Prevalence and Prognostic Implications of Pre-Diabetic State in Patients With Heart Failure

Yuya Matsue, MD; Makoto Suzuki, MD, PhD; Rena Nakamura, MD; Masami Abe, MD; Maki Ono, MD; Seigo Yoshida, MD; Mie Seya, MD; Ryota Iwatsuka, MD; Akira Mizukami, MD; Masahiko Setoguchi, MD; Wataru Nagahori, MD; Masakazu Ohno, MD; Akihiko Matsumura, MD; Yuji Hashimoto, MD, PhD

Background: Diabetes mellitus (DM) is a risk factor of poor prognosis in patients with heart failure (HF). The prevalence and prognostic impact of the pre-diabetic state, however, are not well understood.

Methods and Results: One hundred and thirty-six consecutive patients admitted due to HF were included in this prospective study. The 75-g oral glucose tolerance test (OGTT) was performed in all patients without known DM, and patients were classified into normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and DM groups. Forty-two of the 136 patients had previously been diagnosed with diabetes. Of the remaining 94 patients without known diabetes, 35 (37.2%) patients were classified as NGT, 9 (9.6%) as having IFG, 37 (39.4%) were classified as having IGT, and 13 (13.8%) were newly diagnosed with DM. During follow-up, patients with DM or IGT had significantly lower major adverse cardiac and cerebrovascular event (MACCE)-free rates than NGT patients ($P=0.006$, $P=0.036$, respectively). IFG, however, was not significantly related to increased MACCE risk. The presence of IGT (hazard ratio [HR], 4.51; $P=0.011$) and DM (HR, 4.74; $P=0.005$) were independent predictors of MACCE even after multivariate analysis.

Conclusions: IGT and DM contribute to adverse prognosis in patients with HF. It is feasible to perform diabetes screening using OGTT in patients with HF for risk stratification. (*Circ J* 2011; **75**: 2833–2839)

Key Words: Diabetes; Heart failure; Impaired glucose tolerance

Diabetes mellitus (DM) is an important risk factor for heart failure (HF) independent from coronary heart disease.¹ Recently, epidemiological studies including the Framingham Heart Study have shown that the presence of DM increases the risk of HF by approximately twofold in men and fivefold in women.² Conversely, among patients with a primary hospital discharge diagnosis of HF, 38% had concomitant DM,³ and the presence of DM has also been shown to be an independent predictor of poor outcome.^{4,5} The prevalence of glucose intolerance was reported to be approximately 50% in Japanese patients with symptomatic HF.⁶ Impaired glucose tolerance (IGT), which is considered as an early stage of DM, has also been shown to be a common comorbidity and an independent risk factor for adverse outcome in patients with HF.^{7–10} Precise evaluation of glucose tolerance is required for risk stratification, even in patients with HF. Most studies performed to date, however, have not included diagnosis of glucose intolerance using the oral glucose tolerance test (OGTT).

The present study was performed to clarify the relationship between glucose metabolism and prognosis in Japanese patients

with chronic HF.

Methods

Subjects

We performed a prospective and observational study of all patients admitted to Kameda Medical Center with a diagnosis of congestive HF between January 2009 and April 2011. The attending physician diagnosed HF according to the Framingham criteria.¹¹ Patients with acute myocardial infarction, valvular disease, end-stage chronic kidney disease (estimated glomerular filtration rate $<15 \text{ ml} \cdot \text{kg}^{-1} \cdot 1.73^{-2}$), type 1 diabetes, infection, and malignant disease were excluded. Patients were diagnosed as having HF with preserved ejection fraction (HFPEF) if ejection fraction was $\geq 50\%$, and HF with reduced ejection fraction (HFrEF) if ejection fraction was $<50\%$. According to Japan Diabetes Society guidelines, all patients with newly diagnosed diabetes, IGT, and impaired fasting glucose (IFG) were first treated with therapeutic lifestyle change. All patients gave their written informed consent, and

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Division of Cardiology, Department of Medicine, Kameda Medical Center, Chiba, Japan

Mailing address: Yuya Matsue, MD, Division of Cardiology, Department of Medicine, Kameda Medical Center, 929 Higashi-chou, Kamogawa, Chiba 296-8602, Japan. E-mail: yuyam@kameda.jp

