous function determined by HRV, for elucidation of the clinical implications of atherosclerosis and metabolic diseases [18,19]. One aim of this cohort is to examine clinical impact of subclinical alteration of autonomic nervous function, thus, patients with apparent symptoms and signs of severe autonomic neuropathy (orthostatic hypotension or syncope, dizziness, symptomatic tachycardia, disturbed vision, atonic bladder, etc) were not registered to this cohort. Among 979 patients with at least 1 examined cardiovascular risk factor (obesity, smoking, presence of cardiovascular event history, hypertension, dyslipidemia, and diabetes mellitus) enrolled from October 2010 to December 2018, 603 patients were cross-sectionally analyzed in the present study after excluding 240 with ischemic heart disease, moderate to severe valvular heart disease, hypertrophic cardiomyopathy, atrial fibrillation, plasma brain natriuretic peptide (BNP) level equal or higher than 100 pg/ml, or heart failure diagnosed according to the recommendations of the American Society of Echocardiography [20], and 131 with missing data for HRV or cardiac ultrasonography (Fig. 1). Each completed an echocardiographic examination and underwent measurements related to HRV. Also, 340 subjects without diagnosis of diabetes agreed to receive 75-g oral glucose tolerance test to be classified as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes. Moreover, 404 participants also agreed to undergo abdominal CT examinations for a review of body composition including visceral fat as previously described [11]. All patients were advised to fast overnight in advance to draw blood for biochemical analyses. The HSCAA study was approved by an appropriate institutional ethical committee (approval No. 2351) and informed written consent was obtained from each participant.

2.2. Assessment of classical cardiovascular risk factors

We obtained the medical history of each subject, and measured height and body weight. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Smoking status was based on self-reported habit of cigarette smoking. Blood pressure and pulse rate was measured twice in a sitting position after a deep breath. Mean of the measurements were used for analyses. Type 2 diabetes was diagnosed based on results showing fasting plasma glucose ≥126 mg/dl (7.0 mmol/L), causal plasma glucose ≥200 mg/dl (11.1 mmol/L), or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/L) during a 75-g oral glucose tolerance test, or previous therapy for diabetes [21]. IGT was defined as fasting plasma glucose of 110−125 mg/dl (6.1-6.9 mmol/L), or 2-h plasma glucose 140−199 mg/dl (7.8-11.0 mmol/L) during a 75-g oral glucose tolerance test. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or treatment for hypertension. Dyslipidemia was defined as the presence of low density lipoprotein cholesterol [≥140 mg/dl (3.62 mmol/L)], high density lipoprotein cholesterol [≤40 mg/dl (1.03 mmol/L)], elevated triglyceride level [≥150 mg/dl (1.7 mmol/L)], or treatment for dyslipidemia [22]. Components of metabolic syndrome were defined as 1) raised blood pressure (≥130/85 mmHg or treatment/previous diagnosis of hypertension), 2) raised fasting glucose (>5.6 mmol/L or previously diagnosed type 2 diabetes), 3) dyslipidemia (HDL-cholesterol <1.03 mmol/L or triglyceride => 1.7 mmol/L).

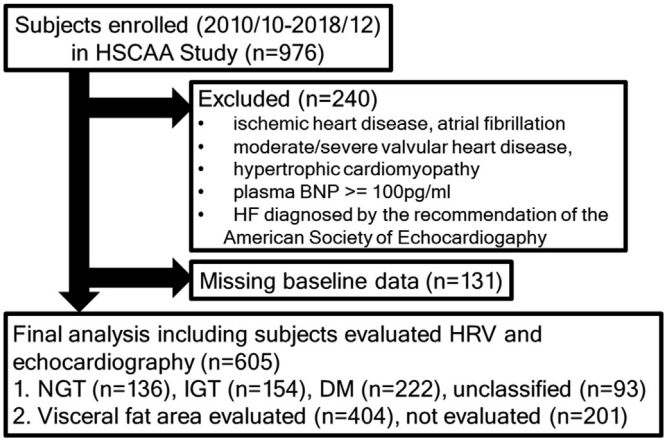

Fig. 1. Subjects enrollment.

2.3. Assessment of LV diastolic function

LV diastolic function was evaluated by echocardiography, which was performed with several devices, including an IE-33, CX50 (Philips Healthcare, Massachusetts, USA), Artida, Aplio300 (Toshiba Medical System Co., Tochigi, Japan), and F75 (Hitachi-Aloka Medical, Tokyo, Japan). To measure LV ejection fraction (LVEF), we used the modified Simpson's method for patients with LV segmental asynergy or deformation, and Teichholz's formula for patients without LV asynergy or deformation. Transmitral early inflow velocity (E-wave), late diastolic filling velocity (A-wave), and E-wave deceleration time (DcT) were determined using pulsed Doppler echocardiography, according to the American Society of Echocardiography guidelines [20]. Early diastolic tissue velocity (e') was measured in the septal basal region using tissue Doppler imaging.

2.4. Assessment of AUTONOMIC nervous FUNCTION

HRV was used to noninvasively measure cardiac modulation based on autonomic nervous function, as reported in previous studies [18,23], using an Active Tracer (AC-301A®, Arm Electronics, Tokyo, Japan), which monitors surface electrocardiogram findings from the upper limbs via 3 channels. We sequentially recorded HRV for 48 h, as HRV parameters obtained for more than 24 h have been shown to be highly reproducible in healthy subjects and moderately reproducible in diseased populations. The latter 24-h series of data from the 48-h recording was analyzed using the MemCalc Chiram 3 system, version 2.0 (Suwa Trust, Tokyo, Japan). Ectopic beats, noise data, and artifacts were manually corrected or excluded from the calculations. According to the recommendations for clinical use of HRV [24], the standard deviation of the NN(RR) interval (SDNN) as a time-domain of HRV was calculated. Following power spectral density estimation, standard frequency-domain HRV values were calculated for 24 h. The low frequency domain (LF) was defined as between 0.04 and 0.15 Hz, and the high frequency domain (HF) as between 0.15 and 0.4 Hz, then the ratio of low-to high-frequency power (LF/HF) was determined.

