Non-alcoholic fatty liver disease, diastolic dysfunction, and impaired myocardial glucose uptake in patients with type 2 diabetes

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Abstract

Background

Non-alcoholic fatty liver disease (NAFLD) is highly prevalent in patients with type 2 diabetes and is associated with cardiovascular risk. We investigated whether the degree of NAFLD was associated with myocardial dysfunction related to impaired myocardial glucose uptake in patients with type 2 diabetes.

Methods

In total, 131 patients with type 2 diabetes from a tertiary care hospital were included. Myocardial glucose uptake was assessed using [^{18}F]-fluorodeoxyglucose-positron emission tomography. Hepatic steatosis and fibrosis were determined using transient liver elastography. Echocardiography was performed to evaluate cardiac structure and function.

Results

Patients with NAFLD revealed cardiac diastolic dysfunction with higher left ventricular filling pressure (E/e' ratio) and left atrial volume index (LAVI) than patients without NAFLD (all $p < 0.05$). Hepatic steatosis correlated with E/e' ratio and LAVI, and hepatic fibrosis also correlated with E/e' ratio (all $p < 0.05$). In linear regression analyses, a higher degree of hepatic steatosis ($r^2 = 0.409$; $p = 0.041$) and a higher degree of fibrosis ($r^2 = 0.423$; $p = 0.009$) were independent determinants for a higher E/e' ratio even after adjusting for confounding factors. Decreased myocardial glucose uptake was associated with a higher degree of steatosis (p for trend = 0.084) and fibrosis (p for trend = 0.012). In addition, decreased myocardial glucose uptake was an independent determinant factor for a higher E/e' ratio ($r^2 = 0.409$; $p = 0.04$).

Conclusions

Hepatic steatosis and fibrosis are significantly associated with diastolic heart dysfunction in patients with type 2 diabetes coupled with impaired myocardial glucose uptake.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the most prevailing cause of chronic liver disease worldwide, with a global prevalence of 25.2%.[1] NAFLD is a disease characterized by hepatic steatosis, assessed either by imaging or histology, and a lack of secondary causes of hepatic fat accumulation.[2] Type 2 diabetes is an important risk factor for NAFLD.[1] The overall prevalence of NAFLD in patients with type 2 diabetes is 55.5%, more than two times higher than that in the general population.[1] The

association between NAFLD and the risk of cardiovascular mortality is supported by sufficien evidence,[3, 4] and NAFLD was associated with a two-fold increased incidence of cardiovascular events in patients with type 2 diabetes.[5] In addion to the overt cardiovascular events, NAFLD is associated with subclinical myocardial remodeling and dysfunction.[6, 7] Increased left ventricular (LV) volume and diastolic dysfunction have been reported as echocardiographic characteristics related to NAFLD,[6–9] and altered myocardial insulin resistance has been suggested as a potential mechanism linking NAFLD and cardiac abnormalities.[6, 10]

The myocardium has a flexible metabolic network involving diverse energy substrates such as free fatty acids, glucose, and lactate.[11] In response to increased energy demands, the heart shifts from using fatty acids as the energetic substrate to glucose, and insulin enhances myocardial glucose uptake and metabolism.[11] Myocardial insulin resistance is characterized by the reduced availability of glucose transporters and consequently, decreased glucose uptake.[10, 12] This cardiac metabolic switch from glucose metabolism to fatty acid oxidation impairs cardiac efficiency, resulting in heart failure.[13] To evaluate the alterations in myocardial energy substrate uptake, [^{18}F]-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) is effectively used as a noninvasive method.[14]

However, study including subjects confined with patients with type 2 diabetes that simultaneously evaluated the patients' degree of NAFLD, cardiac structure and function, and myocardial glucose uptake has not yet been conducted. Thus, the mechanistic linkage between NAFLD and myocardial dysfunction related to myocardial insulin resistance in those with type 2 diabetes has not been fully evaluated.

This study investigated whether the degree of hepatic steatosis and fibrosis was independently associated with myocardial dysfunction related to impaired myocardial glucose uptake in patients with type 2 diabetes using liver FibroScan, echocardiography, and ^{18}FDG-PET.

Methods

Study design and subjects

This study included 171 asymptomatic patients with type 2 diabetes who visited the health promotion center in Severance Hospital, a university-affiliated tertiary care hospital from March 2010 to November 2018. Subjects with type 2 diabetes met at least one of the following criteria: (i) fasting glucose level ≥ 126 mg/dL, (ii) postprandial glucose level ≥ 200 mg/dL, (iii) hemoglobin A1c (HbA1c) level ≥ 6.5%, (iv) previous diagnosis by a clinical physician, or (v) use of any antidiabetic medication. Among the 171 patients, we excluded individuals with the following characteristics: (i) a history of heavy alcohol consumption (n = 14), (ii) a history of cardiovascular diseases including coronary artery disease and heart failure (n = 24), or (iii) a history of viral hepatitis B or C (n = 5). Finally, a total of 131 subjects were included. This study was approved by the independent institutional review board of Severance Hospital, Seoul, Korea (4-2017-1082); the requirement of informed consent and was waived. This study adhered to the tenets of the Declaration of Helsinki.