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Table 1. Baseline Subject Characteristics vs. Glucometabolic Classification

Characteristics	NGT (n=35)	IFG (n=9)	IGT (n=37)	DM (n=55)	P value
Age (years)	62.4±11.3	71.0±11.8	67.2±11.6	74.8±10.2	0.512
Male	18 (51.4)	2 (22.2)	20 (54.1)	22 (40.0)	0.238
Smoking	13 (37.2)	5 (55.6)	16 (43.2)	31 (58.2)	0.443
HF ischemic etiology	9 (25.7)	2 (22.2)	8 (21.6)	17 (30.9)	0.778
NYHA class	1.49±0.51	1.44±0.53	1.38±0.59	1.47±0.66	0.865
BMI	24.4±2.8	24.9±2.8	24.6±3.5	24.7±3.8	0.967
SBP (mmHg)	121.3±14.2	124.4±9.0	119.9±13.5	124.8±14.5	0.343
DBP (mmHg)	69.0±10.2	71.7±12.3	72.7±12.5	73.1±11.1	0.313
Heart rate (beats/min)	59.9±8.8	59.9±8.6	57.8±9.7	58.8±8.5	0.769
LVEF (%)	49.5±12.8	50.7±12.0	48.8±12.5	53.5±14.1	0.328
End-diastolic diameter (mm)	55.0±8.8	56.6±8.6	55.7±6.8	54.2±7.3	0.754
End-systolic diameter (mm)	41.2±9.6	42.3±8.9	41.9±9.6	40.0±9.7	0.79
LAD (mm)	45.7±6.7	46.4±10.6	45.8±7.2	45.4±8.1	0.979
HFPEF	14 (40.0)	4 (44.4)	20 (54.1)	34 (61.8)	0.224
Medical history					
Hypertension	20 (57.1)	7 (77.8)	19 (51.4)	38 (69.1)	0.236
Dyslipidemia	11 (31.4)	2 (22.2)	9 (24.3)	22 (40.0)	0.392
Cerebral infarction	5 (5.5)	3 (12.0)	8 (8.2)	5 (10.4)	0.637
Atrial fibrillation	19 (54.3)	5 (55.6)	22 (59.5)	24 (43.6)	0.481
Medications					
Aspirin	13 (37.1)	5 (55.6)	10 (27.0)	22 (40.0)	0.373
ACEI	9 (25.7)	2 (22.2)	11 (29.7)	17 (30.9)	0.922
ARB	10 (28.6)	3 (33.3)	14 (37.8)	23 (41.8)	0.642
β -blocker	22 (62.9)	4 (44.4)	21 (56.8)	35 (63.6)	0.684
Statin	15 (42.9)	4 (44.4)	15 (40.5)	29 (52.7)	0.662
CCB	16 (45.7)	4 (44.4)	15 (40.5)	19 (34.5)	0.745
Diuretics	32 (91.4)	7 (77.8)	31 (83.8)	48 (87.3)	0.661
Spironolactone	23 (65.7)	5 (55.6)	23 (62.2)	37 (67.3)	0.894
Therapy for diabetes					
Therapeutic lifestyle change	0 (0)	9 (100)	37 (100)	55 (100)	<0.001
Anti-oral diabetes drug	0 (0)	0 (0)	0 (0)	18 (32.7)	<0.001
Insulin	0 (0)	0 (0)	0 (0)	11 (20.0)	<0.001
eGFR (ml·min ⁻¹ ·1.73m ⁻²)	49.0±23.6	41.7±23.0	50.2±31.6	46.2±24.3	0.682
Hemoglobin (g/dl)	12.1±1.67	12.3±1.91	12.3±1.67	12.5±1.63	0.713
HbA _{1c} (%)	5.26±0.27	5.68±0.26	5.90±0.3	6.28±0.41	<0.001
BNP (pg/dl)	280.1±279.9	293.1±237.6	291.5±375.5	312.9±330.0	0.971

Data given as mean±SD or n (%).

NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, diabetes mellitus; HF, heart failure; NYHA, New York Heart Association; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LAD, left atrium diameter; HFPEF, heart failure with preserved ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; BNP, brain natriuretic peptide.