2.5. Plasma biochemical parameters

Blood samples were obtained in the morning after an overnight fast for measurement of HRV and then quickly centrifuged to obtain plasma. Whole blood was used for hemoglobin A1c, EDTA-plasma for glucose, insulin, and lipids, and serum for other biochemical

assays. Glucose was measured by a glucose oxidase method. Insulin was measured by radioimmunometric assay (Insulin RIA-BEAD II; Dinabot Co., Tokyo, Japan). For subjects not receiving insulin therapy (n = 568), insulin resistance was assessed by utilizing the homeostasis model assessment (HOMA-IR) as calculated by following formula: HOMA-IR (mmol/L × μU/ml) = fasting glucose (mmol/L) × fasting insulin (μU/ml)/22.5. HOMA-IR was shown to be correlated to the insulin sensitivity index by the standard euglycemic hyperinsulinemic clamp [25]. Serum creatinine concentrations were determined using an enzymatic method. Estimated glomerular filtration rate (eGFR) in each patient was calculated using an equation for Japanese subjects, as follows: eGFR (ml/min/1.73 m^2) = 194 × age (years)$^{-0.287}$ × S-creatinine$^{-1.094}$ (if female, × 0.739) [26]. Plasma BNP was determined by use of a chemiluminescent enzyme immunoassay (SRL Inc, Tokyo, Japan).

2.6. Statistical analyses

To compare means among groups, we used a Student's t-test for 2 groups (with and without visceral adiposity) and a Turkey-Kramer test with ANOVA for 3 groups (NGT, IGT and diabetes). To compare median among groups, a Mann-Whitney test was used for 2 groups, and a Kruskal-Wallis test for 3 groups. Chi-square test was used for comparisons for dichotomous variables. To analyze associations between factors, parameters with skewed distribution were natural logarithm-transformed (ln) to normalize distribution. Pearson's correlation coefficient was used to analyze associations of clinical data. Multiple linear regression analysis was employed to explore independent relationships between clinical factors. All statistical analyses were performed using the Statistical Package for Social Sciences software package (PASW Statistics version 18.0). All reported p values are 2-tailed and were considered statistically significant at <0.05.

3. Results

3.1. Subjects

Among 976 patients with cardiovascular risk factors registered in the HSCAA cohort study between October 2010 and December 2018, those without heart failure and heart disease who underwent both cardiac echocardiography examinations and measurements of heart rate variability (n = 605) were analyzed in the present study (Fig. 1). Table 1 summarizes the baseline/demographic characteristics of the enrolled subjects, who were categorized by different glycemic abnormalities, and the presence or absence of visceral fat obesity. In diabetes group, 37 subjects were on insulin therapy. As compared with NGT or IGT, diabetic group exhibited significantly higher age, male prevalence, more smoker, more comorbidities of hypertension and dyslipidemia, more visceral adiposity, higher systolic blood pressure, plasma glucose and HbA1c. BMI and HOMA-IR in diabetes group were significantly higher than those of NGT, but not IGT group. As compared with NGT, IGT group also showed similar trends, including male prevalence, higher prevalence of hypertension and dyslipidemia, higher body mass index, and higher plasma insulin and HOMA-IR. Plasma BNP levels were

Table 1
Baseline/demographic characteristics of subjects.