Measurement of clinical and biochemical parameters

Patients' data included data on previous medical history, lifestyle habits including alcohol consumption and smoking status, and use of medications at the time of enrolment. After overnight fasting, blood samples were collected to measure glucometabolic parameters. Blood samples for the measurement of postprandial glucose level were collected 2 h after a normal meal. Measurements of body mass index (BMI), blood pressure, and biochemical parameters, such as glucometabolic and hepatic parameters, were performed as previously described.[15] The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Echocardiography

Comprehensive echocardiography, including M-mode, pulsed Doppler, and tissue Doppler imaging, was performed by experienced sonographers according to the recommendation by the American Society of Echocardiography using a Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway) with a 2.5-Hz probe.[16] Quality control and image analysis were performed in the Severance Cardiovascular Center as previously described.[17] According to the method of Devereux et al.,[18] LV mass was assessed, and left atrial (LA) volume was measured from the parasternal long-axis view and apical four-chamber view using the prolate ellipse method. LV mass index and LA volume index were determined by dividing the LV mass and LA volume, respectively, by body surface area.[19] Mitral valve inflow was estimated by Doppler echocardiography from the apical four chamber view. The Doppler beam was arranged in parallel to the direction of flow with a 1–2-mm sample volume placed between the tips of the mitral leaflets during diastole. Mitral inflow profiles were applied to measure the peak velocities at the early (E) and late (A) diastole and the deceleration time. Septal tissue Doppler imaging was performed using the apical four-chamber view, and the average of the two values was used to evaluate the early (E') and late (A') diastolic peak velocities. LV filling pressure was determined based on the early trans mitral velocity ratio E/e',[19, 20] and E/e' ratio was categorized as low and high according to the median value of E/e' in the analyses. Measurements were acquired in end-systole from the frame preceding the mitral valve opening.

Evaluation of hepatic steatosis and fibrosis using transient liver elastography

Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were evaluated using transient elastography (TE) as described previously.[21, 22] TE was performed by an experienced technician (>10,000 examinations) in a clinical data-blinded manner. Results are presented as dB/m for CAP and kilopascals (kPa) for LSM. The degree of hepatic steatosis was estimated using CAP values. For the CAP measurement, a FibroScan 501® (Echosens, Paris, France) was used, and the tip of the M probe was placed on the skin between the ribs, over the right lobe of the liver. To estimate variability, we calculated the ratio of the interquartile range (IQR) of LSM to the median. To ascertain the accuracy of the CAP value, we assessed ultrasound attenuation only when the matched LSM was valid, and we attempted to collect ≥10 valid LSMs. The results were considered reliable when the success rate was ≥

60% and the ratio of IQR to median LSM was ≤ 30%. The CAP value was considered to be valid only when the LSM was reliable for the same signal, at the same volume of the liver parenchyma.

[^{18}F]-fluorodeoxyglucose-positron emission tomography and image analysis

Imaging protocols of ^{18}FDG-PET were described in detail previously.[15] Whole-body PET-computed tomography (CT) was performed using either one of the two combination PET-CT scanners: a Biograph TruePoint 40 (Siemens Medical Solutions, Hoffman Estates, IL, USA) or a Discovery 600 (General Electric Medical Systems, Milwaukee, WI, USA). After the subjects had fasted for at least 8 h, blood glucose levels were measured before administering ^{18}FDG intravenously (approximately 5.5 Bq of ^{18}FDG per kilogram of body weight). At 60 min after the injection, PET-CT was performed from the skull base to the mid-thigh. Following CT, PET was performed as follows: 2.5 min per bed position of 21.6 m in a three dimensional acquisition mode (Biograph TruePoint 40) or 2 min per bed position of 15.7 m in a three-dimensional acquisition mode (Discovery 600). The CT images were rebuilt using a 512 × 512 matrix and were converted into 511 eV equivalent attenuation factors for attenuation correction. Reconstructed PET images were obtained using a 128 × 128 matrix with ordered subset expectation maximization and correction for attenuation.

Experts in nuclear medicine calculated the standardized uptake value (SUV) as follows: SUV = (decay-corrected activity [kBq] per ml of tissue volume)/(injected ^{18}FDG activity [kBq]/body mass [g]) in a clinical data-blinded manner. Measurements of SUV_{max} of the myocardium and the SUV_{mean} of the liver were drawn from multiple regions of interest (ROIs) for a semi-quantitative analysis. Two-dimensional ROIs were drawn through the transaxial images to calculate the SUV_{max} of the LV myocardium within an inner edge. We measured the SUV of the liver from the circular ROI along the periphery of the right lobe, 1 m from the margin. In FDG-PET for detecting malignancies, the liver has been considered as an internal standard to grade the FDG uptake of whole-body lesions, as the SUV of the liver remains stable over time when measuring a mean uptake in the right lobe, even in patients with diffuse fatty liver disease.[23, 24] To minimize variability, the heart SUV to the liver FDG uptake ratio (SUV heart/SUV liver) was used to evaluate myocardial glucose uptake.[24, 25] The low myocardial glucose uptake group comprised the subjects in the lowest quartile of myocardial glucose uptake.

Statistical analyses

Data are presented as means with standard deviations for normally distributed continuous variables, medians with IQRs for non-normally distributed continuous variables, and as numbers with percentages for categorical variables. The Student's t-test and Mann Whitney U test were used for comparisons of normally and non-normally distributed continuous variables, respectively. Comparisons of categorical variables were conducted using the χ^2 test or Fisher's exact test. Pearson's correlation was performed; Pearson's correlation coefficients (*r*) were presented to evaluate the correlations between parameters. Multivariate linear regression models were used to determine the independent determinant factors for a higher E/e' ratio. *P*-values < 0.05 were considered statistically significant. All statistical analyses were

performed using the Statistical Package for the Social Sciences software version 23.0 for Windows (International Business Machines Corp., Armonk, NY, USA).