Table 2. Adverse Events vs. Glucometabolic Classification

Characteristics	NGT (n=35)	IFG (n=9)	IGT (n=37)	DM (n=55)	P value
Rehospitalization for HF	2 (5.9)	0 (0)	9 (23.7)	15 (27.3)	0.031
Cardiovascular death	1 (2.9)	1 (11.1)	2 (5.3)	4 (7.3)	0.754
Cerebral infarction	1 (2.9)	0 (0)	1 (2.6)	1 (1.8)	0.949
MACCE	4 (11.8)	1 (11.1)	12 (31.6)	20 (36.4)	0.047
Cardiovascular events	3 (8.8)	1 (11.1)	11 (28.9)	19 (34.5)	0.034

Data given as n (%).

MACCE, major adverse cardiac and cerebrovascular events. Other abbreviations see in Table 1.

the study was approved by the local ethics committee.

Classification of Abnormal Glucose Tolerance

All patients included in this study who did not have a previous history of DM underwent 75-g OGTT on the day of discharge via the standard method after overnight fasting. Sub-

jects with abnormal glucose tolerance were classified into 4 groups, that is, normal glucose tolerance (NGT), IFG, IGT, and DM, according to the Criteria for Glucometabolic Disturbance established by the World Health Organization.¹² Previously known DM was defined as clinical history of oral hypoglycemic agent and/or insulin use and fasting plasma glucose

levels >126mg/dl. The other patients were urged to have their glucose tolerance evaluated on 75-g OGTT. NGT was defined as fasting glucose level <126mg/dl and a 2-h glucose level $\geq$ 200mg/dl. NGT was defined as fasting glucose level <110mg/dl and 2-h glucose level <140mg/dl. In the remaining patients, IGT was defined as fasting glucose level <126mg/dl and 2-h glucose level $\geq$ 140mg/dl or fasting glu-

cose level 110–125mg/dl and 2-h glucose level <140mg/dl.

Data Measurement

Patients with systolic blood pressure >140mmHg and/or diastolic pressure >90mmHg and those taking anti-hypertensive agents were considered to have hypertension. Hypercholesterolemia was defined as serum total cholesterol level

Table 3. Univariate and Multivariate Predictors of MACCE

	Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (years)	1.06 (1.01–1.11)	0.007	1.04 (0.99–1.08)	0.099
Male	1.02 (0.48–2.18)	0.959		
Smoking	0.82 (0.39–1.68)	0.585		
HF ischemic etiology	1.25 (0.54–2.89)	0.599		
NYHA class	0.82 (0.42–1.59)	0.561		
BMI	0.93 (0.83–1.05)	0.237		
SBP (mmHg)	1.03 (1.01–1.06)	0.044	1.02 (0.99–1.04)	0.173
DBP (mmHg)	1.01 (0.97–1.04)	0.827		
Heart rate (beats/min)	0.99 (0.95–1.03)	0.642		
LVEF (%)	0.99 (0.97–1.03)	0.858		
End-diastolic diameter (mm)	1.02 (0.97–1.07)	0.568		
End-systolic diameter (mm)	1.01 (0.97–1.05)	0.589		
LAD (mm)	0.95 (0.91–1.01)	0.113		
HFPEF	1.291 (0.67–2.49)	0.446		
Medical history				
Hypertension	1.20 (0.55–2.63)	0.649		
Dyslipidemia	1.12 (0.87–1.92)	0.689		
Atrial fibrillation	0.55 (0.25–1.17)	0.121		
Medications				
Aspirin	1.70 (0.79–3.67)	0.177		
ACEI	0.61 (0.25–1.47)	0.269		
ARB	1.06 (0.49–2.33)	0.874		
β -blocker	0.82 (0.38–1.76)	0.607		
Statin	0.98 (0.46–2.09)	0.957		
CCB	1.05 (0.49–2.27)	0.903		
Diuretics	0.54 (0.19–1.51)	0.237		
Spironolactone	1.19 (0.53–2.65)	0.67		
eGFR ($\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)	1.01 (0.99–1.02)	0.678		
Hemoglobin (g/dl)	0.97 (0.94–1.60)	0.054	1.13 (0.92–1.38)	0.256
HbA _{1c} (%)	1.67 (0.83–3.50)	0.151		
BNP (pg/dl)	1.002 (1.001–1.004)	0.002	1.001 (1.000–1.002)	0.023
Glucose intolerance				
NGT	1.0		1.0	
IFG	0.94 (0.09–9.60)	0.957	1.08 (0.12–9.68)	0.948
IGT	3.46 (0.99–12.05)	0.051	4.51 (1.41–14.47)	0.011
DM	4.29 (1.32–13.94)	0.016	4.74 (1.58–14.23)	0.005