	Total (n = 605)	Glycemic stages determined (n = 510)				Visceral fat area determined (n = 404)		
		NGT	IGT	diabetes	*p*	Visceral fat < 100	Visceral fat ≥ 100	*p*
Numbers	605	136	154	222	–	280	124	–
Age, years	58.4 ± 0.5	57.1 ± 1.2	55.9 ± 1.1	62.8 ± 0.7[a,b]	<0.01	57.5 ± 0.8	61.3 ± 1.0	<0.01
Male gender, n (%)	289 (47.7%)	45 (33.1%)	65 (42.2%)[a]	139 (62.6%)[a,b]	<0.01	106 (37.9%)	80 (64.5%)	<0.01
Current smoking, n (%)	146 (24.1%)	27 (19.8%)	35 (22.7%)	69 (31.1%)[a,b]	0.04	54 (19.3%)	36 (29.0%)	0.020
Hypertension, n (%)	372 (61.4%)	67 (49.2%)	89 (57.7%)[a]	166 (74.8%)[a,b]	<0.01	150 (53.6%)	96 (77.4%)	<0.01
SBP, mmHg	125.0 ± 0.6	122.1 ± 1.3	123.3 ± 1.1	128.6 ± 1.0[a,b]	<0.01	122.0 ± 0.9	130.1 ± 1.5	<0.01
DBP, mmHg	75.2 ± 9.0	73.8 ± 0.7	74.8 ± 0.7	76.1 ± 0.5	0.06	73.5 ± 0.5	77.3 ± 0.8	<0.01
Pulse rate, bpm	68.4 ± 8.9	67.6 ± 0.9	68.9 ± 1.0	68.8 ± 0.7	0.64	68.2 ± 0.6	68.4 ± 1.1	0.82
Dyslipidemia, n (%)	356 (58.8%)	66 (48.5%)	91 (59.0%)[a]	154 (69.4%)[a,b]	<0.01	159 (56.8%)	87 (70.2%)	<0.01
Diabetes, n (%)	222 (36.6%)	–	–	–	–	67 (23.9%)	62 (50.0%)	<0.01
Metformin, n (%)	62 (10.2%)	–	–	62 (27.9%)	–	18 (6.4%)	23 (18.5%)	<0.01
Sulfonylurea, n (%)	53 (8.7%)	–	–	53 (23.8%)	–	14 (5.0%)	21 (16.9%)	<0.01
Thiazolidine, n (%)	19 (3.1%)	–	–	19 (8.5%)	–	6 (2.1%)	6 (4.8%)	0.20
DPP-4 inhibitor, n (%)	57 (9.4%)	–	–	57 (25.6%)	–	30 (10.7%)	20 (16.1%)	0.14
SGLT2 inhibitor, n (%)	5 (0.8%)	–	–	5 (2.2%)	–	0 (0.0%)	3 (2.4%)	0.02
GLP-1 receptor, n (%)	6 (0.9%)	–	–	6 (2.7%)	–	2 (0.7%)	3 (2.4%)	0.17
Insulin, n (%)	37 (6.1%)	–	–	37 (16.6%)	–	12 (4.2%)	11 (8.8%)	0.10
BMI, kg/m^2	24.2 ± 0.1	22.5 ± 0.3	24.8 ± 0.4[a]	25.4 ± 0.2[a]	<0.01	22.7 ± 0.2	27.8 ± 0.4	<0.01
Visceral fat area, cm^2	83.8 ± 2.8	70.3 ± 7.1 (n = 97)	78.9 ± 4.8 (n = 105)	103.1 ± 4.3[a,b] (n = 153)	<0.01	55.2 ± 1.6	148.5 ± 4.9	<0.01
FPG, mmol/L	5.87 ± 0.07	5.08 ± 0.01	5.39 ± 0.06	6.97 ± 1.50[a,b]	<0.01	5.67 ± 0.09	6.39 ± 0.18	<0.01
HbA1c, %	5.8 ± 0.0	5.1 ± 0.0	5.3 ± 0.0	6.9 ± 0.1[a,b]	<0.01	5.6 ± 0.0	6.3 ± 0.1	<0.01
IRI, pmol/L	46.5 ± 1.4 (n = 568)	38.9 ± 2.1	54.2 ± 3.5[a]	47.2 ± 2.1 (n = 185)	<0.01	41.7 ± 1.4 (n = 268)	57.6 ± 2.8 (n = 113)	<0.01
HOMA-IR	1.7 ± 0.0 (n = 568)	1.3 ± 0.0	1.9 ± 0.1[a]	2.0 ± 0.1[a] (n = 185)	<0.01	1.5 ± 0.0 (n = 268)	2.2 ± 0.1 (n = 113)	<0.01
eGFR, ml/min/1.73m^2	83.2 ± 1.0	85.4 ± 2.4	85.5 ± 1.9	81.5 ± 1.7	0.23	85.3 ± 1.4	80.2 ± 2.5	0.08
Autonomic function								
SDNN, ms^2	117.2 (97.2–141.6)	123.7 (102.7–146.5)	115.0[a] (96.5–142.9)	113.1[a] (93.8–135.2)	0.03	118.9 (98.2–146.4)	114.7 (91.7–135.8)	0.04
LF, ms^2	329.4 (177.0–535.3)	369.8 (224.7–585.7)	324.2[a] (183.7–544.0)	296.6[a,b] (162.1–500.2)	0.04	360.0 (199.1–569.2)	266.2 (156.5–475.8)	<0.01
HF, ms^2	118.3 (60.1–219.1)	133.0 (73.8–257.5)	125.0[a] (80.5–221.1)	97.0[a,b] (50.8–182.4)	<0.01	135.8 (68.0–236.1)	99.9 (47.5–179.4)	0.01
LF/HF	3.6 (2.5–5.5)	3.5 (2.5–5.4)	3.3 (2.4–4.8)	3.9 (2.5–6.2)	0.05	3.5 (2.4–4.9)	4.2 (2.6–6.2)	0.04
Plasma BNP, pg/ml	2.0 (2.0–10.5)	2.8 (2.0–14.2)	2.1 (2.0–10.2)	2.0 (2.0–10.7)	0.49	2.0 (2.0–9.4)	2.0 (2.0–10.4)	0.96

Date are presented as mean ± standard error or median (25th-75th percentile) for continuous variables, and n (%) for dichotomous variables. P values are shown comparisons of means (ANOVA) and median (Kruskal-Wallis test) for 3 groups, or means (unrepeated t-test) and median (Mann-whitney test) for 2 groups, or percentages (Chi-square test). NGT, normal glucose tolerance; IGT, impaired glucose tolerance; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FPG, fasting plasma glucose; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment-insulin resistance; eGFR, estimated glomerular filtration rate; BMI, body mass index; BNP, brain natriuretic peptide; SDNN, standard deviation of NN(RR) interval; LF, low frequency power; HF, high frequency power. p < 0.05, a vs. NGT, b vs. IGT (post-hoc analysis, Tukey-Kramer test for ANOVA, Steel-Dwass test for Kruskal-Wallis test, Chi-square test).

comparable among the 3 glycemic stages. In 404 subjects with their visceral fat area determined, those with visceral adiposity (visceral fat area equal or larger than 100 cm^2) exhibited higher age, male prevalence, more smoker, higher percentages of hypertension, dyslipidemia and diabetes, higher BMI, higher systolic and diastolic blood pressure, higher plasma glucose and HbA1c, and higher plasma insulin and HOMA-IR.