Results

Baseline and echocardiographic characteristics according to the presence of non-alcoholic fatty liver disease (NAFLD)

In total, 131 patients with type 2 diabetes (83 patients in the NAFLD group and 48 patients in the no-NAFLD group) were included. Clinical characteristics of the study subjects are listed in Table 1. The mean age of overall study subjects was 60.8 years. Of the total subjects, 77 (55.7%) were male and the sex ratio was not different according to the presence of NAFLD. Patients in the NAFLD group had a significantly higher BMI, waist circumference, and hip circumference (all $p < 0.001$) and were more likely to have hypertension ($p = 0.010$) than patients in the no-NAFLD group. Patients in the NAFLD group had significantly higher fasting glucose and homeostatic model assessment (HOMA) of insulin resistance levels than patients in the no-NAFLD group (all $p < 0.001$). HbA1c and HOMA of β-cell function levels were similar between the two groups. Serum fasting and postprandial triglyceride levels were higher and serum high-density lipoprotein cholesterol and lipoprotein (a) levels were lower in the NAFLD group than in the no-NAFLD group. Serum liver enzymes and gamma-glutamyl transferase levels were markedly elevated in the NAFLD group. Insulin use was more prevalent in the NAFLD group ($p = 0.025$) than in the no-NAFLD group, whereas the use of other antidiabetic medications was not different between the two groups. The degree of hepatic steatosis (CAP) and liver stiffness measured by FibroScan were significantly associated with BMI, fasting glucose, and serum liver enzyme levels (Supplemental Table S1).

Table 1
Baseline clinical characteristics of patients with type 2 diabetes according to NAFLD status

	Total	NAFLD group	No NAFLD group	*P*-value
	(N = 131)	(N = 83)	(N = 48)	
Age (years)	60.8 ± 9.6	60.7 ± 8.9	60.8 ± 10.8	0.944
Male (n,%)	73 (55.7)	50 (60.2)	23 (47.9)	0.171
Ever smoker (n, %)	43 (32.8)	26 (31.3)	17 (35.4)	0.631
BMI	24.5 ± 3.1	25.2 (23.6–27.4)	22.9 (21.4–24.0)	**< 0.001**
Waist circumference (cm)	83.7 ± 8.1	86.4 ± 8.2	79.7 ± 6.0	**< 0.001**
Hip circumference (cm)	94.0 ± 5.4	95.7 ± 5.3	91.5 ± 4.5	**< 0.001**
SBP (mmgHg)	125 ± 15	130 (116–137)	122 (110–130)	**0.010**
DBP (mmHg)	80 (70–86)	80 (70–88)	76 (68–82.8)	**0.025**
Comorbidities				
Hypertension (n, (%))	84 (64.1)	60 (72.3)	24 (50.0)	**0.010**
Dyslipidemia (n, (%))	84 (64.1)	58 (69.9)	26 (54.2)	0.071
HbA1c (%)	6.3 (5.9–6.9)	6.4 (6.0–6.9)	6.1 (5.9–6.7)	0.182
Fasting glucose (mg/dL)	105 (94–123)	112 (101–128)	97 (86–113)	**< 0.001**
Postprandial 90 min glucose (mg/dL)	163 (119–221)	153 (123–213)	190 (113–230)	0.668
Fasting c-peptide (ng/mL)	2.1 (1.6–2.9)	2.6 (1.8–3.1)	1.8 (1.5–2.1)	**< 0.001**
Postprandial 90 min c-peptide (ng/mL)	6.6 (3.8–10.2)	6.7 (3.9–9.6)	6.4 (3.5–11.4)	0.916

Data are described as mean with standard deviation (SD), median with interquartile range (IQR), or as numbers (%).Statistically significant values are indicated in **Bold** ($p < 0.05$).

ACEi, Angiotensin-converting-enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin II receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure, DPP-4i, dipeptidyl peptidase-4 inhibitors; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-β, homeostatic model assessment for β-cell function; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TZD, thiazolidinediones

	Total	NAFLD group	No NAFLD group	*P*-value
	(N = 131)	(N = 83)	(N = 48)	
Fasting insulin(μIU/mL)	6.6 (4.3–10.7)	8.7 (5.0–13.4)	4.7 (3.1–6.6)	**< 0.001**
Postprandial 90 min insulin (μIU/mL)	36.2 (14.9–64.0)	37.5 (15.3–67.4)	26.3 (13.6–60.1)	0.264
HOMA-IR (mg/dL*μIU/mL)	1.9 (1.1–3.4)	2.6 (1.4–4.1)	1.2 (0.8–1.9)	**< 0.001**
HOMA-β (%)	61.2 (31.0–83.6)	62.3 (32.5–82.1)	51.5 (28.0–84.4)	0.376
Fasting triglyceride (mg/dL)	114 (80–155)	132 (84–178)	102 (74–121)	**0.003**
Postprandial triglyceride (mg/dL)	108 (74–163)	147 (93–196)	100 (71–114)	**0.016**
Fasting FFA (μEq/L)	619 (460–805)	637 (549–837)	541 (387–776)	**0.050**
Postprandial FFA (μEq/L)	145 (81–289)	165 (109–370)	127 (64–188)	0.118
HDL-C (mg/dL)	46 (38–56)	44 (37–53)	49 (42–60)	**0.022**
LDL-C (mg/dL)	106.4 ± 31.6	105.6 ± 31.2	107.9 ± 32.6	0.693
Lipoprotein (a) (mg/dL)	13.6 (6.8–28.6)	11.7 (6.4–24.8)	16.7 (8.8–47.6)	**0.025**
eGFR (CKD-EPI)	93.0 (83.0–99.9)	94.1 (85.8–100.0)	90.0 (72.3–99.0)	0.139
AST (IU/L)	21 (18–27)	23 (19–28)	20 (17–23)	**0.007**
ALT (IU/L)	20 (15–30)	23 (17–33)	18 (15–22)	**0.004**
GGT (IU/L)	29 (19–41)	32 (20–42)	22 (14–32)	**0.002**
CAP, dB/m	260.8 ± 53.5	288.0 (257.8–320.5)	212.5 (189.0–224.0)	**< 0.001**
Liver stiffness, kPa	4.4 (3.7–5.3)	4.5 (3.8–5.4)	4.3 (3.6–5.0)	0.109

Data are described as mean with standard deviation (SD), median with interquartile range (IQR), or as numbers (%).Statistically significant values are indicated in **Bold** ($p < 0.05$).