Even in pre-heart failure phase, subjects with diabetes showed significantly lower E/A, e', and significantly higher DcT and E/e' than those with NGT. E/A, e' and E/e' levels were even significantly different in diabetes than IGT subjects (Fig. 2A). E/A in IGT was significantly lower than that in NGT. LVEF was identical among the 3 groups. With regard to glycemic parameters, HbA1c was significantly and inversely associated with all cardiac diastolic functions, including E/A (Table 2). HOMA-IR, an insulin resistance index, was not significantly associated with E/A, but showed weak but significant associations with E, A and E/e' in simple regression analyses (Table 2).

Among clinical factors, age was the strongest factor with an inverse association with LV diastolic function, including E/A ($r = -0.654$, Table 2). Additionally, female gender was shown to have a modest association with LV diastolic parameters, including low E/A, low E wave velocity, high DcT, low e' as well as low EF (Table 2). Smoking was not significantly associated with cardiac diastolic parameters, but significantly and inversely with LVEF. Presence of hypertension, systolic and diastolic blood pressure, or dyslipidemia was significantly and inversely associated with all or many parameters of the LV diastolic functions, but not with LVEF. Body mass index was weakly but significantly associated with some parameters of LV diastolic functions. Moreover, subjects with visceral adiposity exhibited a significantly worse LV diastolic function as compared to those without that condition (Fig. 2B, Table 2). LVEF was also significantly lower in subjects with than without visceral adiposity. We also examined whether components of metabolic syndrome as well as general or visceral obesity may affect cardiac diastolic function (Fig. 3). As shown in Fig. 3A, addition of numbers of metabolic components did not affect association of visceral adiposity with E/A. In contrast, even in subjects with BMI => 25 kg/m^2, those with 3 components of metabolic syndrome exhibited significantly lower E/A than those with 0, 1, or 2 components (Fig. 3B).

3.2. Cardiac autonomic and diastolic functions

As shown in Table 1, diabetic subjects who showed decreased cardiac diastolic functions, showed significantly lower HRV parameters than NGT, among which LF and HF were significantly lower than those in IGT. SDNN, LF and HF, were also significantly lower in IGT than those in NGT. In 404 subjects with their visceral fat area determined, those with visceral adiposity, who also demonstrated decreased LV diastolic functions, exhibited lower SDNN, LF, HF and higher LF/HF. These results suggest that autonomic nervous function or a lower level of parasympathetic activity may explain lower LV diastolic function in association with diabetes

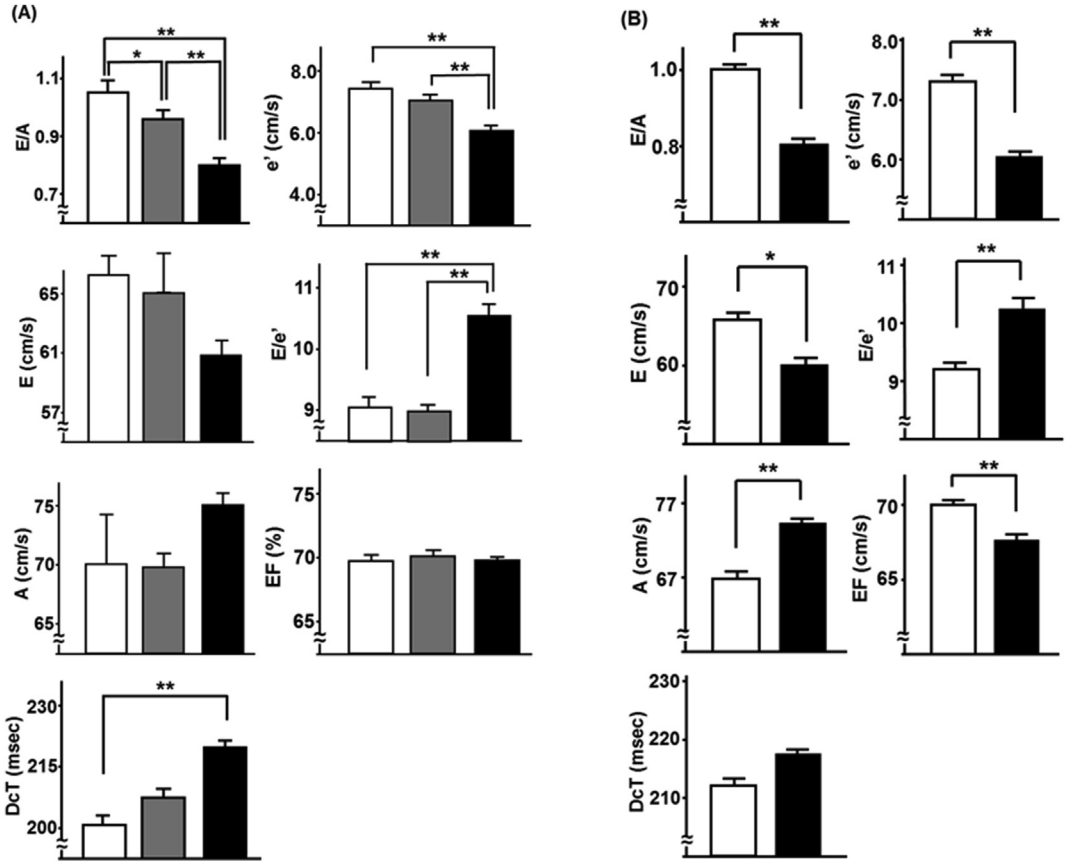

Fig. 2. Cardiac diastolic and systolic functions in different glycemic abnormalities (A) and with and without visceral adiposity (B). Cardiac diastolic functions determined by cardiac ultrasonography include E/A, E wave velocity (E), A wave velocity (A), E-wave deceleration time (DcT), early diastolic tissue velocity (e') and E/e'. Cardiac systolic function was represented by left ventricular ejection fraction (EF). Each column represents mean ± standard error. (A) Open column: normal glucose tolerance (n = 136), grey column: impaired glucose tolerance (n = 154), closed column: type 2 diabetes (n = 222). *: $p < 0.05$, **; $p < 0.01$, Turkey-Kramer test with ANOVA <0.05. (B) Open column: visceral fat area <100 cm^2, closed column: ≥100 cm2 *: $p < 0.05$, **: $p < 0.01$, Student's t-test.

Table 2
Simple regression analyses of the factors associated with cardiac diastolic and systolic functions.

	E/A	A	E	DcT	e'	E/e'	LVEF
Age	−0.654 **	0.389 **	−0.181 **	0.328 **	−0.618 **	0.349 **	0.058
Male gender (yes = 1, no = 0)	−0.158 **	0.018	−0.176 **	0.100 *	−0.134 **	−0.025	−0.152 **
Current smoking (yes = 1, no = 0)	0.010	−0.035	−0.028	−0.033	0.027	−0.053	−0.131 **
Hypertension (yes = 1, no = 0)	−0.283 **	0.147 **	−0.009	0.157 **	−0.331**	0.275 **	0.028
Systolic blood pressure	−0.301**	0.135**	−0.034	0.168**	−0.357**	0.302**	0.024
Diastolic blood pressure	−0.204**	0.008	−0.068	0.099*	−0.227**	0.088*	−0.116
Pulse rate	−0.104	0.049	−0.044	−0.124**	−0.006	−0.027	−0.220**
Dyslipidemia (yes = 1, no = 0)	−0.234 **	0.024	−0.150 **	0.101 *	−0.190 **	0.048	−0.018
eGFR	0.274 **	−0.314 **	0.039	−0.189 **	0.318 **	−0.246 **	0.015
Body mass index	−0.119 **	0.022	−0.009	−0.017	−0.152 **	0.136 **	−0.099 *
Visceral adiposity (yes = 1, no = 0)	−0.232**	0.224	−0.099*	0.061	−0.275**	0.193**	−0.148**
HbA1c	−0.204**	0.149**	−0.086*	0.105*	−0.265**	0.159**	−0.038
HOMA-IR	−0.050	0.111*	0.096*	−0.064	−0.051	0.093*	0.010

Pearson's correlation coefficients are shown. eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment-insulin resistance. *p < 0.05, **p < 0.01.

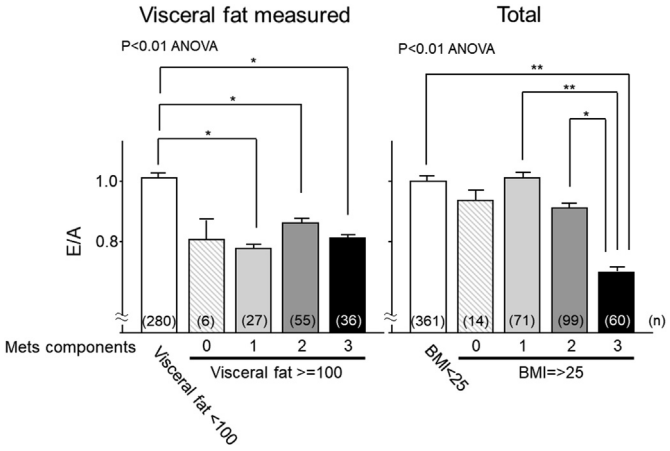

Fig. 3. Effects of components of metabolic syndrome (Mets) on a parameter of cardiac diastolic function, E/A. Cardiac diastolic function (E/A) was determined by cardiac ultrasonography. Each column represents mean ± standard error. *: p < 0.05, **; p < 0.01, Turkey-Kramer test with ANOVA <0.05. Mets components include 1) raised blood pressure (≥130/85 or treatment/previous diagnosis of hypertension), 2) raised fasting glucose (>5.6 mmol/L or previously diagnosed type 2 diabetes), 3) dyslipidemia (HDL-cholesterol <1.03 mmol/L or triglyceride => 1.7 mmol/L). (A): Analyses in subjects with their visceral fat area were measured (n = 404). Subjects with visceral fat area => 100 cm^2 were categorized with numbers of Mets components. (B) Analyses in total subjects (n = 605). Subjects with BMI => 25 kg/m_2 were categorized with numbers of Mets components.

and visceral adiposity. As shown in Fig. 4 and Table 3, SDNN, LF, and HF were significantly and positively associated with E/A, E wave velocity, and e', and inversely with A wave velocity, DcT, and E/e', suggesting a relationship of better autonomic function with better LV diastolic function. LF/HF showed significant though weak associations only with A wave velocity. None of the autonomic parameters were significantly associated with LVEF.

To further examine whether autonomic nervous function is involved in altered LV diastolic function in association with different glycemic abnormalities and adiposity, multiple linear regression analyses were performed (Tables 4 and 5). We used E/A as a representative parameter of cardiac diastolic function, since its decrease may indicate early impairment of cardiac diastolic function [27]. In all models examined, age, hypertension and dyslipidemia were significantly and inversely associated with E/A, with the association independent of other clinical factors. When stages of glycemic abnormalities (NGT, IGT, diabetes) instead of HbA1c were used as covariates in multiple linear regression analyses (Table 5), diabetes was significantly and inversely associated with E/A, independent of other clinical parameters. When HbA1c instead of glycemic stages was used as a covariate (Model 1, Table 4), HbA1c was not independently associated with E/A, even though it was significantly and inversely associated with E/A in simple regression analysis (r = −0.204). In this model, BMI (Model 1), but not visceral adiposity (Model 4), remained significantly associated with E/A, even though visceral adiposity showed stronger association with E/A than BMI in simple regression analyses. Of interest, although HOMA-IR was not significantly associated with E/A in simple regression analysis, it turned out to be significantly and inversely associated with E/A after adjustment for other clinical factors (Model 7). In any models including BMI, visceral adiposity or HOMA-IR besides other clinical factors, both SDNN (Models 2, 5, 8) and HF (Models 3, 6, 9) were significantly and positively associated with E/A (Table 4). Significant association of SDNN or HF with E/A was independent of the presence of IGT or diabetes (Table 5). These results suggest that autonomic nervous function or parasympathetic nervous activity is positively associated with a cardiac diastolic function in pre-heart failure subjects, with the association independent of age, obesity, glycemic parameters and stages, and insulin resistance, all of which are well known risk factors of HFpEF.