ACEi, Angiotensin-converting-enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin II receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure, DPP-4i, dipeptidyl peptidase-4 inhibitors; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-β, homeostatic model assessment for β-cell function; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TZD, thiazolidinediones

	Total	NAFLD group	No NAFLD group	*P*-value
	(N = 131)	(N = 83)	(N = 48)	
Antidiabetic medication use (n, (%))	43 (32.8)	29 (34.9)	14 (29.2)	0.498
Insulin use (n, (%))	6 (4.6)	1 (1.2)	5 (10.4)	**0.025**
Biguanides use (n, (%))	35 (26.7)	26 (31.3)	9 (18.8)	0.117
Sulfonylureas use (n, (%))	16 (12.2)	11 (13.3)	5 (10.4)	0.633
TZD use (n, (%))	5 (3.8)	4 (4.8)	1 (2.1)	0.652
DPP-4i use (n, (%))	17 (13.0)	14 (16.9)	3 (6.3)	0.081
ARB use (n, (%))	48 (36.6)	35 (42.2)	13 (27.1)	0.084
ACEi use (n, (%))	3 (2.3)	2 (2.4)	1 (2.1)	> 0.999
Statin use (n, (%))	50 (38.2)	34 (41.0)	16 (33.3)	0.386

Data are described as mean with standard deviation (SD), median with interquartile range (IQR), or as numbers (%).Statistically significant values are indicated in **Bold** ($p < 0.05$).

ACEi, Angiotensin-converting-enzyme inhibitors; ALT, alanine aminotransferase; ARB, angiotensin II receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure, DPP-4i, dipeptidyl peptidase-4 inhibitors; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-β, homeostatic model assessment for β-cell function; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; TZD, thiazolidinediones

Patients with NAFLD exhibited myocardial remodeling and dysfunction (Table 2). LV mass, LV end-systolic and end-diastolic diameters (mm), and LA volume and LA volume index were significantly increased in the NAFLD group compared with the no-NAFLD group (all $p < 0.05$). Furthermore, patients in the NAFLD group revealed worse echocardiographic parameters associated with myocardial diastolic dysfunction. Septal tissue Doppler e' velocity was significantly decreased and E/e' ratio was significantly increased in the patients with NAFLD (all $p < 0.05$, Fig. 1A).

Table 2
Echocardiographic characteristics of patients according to NAFLD status

	Total	NAFLD group	no NAFLD group	*P*-value
	(N = 131)	(N = 83)	(N = 48)	
Cardiac dimension				
LV mass (g)	158.2 (126.9–182.0)	165.9 ± 39.9	145.6 ± 36.7	**0.005**
LV mass index (g/m^2)	88.0 (75.0–101.2)	91.3 ± 18.4	86.9 ± 18.4	0.196
LV end-systolic diameter (mm)	31 (29–34)	32 (29–35)	30 (28–33)	**0.018**
LV end-diastolic diameter (mm)	48 (46–51)	50 (47–52)	47 (44–50)	**0.006**
Left atrial volume (ml)	38.1 (30.6–46.0)	41.5 ± 9.9	34.5 ± 9.0	**< 0.001**
Left atrial volume index (ml/m^2)	22.0 ± 4.6	22.8 ± 4.5	20.6 ± 4.6	**0.009**
LV systolic function				
LV ejection fraction (%)	68.2 ± 4.9	67.9 ± 4.9	68.6 ± 5.0	0.412
LV diastolic function				
E velocity (m/s)	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.958
A velocity (m/s)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.158
E/A ratio	0.82 (0.68–0.94)	0.81 (0.67–0.93)	0.82 (0.76–1.13)	0.304
Deceleration time (m/s)	211 (187–239)	200 (190–239)	211 (183–250)	0.612
Septal tissue Doppler E' velocity (cm/s)	6.0 (4.9–7.0)	5.3 (4.5–6.9)	6.0 (5.0–7.4)	**0.049**
Septal tissue Doppler S' velocity (cm/s)	7.0 (6.0–7.0)	7.0 (6.0–7.0)	7.0 (6.0–7.20)	0.818
Septal tissue Doppler A' velocity (cm/s)	8.5 (8.0–9.0)	9.0 (8.0–9.0)	8.0 (7.3–9.0)	0.063
E/e' ratio	9.8 (8.0–12.5)	10.6 (8.4–12.7)	9.0 (7.0–11.9)	**0.027**

Data are described as mean with standard deviation (SD), median with interquartile range (IQR), or as numbers (%).Statistically significant values are indicated in **Bold** ($p < 0.05$).

Association between the degree of hepatic steatosis and fibrosis degree and myocardial diastolic dysfunction and myocardial insulin resistance

Both hepatic steatosis and fibrosis were associated with myocardial diastolic dysfunction. The proportion of higher E/e' ratio (above the median) significantly increased with an increasing degree of hepatic steatosis based on CAP score categories (p for trend = 0.001, Fig. 1B). Subjects with fibrosis stage ≥ 2 had a significantly increased E/e' ratio ($p < 0.01$, Fig. 1C); the proportion of higher E/e' ratio also increased significantly with an increasing degree of hepatic fibrosis (p for trend = 0.006, Fig. 1D). Both hepatic steatosis (CAP score, dB/m) and fibrosis (stiffness, kPa) were positively correlated with E/e' ratio (Fig. 1E and 1F). Hepatic steatosis was additionally associated with LV mass, LA volume, LA volume index, and septal tissue Doppler e' velocity (all $p < 0.05$, Supplemental Table S2). Furthermore, even after adjustment for clinical confounding factors, hepatic steatosis and fibrosis were independent determinant factors for a higher E/e' ratio in multivariate linear regression analyses ($r^2 = 0.409$, $p = 0.041$ for steatosis and $r^2 = 0.423$, $p = 0.009$ for fibrosis, Table 3).