4. Discussion

This is the first known study to examine involvement of autonomic nervous function in cardiac diastolic function in patients with metabolic disorders without heart failure. The strength of the study includes, 1) potential risk factors for HFpEF such as glycemic abnormalities, whole and visceral adiposity, and insulin resistance were thoroughly examined, 2) patients with asymptomatic heart failure were carefully excluded based on cardiac ultrasonography findings and plasma BNP level, and 3) large numbers of subjects were recruited to carefully analyze their mutual associations. We found that decreased autonomic nervous activity, and low parasympathetic activity were significantly associated with decreased LV diastolic functions, with their associations independent of glycemic abnormalities, adiposity and insulin resistance.

4.1. Stages of glycemic abnormalities, adiposity and cardiac diastolic functions

The risk of HFpEF increases sharply with age, while diabetes, hypertension, and obesity are also well recognized risk factors [5,28–30]. LV diastolic dysfunction is an important cause of HFpEF in individuals with diabetes [31], and epidemiologic studies have shown the potential presence of diastolic dysfunction in type 2 diabetes patients [32–34]. In the present cohort, patients with IGT already exhibited significantly lower E/A as compared to those with

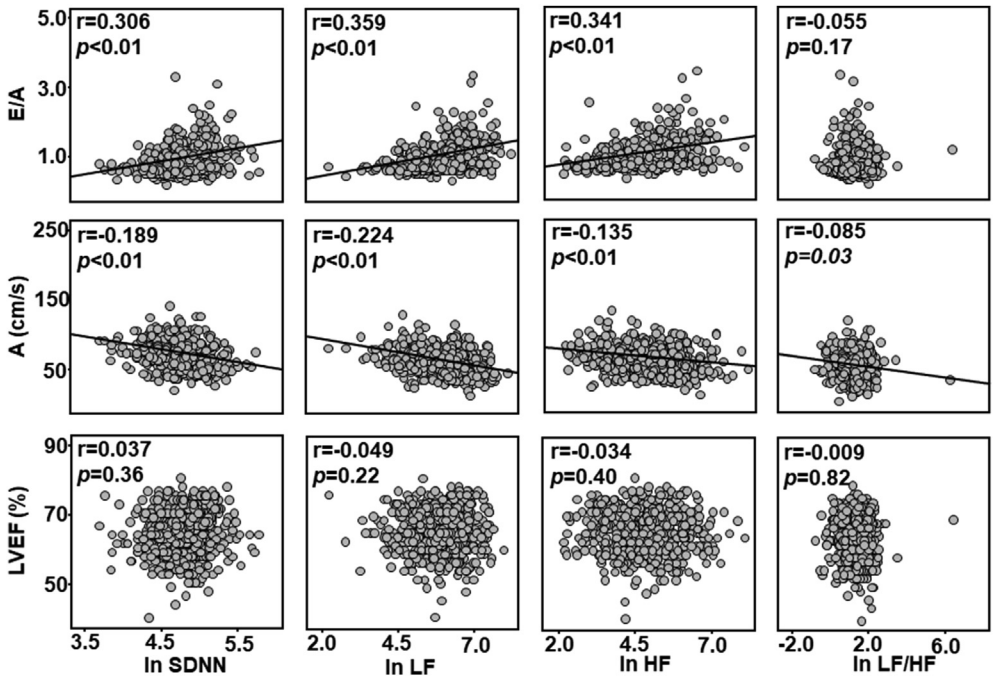

Fig. 4. Associations between cardiac functions and HRV parameters. E/A and A wave velocity (A) represent cardiac diastolic function, while left ventricular ejection fraction (EF) represents systolic function. Pearson's correlation coefficients (r) are shown.

Table 3
Simple regression analyses between HRV parameters and cardiac diastolic and systolic functions.

	E/A	A	E	DcT	e'	E/e'	LVEF
ln SDNN	0.306 **	−0.189 **	0.086 *	−0.123 **	0.215 **	−0.092 *	0.037
ln LF	0.359 **	−0.224 **	0.090 *	−0.123 **	0.348 **	−0.205 **	−0.049
ln HF	0.341 **	−0.135 **	0.102 *	−0.115 **	−0.294 **	−0.104 *	−0.034
ln LF/HF	−0.055	−0.085 *	−0.039	0.008	−0.030	−0.073	−0.009

Pearson's correlation coefficients are shown. SDNN, standard deviation of NN(RR) interval; LF, low frequency power; HF, high frequency power. *p < 0.05, **p < 0.01.