Table 3
Steatosis and fibrosis as determinant factors for a higher E/e' ratio in type 2 diabetes

	R^2 = 0.409			**R^2 = 0.423**		
	Regression coefficient	SE	*p*-values	Regression coefficient	SE	*p*-values
Age (years)	0.117	0.025	**< 0.001**	0.107	0.025	**< 0.001**
Sex (female vs. male)	0.990	0.482	**0.042**	0.938	0.473	0.050
sBP (mmHg)	0.062	0.017	**< 0.001**	0.057	0.017	**0.001**
BMI ≥ 30 (kg/m^2)	1.376	0.991	0.168	1.774	0.944	0.063
HbA1c	0.430	0.243	0.079	0.258	0.253	0.310
Insulin use	2.146	1.284	0.097	2.189	1.258	0.084
Steatosis (CAP, dB/m)	0.010	0.005	**0.041**	–	–	–
Fibrosis (Liver stiffness, kPa)	–	–	–	0.248	0.093	**0.009**

Multiple linear regression analysis was performed. Bold-italics represent statistically significant values ($p < 0.05$).

BMI, body mass index; CAP, controlled attenuation parameter; HbA1c, glycated hemoglobin; sBP, systolic blood pressure; SE, standard error.

Association between myocardial glucose uptake and NAFLD and myocardial diastolic function

Subjects with NAFLD demonstrated a significantly decreased myocardial glucose uptake (p = 0.018, Fig. 2A). The proportion of lower myocardial glucose uptake (above the median) tended to increase with an increasing degree of hepatic steatosis (*p* for trend = 0.084, Fig. 2B). In addition, myocardial glucose uptake was significantly decreased in subjects with fibrosis stage ≥ 3, and lower myocardial glucose uptake was more likely to be observed in those with advanced fibrosis stages (*p* for trend = 0.012, Fig. 2D).

Lower myocardial glucose uptake was also closely associated with myocardial diastolic dysfunction. Subjects with myocardial diastolic dysfunction presenting with a high E/e' ratio showed a marginal significant decrease in myocardial glucose uptake (*p* = 0.058, Fig. 2E and 2F). Myocardial glucose uptake decreased as E/e' increased (*r* = 0.185, *p* = 0.037, Fig. 2G). Decreased myocardial glucose uptake was still an independent determinant factor for a higher E/e' ratio in patients with type 2 diabetes after adjustment for potential confounding factors (r^2 = 0.409, *p* = 0.040, Table 4).

Table 4
Myocardial glucose uptake as a determinant factor for a higher E/e' ratio in type 2 diabetes

	R^2 = 0.409		
	Regression coefficient	SE	*p*-values
Age (years)	0.118	0.025	**< 0.001**
Sex (female vs. male)	1.070	0.481	**0.028**
sBP (mmHg)	0.065	0.017	**< 0.001**
BMI ≥ 30 (kg/m^2)	1.845	0.953	0.055
HbA1c	0.453	0.241	0.063
Insulin use	1.368	1.254	0.278
Decreased myocardial glucose uptake (Lowest quartile vs. others)	1.109	0.533	**0.040**
Multiple linear regression analysis was performed. Bold-italics represent statistically significant values (*p* < 0.05).			
BMI, body mass index; HbA1c, glycated hemoglobin; sBP, systolic blood pressure; SE, standard error.			

Discussion

The present study demonstrated that the presence of NAFLD was associated with cardiac remodeling and myocardial diastolic dysfunction, and the degrees of hepatic steatosis and fibrosis were determinant factors for diastolic dysfunction in patients with type 2 diabetes. In addtion, impaired myocardial glucose

uptake, examined using ^{18}FDG-PET, was observed in subjects with a higher degree of hepatic steatosis and fibrosis and in subjects with diastolic dysfunction. This indicated that myocardial insulin resistance, presenting as impaired myocardial glucose uptake, potentially mediates the pathophysiological association between NAFLD and diastolic dysfunction in those with type 2 diabetes (Fig. 3).

Diabetes mellitus involves cardiovascular complications such as coronary atherosclerosis, but it can also affect cardiac structure and function in the absence of coronary artery disease; this condition is called diabetic cardiomyopathy.[26] Diabetic cardiomyopathy has been defined as ventricular dysfunction that develops independent of coronary artery disease and hypertension.[26] Diabetic cardiomyopathy is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction.[27] The prevalence of diastolic dysfunction is up to 30% in patients with uncomplicated type 2 diabetes.[28, 29] Several mechanistic associations have been suggested, including autonomic dysfunction, abnormalities in ion homeostasis, alteration in structural proteins, and interstitial fibrosis.[26] These pathogenic mechanisms could be mainly associated with insulin resistance,[30] but sustained hyperglycemia also may result in myocardial stiffness and contractile dysfunction.[26, 31]

Subclinical myocardial remodeling and diastolic dysfunction are also associated with NAFLD, independent of diabetes.[6, 8, 9, 32] NAFLD was associated with a 29%-increase in diastolic dysfunction risk compared with that in controls.[32] Diastolic dysfunction risk increases significantly according to the grades of steatosis and fibrosis.[6, 32] However, limited studies have investigated the independent association between the degree of NAFLD and diastolic dysfunction in subjects confined to patients with type 2 diabetes.[7, 33] In addition, previous evidence supporting that myocardial insulin resistance would be the link in the pathological association between NAFLD and myocardial dysfunction in patients with type 2 diabetes is insufficient. Myocardial insulin resistance is not always accompanied by systemic insulin resistance, and it is considered to develop independent of systemic insulin resistance and hyperglycemia severity.[13, 34, 35] Thus, to investigate the contributions of myocardial insulin resistance to the association between NAFLD and myocardial dysfunction, cardiac glucose metabolism has to be concomitantly estimated while measuring the degree of NAFLD and cardiac dysfunction. In this study, we examined myocardial glucose uptake using ^{18}FDG-PET, and we could demonstrate the association between myocardial glucose uptake, hepatic steatosis and fibrosis, and diastolic function.