Table 4
Simple and multiple linear regression analyses of the factors associated with E/A.

	r	β								
		Model 1 (n = 605)	2 (n = 605)	3 (n = 605)	4 (n = 404)	5 (n = 404)	6 (n = 404)	7 (n = 568)	8 (n = 568)	9 (n = 568)
Age	−0.654 **	−0.663 **	−0.624 **	−0.619 **	−0.612 **	−0.554 **	−0.569 **	−0.659 **	−0.619 **	−0.613 **
Male gender (yes = 1, no = 0)	−0.158 **	−0.091 **	−0.100 **	−0.076 *	−0.060	−0.062	−0.041	−0.103 **	−0.109 **	−0.087 *
Current smoking (yes = 1, no = 0)	0.010	0.002	0.006	0.004	0.015	−0.006	−0.013	0.001	−0.006	−0.004
Hypertension (yes = 1, no = 0)	−0.283 **	−0.078 *	−0.082 *	−0.082 *	−0.103 *	−0.102 *	−0.104 *	−0.107 **	−0.107 **	−0.110 **
Dyslipidemia (yes = 1, no = 0)	−0.234 **	−0.082 *	−0.082 *	−0.091 **	−0.111 **	−0.101 *	−0.119 **	−0.094 **	−0.094 **	−0.102 **
eGFR	0.274 **	−0.053	−0.042	−0.055	−0.049	−0.025	−0.048	−0.067	−0.056	−0.068
HbA1c	−0.204 **	−0.014	−0.014	−0.005	−0.048	−0.046	−0.037	−0.013	−0.012	−0.008
Body mass index	−0.119 **	−0.162 **	−0.141 **	−0.156 **	–	–	–	–	–	–
Visceral fat area (<100 =0, ≥100 = 1)	−0.232 **	–	–	–	−0.081	−0.076	−0.078	–	–	–
HOMA-IR	−0.050	–	–	–	–	–		−0.098 **	−0.073 *	−0.090 **
ln SDNN	0.306 **	–	0.129 **	–	–	0.176 **		–	0.124 **	–
ln HF	0.341 **	–	–	0.131 **	–	–	0.121 **		–	0.122 **
R^2	–	0.502 **	0.517 **	0.516 **	0.469 **	0.496 **	0.480 **	0.495 **	0.508 **	0.506 **

Simple and multiple linear regression analyses were performed. NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SDNN, standard deviation of NN(RR) interval; HF, high frequency power. SDNN and HF were natural logarithm-transformed to achieve a normal distribution. *p < 0.05, **p < 0.01. r: Pearson's correlation coefficients, β: standard regression coefficients. -; variable not included.

NGT, with the level between that of NGT and diabetes. Besides E/A, diabetic subjects exhibited significantly lower DcT, e', and higher E/e' as compared with NGT or IGT, obviously showing a phenotype of decreased cardiac diastolic functions. Regarding underlying biochemical factors attributable to decreased cardiac diastolic functions in IGT or diabetes, hyperglycemia is a potential candidate, since previous study showed that E/A was inversely associated with HbA1c even in a population with NGT [15]. In the present study, although HbA1c was inversely and significantly associated with E/A, its significant association was lost after adjustment for other clinical factors. Of interest, even though HOMA-IR, an insulin resistance index, was not significantly associated with E/A in simple

Table 5
Simple and multiple linear regression analyses of the associations of stages of glycemic abnormalities and autonomic nervous function with E/A.

	r (n = 605)	β						
		Model 1 (n = 605)	2 (n = 290)	3 (n = 290)	4 (n = 290)	5 (n = 358)	6 (n = 358)	7 (n = 358)
Age	−0.654**	−0.666**	−0.776**	−0.731**	−0.703**	−0.570**	−0.541**	−0.545**
Male gender (yes = 1, no = 0)	−0.158**	−0.093**	−0.076	−0.091*	−0.057	−0.032	−0.036	−0.020
Current smoking (yes = 1, no = 0)	0.010	−0.002	0.013	0.023	0.010	0.021	0.028	0.029
Hypertension (yes = 1, no = 0)	−0.283**	−0.077*	−0.059	−0.072	−0.076	−0.076	−0.079	−0.076
Dyslipidemia (yes = 1, no = 0)	−0.234**	−0.086*	−0.048	−0.045	−0.044	−0.075	−0.071	−0.078
eGFR	0.274**	−0.053	−0.083	−0.075	−0.084	0.040	0.054	0.039
Body mass index	−0.119**	−0.165**	−0.134**	−0.115*	−0.133**	−0.158**	−0.139**	−0.150**
IGT (NGT = 0, IGT = 1)	−0.132*	–	−0.092*	−0.086*	−0.091*	–	–	–
Diabetes (NGT = 0, diabetes = 1)	−0.356**	–	–	–	–	−0.129**	−0.128**	−0.128**
ln SDNN	0.306**	–	–	0.133**	–	–	0.113**	–
ln HF	0.341**	–	–	–	0.162**	–	–	0.102*
R^2	–	0.573**	0.503**	0.587**	0.592**	0.469**	0.480**	0.477**

Simple and multiple linear regression analyses were performed. NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; GFR, estimated glomerular filtration rate; SDNN, standard deviation of NN(RR) interval; HF, high frequency power. SDNN and HF were natural logarithm-transformed to achieve a normal distribution.
*p < 0.05, **p < 0.01. r: Pearson's correlation coefficients, β: standard regression coefficients. -; variable not included.

regression analysis, it was significantly and inversely associated with E/A after adjustment for other clinical factors, suggesting that insulin resistance may be a potential predictor of preclinical cardiac diastolic dysfunction. Limited numbers of population based studies suggest insulin resistance may enhance the impact of hypertension on preclinical cardiac diastolic dysfunction [35,36]. Our results clearly show importance of insulin resistance in the pathogenesis of LV diastolic dysfunction in patients with glycemic abnormalities.

Adiposity is also associated with increasing LV stiffness, thus can be attributed to diastolic dysfunction in patients with HFpEF [5]. However, information regarding the relationship of cardiac diastolic functions with obesity in individuals without heart failure is limited [16,17]. In the present study, simple regression analyses showed that BMI and visceral adiposity were each significantly associated with many of the examined parameters of LV diastolic functions.