The independent association between NAFLD and diastolic dysfunction in patients with type 2 diabetes with underlying systemic insulin resistance and hyperglycemia is noteworthy. Hepatic insulin resistance could be one of the mechanisms that explain this independent association between the liver and heart in type 2 diabetes. Insulin resistance could be either the whole-body or central (hepatic), and hepetic insulin resistance is distinguished from systemic/peripheral insulin resistance which is a major factor in the pathogenesis of type 2 diabetes.[36–38] Patients with NAFLD almost universally have hepatic insulin resistance, and there are comparative differences in the hepatic and whole-body insulin resistance along the spectrum of NAFLD.[39, 40] Hepatic steatosis with hepatic insulin resistance correlates with epicardial fat volume, which is an independent predictor of diastolic dysfunction.[39, 41, 42] Hepatic insulin resistance also leads to the overproduction of very-low-density lipoproteins and glucose, and increased

lipid accumulation and hyperglycemia-induced oxidation in myocardial cells induce myocardial remodeling, diastolic dysfunction and myocardial insulin resistance.[13, 43] Fibroblast growth factor 21 (FGF21), a protein synthetized by the liver, originally improves hepatic insulin sensitivity, but some investigators have suggested that FGF21 resistance observed in NAFLD could be associated with cardiac damage in patients with NAFLD.[44, 45] FGF21 resistance may contribute to myocardial insulin resistance due to altered lipid homeostasis in cardiomyocytes.[13, 46] In addition, the role of the liver as a generator of circulating mediators that affect cardiac remodeling has been hypothesized.[45] The production of pro-inflammatory and pro-atherogenic cytokines (e.g., interleukin 6, interleukin 12, tumor necrosis factor-alpha, etc.) is increased in patients with NAFLD, and these compounds could be involved in cardiac morphology and dynamics as well as myocardial insulin resistance.[13, 45] Several dysregulated hepatokines (e.g., fetuin A, eukocyte cell-derived chemotaxin-2, retinol binding protein, etc.) might also promote inflammatory pathways and cardiac dysfunction.[7] Thus, the superimposed hepatic insulin resistance and inflammation due to the presence of NAFLD in patients with type 2 diabetes might have increased the risk for myocaridal dysfunction.

The clinical relevance of the present study is attributed to several strengths. First, this study was restricted to patients with type 2 diabetes to investigate the independent assocation between NAFLD and myocardial dysfunction, even in the presence of hyperglycemia and systemic insulin resistance. Second, myocardial glucose uptake, reflecting myocardial insulin resistance, was estimated using ^{18}FDG-PET. Two previous studies have demonstrated the relation between NAFLD and diastolic dysfunction in patients with type 2 diabetes.[7, 33] However, neither of these studies investigated myocardial glucose uptake. To the best of our knowledge, this is the first study to suggest the potential that myocardial insulin resistance would pathophysiologically mediate the association between NAFLD and myocardial dysfunction in patients with type 2 diabetes by measuring myocardial glucose uptake using ^{18}FDG-PET.

The present study has some limitations. First, a causal relationship between NAFLD and myocardial dysfunction could not be drawn due to the cross-sectional design of this study. Second, this study was conducted in a single center with a limited number of subjects. A multicenter study should be conducted with a larger number of subjects to generate more confound evidence. Third, subjects were in a fasting condition when myocardial glucose uptake was assessed by ^{18}FDG-PET, as ^{18}FDG-PET was performed for cancer screening purposes to detect tumor glucose uptake. To estimate myocardial insulin sensitivity, PET with insulin-stimulated ^{18}FDG uptake or the standardization of myocardial substrate metabolism environment (euglycemic-hyperinsulinemic clamp) would be more accurate, and those methods should be considered in further studies.

Conclusions

In conclusion, hepatic steatosis and fibrosis were associated with cardiac remodeling and diastolic dysfunction in patients with type 2 diabetes. Myocardial glucose uptake significantly decreased according to the degree of hepatic steatosis and fibrosis along with diastolic dysfunction, suggesting that myocardial insulin resistance could mechanistically mediate the association between NAFLD and

diastolic dysfunction in patients with type 2 diabetes. Multicenter longitudinal studies with comprehensive measurements of the hepatic and cardiac parameters, and myocardial insulin resistance are required to confirm the pathophysiological interorgan relationship between the liver and heart in patients with type 2 diabetes.

Abbreviations

BMI: Body mass index; CAP:Controlled attenuation parameter; CT:Computed tomography; LA:Left atrial; LAVI:Left atrial volume index; LSM:Liver stiffness measurement; LV:Left ventricular; NAFLD:Non-alcoholic fatty liver disease; ROI:Regions of interest; SUV:Standardized uptake value; TE:Transient elastography; FDG:[^{18}F]-fluorodeoxyglucose; IQR:Interquartile range; PET:Positron emission tomography.