Even though glycemic stages and adiposity were closely related (Table 1), the association of BMI with cardiac diastolic functions was independent of the presence of IGT or diabetes (Table 5). However, rather surprisingly, even though visceral adiposity (r = −0.232) was more strongly associated with a cardiac diastolic function (E/A) than BMI (r = −0.119) in simple regression analysis, its significant association was profoundly confounded by other risk factors, including hypertension, dyslipidemia, HbA1c, and HOMA-IR. As generally recognized, visceral adiposity is more closely associated with glycemic abnormalities, insulin resistance and other atherogenic risk factors than whole obesity, resulting in its blunted association with cardiac diastolic functions in multiple regression analyses. Indeed, association of visceral adiposity with reduced cardiac diastolic function was not affected by the components of metabolic syndrome including raised blood pressure, raised fasting glucose, and dyslipidemia (low HDL-cholesterol or high triglyceride) (Fig. 3A), suggesting strong interaction between visceral adiposity and metabolic syndrome. Whereas in the subjects with higher BMI, only those with 3 components of metabolic syndrome exhibited lower cardiac diastolic function.

4.2. Autonomic nervous function and LV diastolic dysfunction

Heart failure due to LV systolic dysfunction is considered to be a state of timely and target organ-specific sympathetic activation [37]. HFpEF is also characterized by decreased parasympathetic activity, as well as decreased heart rate variability [6], which appear to be related to the progression of heart failure [7]. Patients with HFpEF are known to be extremely sensitive to volume overload, while failure of autonomic nervous function, such as arterial baroreflex, appears to be responsible for stressed blood volume [38]. Moreover, decreased baroreflex sensitivity is linked to sympathovagal imbalance, body fat mass and altered cardiometabolic profile in pre-obesity and obesity [39]. However, understanding of the relationships between LV diastolic function and HRV parameters in patients without heart failure is quite vague. In small numbers of type 1 diabetic subjects (n = 20), decreased parasympathetic function was closely associated with diastolic deficits [40]. The present study is the first to examine those relationships in sufficient numbers of patients with various metabolic abnormalities without heart failure.

In the present cohort, SDNN, a parameter of time-domain HRV, was found to be positively associated with E/A, with the association independent of the other examined atherosclerotic risk factors including glycemic abnormalities, insulin resistance or adiposity. Among the frequency domains of HRV, HF was also strongly associated with E/A, independent of the other risk factors. HF mainly represents parasympathetic activity [24], thus our results suggest that reduced cardiac parasympathetic activity may be associated with a lower level of LV diastolic functions. This speculation is in good agreement with the concept stating that decreased total autonomic and parasympathetic activities contribute to the pathogenesis of HFpEF [6]. Our findings also suggest that close relationships between glycemic abnormalities and LV diastolic functions are not completely explained by altered autonomic functions, since both factors were independently associated with LV diastolic functions. There should exist other diabetes-related unveiled factors in the pathophysiology of LV diastolic dysfunction, which is an intriguing question to be addressed in a future.

A recent review that focused on echocardiographic assessment of LV diastolic dysfunction showed that changes in function of the left atria to moderate LV filling may become evident during the earliest stages of LV diastolic dysfunction [27], while changes in e' and E/e' appear to occur in a rather late phase. In the present study, significant and independent associations of cardiac autonomic function were observed only with E/A and A wave velocity, but not with DcT, e', or E/e'. These results suggest that early changes in atrial structure and functions may be under the control of cardiac autonomic nervous function. Although the pathophysiological role of the autonomic nervous system on atrial structure has yet to be revealed, its role in the pathogeneses of atrial fibrillation and supraventricular tachycardia is well recognized [41,42]. Taken together, reduced autonomic nervous activity and impaired parasympathetic activation in metabolic abnormalities may potentially

predict an early decrease in LV diastolic function in patients with metabolic disorders who are in a pre-heart failure phase.

4.3. Limitations

This study has several limitations, with the most important the cross-sectional design, which negates the ability to demonstrate causal relationships, a major shortcoming of this trial. We also decided not to analyze the data in subgroups of different glycemic abnormalities (NGT, IGT, diabetes), to avoid reduction of statistical power and type I or II error. Nevertheless, our results provide important initial findings to unveil the pathophysiological significance of autonomic dysfunction in patients with metabolic abnormalities with an HFpEF etiology. Ongoing follow-up examinations of the cardiac ultrasound findings will potentially reveal underlying mechanisms or potential therapeutic targets of HFpEF etiology in patients with diabetes or glucose intolerance.

5. Conclusions

In pre-heart failure patients with metabolic diseases, reduced total and parasympathetic autonomic nervous activity are associated with a reduction in parameters related to cardiac diastolic functions, with the association independent of stages of glucose intolerance, insulin resistance, and whole or visceral adiposity.

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Ethics

This study was approved by an appropriate institutional ethical committee (approval No. 2351) and informed written consent was obtained from each participant.

Declaration of competing interest

None of the authors have conflicts of interest to declare.

CRediT authorship contribution statement

Akiko Morimoto: Data curation, Writing - original draft. **Manabu Kadoya:** Conceptualization, Methodology, Software, Validation. **Miki Kakutani-Hatayama:** Data curation. **Kae Kosaka-Hamamoto:** Data curation. **Akio Miyoshi:** Visualization, Investigation. **Takuhito Shoji:** Visualization, Investigation. **Akiko Goda:** Visualization, Investigation. **Masanori Asakura:** Supervision. **Hidenori Koyama:** Conceptualization, Methodology, Software, Writing - original draft, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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