Declarations

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the independent institutional review board of Severance Hospital, Seoul, Korea (4-2017-1082). Informed consent was waived due to the retrospective nature of the study and anonymized data.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Study concept and design: M.L., E.S.K. Analysis and interpretation of data: M.L., K.J.K., T.H.C., M.Y., E.S.K. Drafting of the manuscript: M.L., E.S.K. Critical revision of the manuscript for important intellectual

content: K.J.K., T.H.C., J.B., Y-H.L., B-W.L., B-S.C., M.Y. Statistical analysis: M.L. Administrative, technical, or material support: K.J.K., T.H.C., M.Y., E.S.K

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Figures

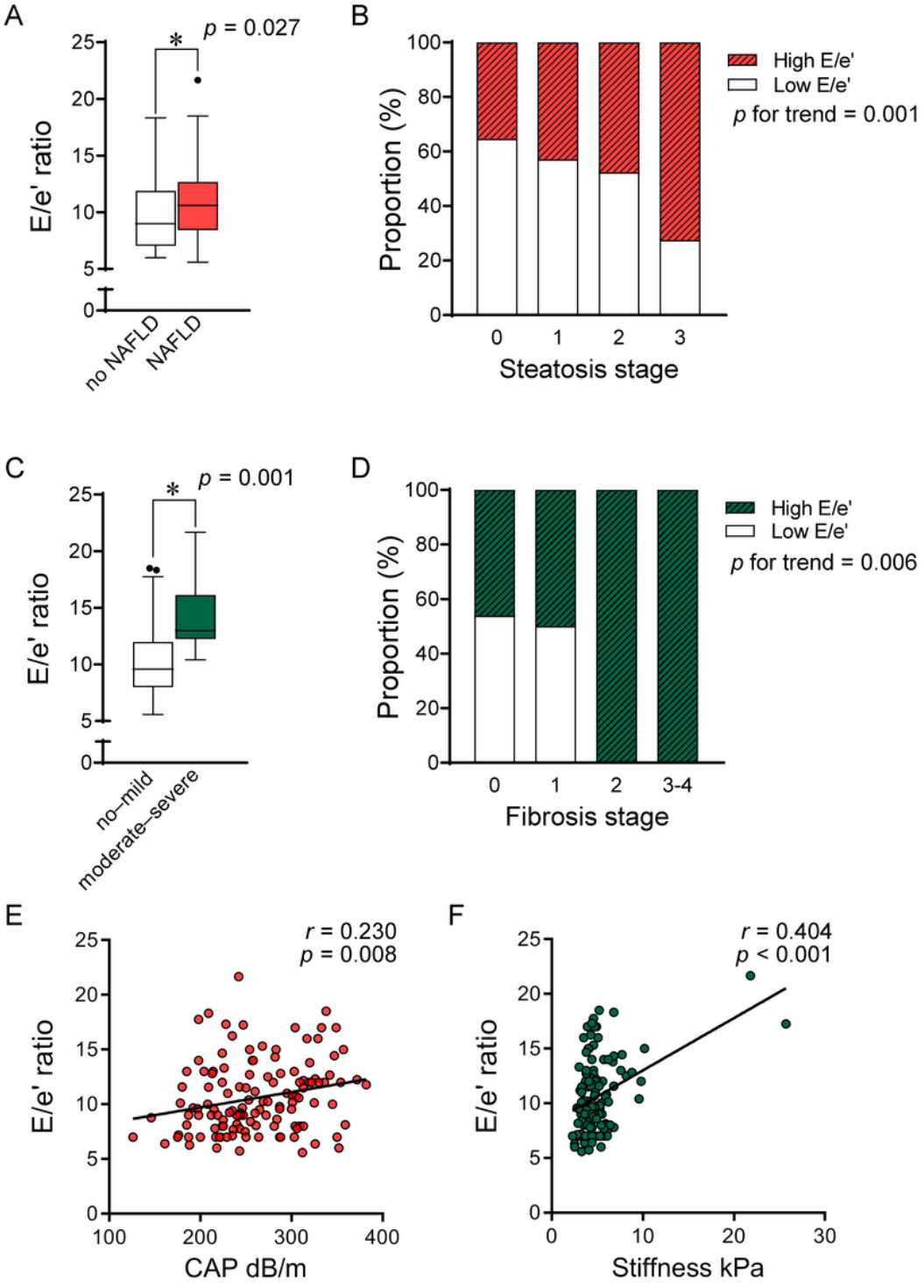

Figure 1

Hepatic steatosis and fibrosis associated with myocardial diastolic dysfunction (A) E/e' ratio according to the presence of non-alcoholic fatty liver disease (B) Increasing percentage of higher E/e' ratio according to the steatosis stage (C) E/e' ratio according to the presence of moderate to severe fibrosis (fibrosis stage ≥2) (D) Increasing percentage of higher E/e' ratio according to the fibrosis stage (E) Association

between steatosis (controlled attenuation parameter score, dB/m) and E/e' ratio (F) Association between liver stiffness (kPa) and E/e' ratio

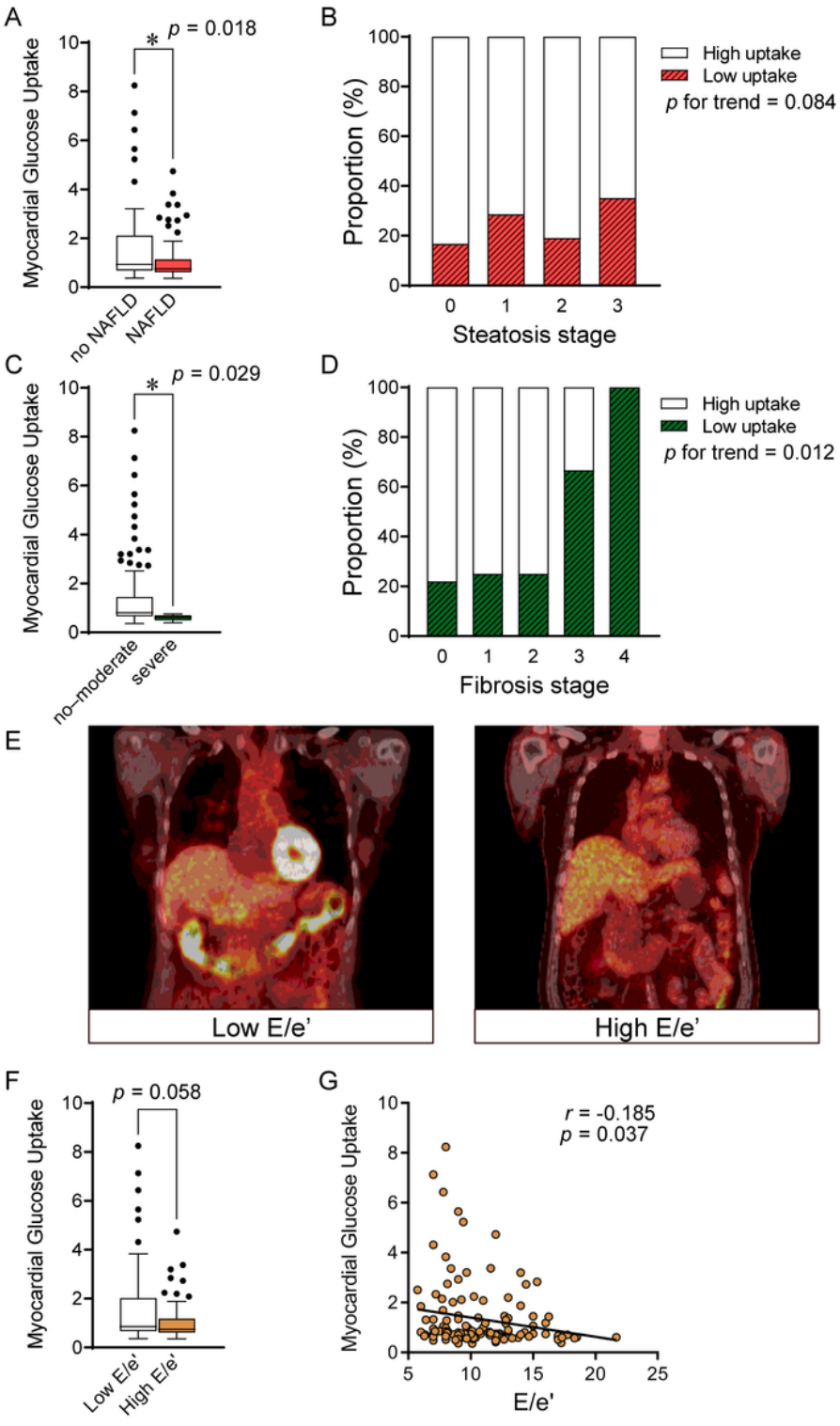

Figure 2

NAFLD and diastolic dysfunction associated with decreased myocardial glucose uptake determined by 18FDG-PET (A) Myocardial glucose uptake according to the presence of NAFLD (B) Increasing percentage of lower myocardial glucose uptake according to the steatosis stage (C) Myocardial glucose

uptake according to the presence of severe fibrosis (fibrosis stage ≥3) (D) Increasing percentage of lower myocardial glucose uptake according to the fibrosis stage (E) Representative images showing myocardial glucose uptake on [18F]-FDG-PET according to myocardial diastolic function, presented in terms of low and high E/e' ratios (F) Myocardial glucose uptake according to low and high E/e' ratios (G) Association between E/e' ratio and myocardial glucose uptake

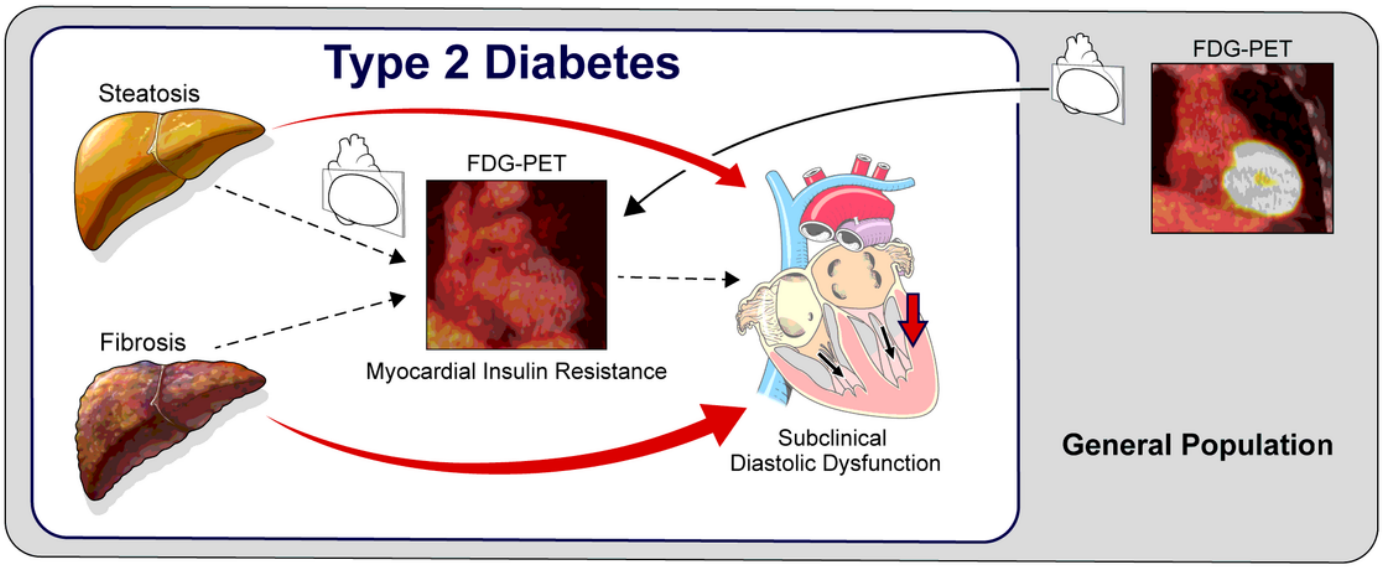

Figure 3

Associations between NAFLD, diastolic dysfunction, and impaired myocardial glucose uptake in patients with type 2 diabetes

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