Variables with $P < 0.1$ on univariate analysis were included in the multivariate model.
HR, hazard ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

≥ 220 mg/dl or the requirement of treatment with lipid-lowering agents. Patients were considered smokers if they were current smokers.

A baseline blood sample was collected on the day of discharge. Estimated glomerular filtration rate was calculated using the Modification of Diet and Renal Disease equation coefficients modified for Japanese patients.¹³ Left ventricular ejection fraction was measured at the time of discharge on 2-D echocardiography using the modified Simpson method. Medication data were collected at the end of follow-up.

Follow-up

All patients were followed up at the outpatient clinic and data regarding major adverse cardiac and cerebrovascular events (MACCE) were collected. Patient outcomes were assessed based on MACCE, which included death from cardiac causes, non-fatal myocardial infarction, unstable angina, rehospitalization because of congestive HF, and cerebral infarction. Apart

from MACCE, only cardiovascular death and rehospitalization because of congestive HF were classified as cardiovascular events. Cerebral infarction was diagnosed by the presence of a neurological deficit confirmed on computed tomography or magnetic resonance imaging.

Statistical Analysis

Baseline characteristics were analyzed for significance of differences between groups using 1-way analysis of variance (ANOVA) for continuous variables and the chi-squared or Fisher's exact test for categorical variables. Event-free survival curves were constructed using the Kaplan–Meier survival method and were compared using log-rank statistics. Survival period was defined as the interval between the day of discharge and the time of MACCE.

We calculated hazard ratios (HRs) derived from the Cox proportional hazard model to evaluate the prognostic effects of the presence of IFG, IGT, and DM for the study period. All base-

line variables, including echocardiographic parameters, were included in regression analysis. Multivariate analysis was performed using all variables with $P < 0.1$ on univariate analysis.

Results are given as mean $\pm$ SD, n (%), or HR with 95% confidence interval (95%CI). All statistical tests were 2-sided, and $P < 0.05$ was considered significant in all analyses. Data analysis was performed using SPSS 19.0 (SPSS, Chicago, IL, USA).

Results

Baseline Subject Characteristics

Of the 152 patients admitted during the study period, 5 died due to deterioration of HF, 4 patients required hemodialysis, and 7 patients had hemodynamically significant valvular disease. Therefore, 136 patients were included in the present study. None of the participants dropped out, and all patients were completely followed up at the outpatient clinic. The clinical characteristics of the present patients are listed in [Table 1](#). Forty-two patients were previously diagnosis as having diabetes. Of the 94 patients without known diabetes, 35 (37.2%) were classified as NGT, 9 (9.6%) were classified as IFG, 37 (39.4%) were IGT, and 13 (13.8%) were newly diagnosed as having DM according to 75-g OGTT.

There were no significant differences between the 4 groups except in hemoglobin A_{1c} (HbA_{1c}), which was higher in DM and IGT patients compared to NGT patients.

MACCE

Median follow-up was 150 days. The number of MACCE and cardiovascular events are given in [Table 2](#).

The Kaplan–Meier curves in [Figure 1A](#) illustrate time to MACCE according to glucose intolerance classification during follow-up, and [Figure 1B](#) illustrates time to cardiovascular events. Compared to NGT, the IGT group and DM group had higher risks for MACCE (log-rank=0.018 and 0.006, respectively). There were no significant differences in MACCE-free survival rate between the NGT group and IFG group (log-rank=0.926) or between the IGT group and DM group (log-rank=0.806). Concerning cardiovascular events, the IGT group and DM group also had higher risk compared to the NGT group (log-rank=0.010 and 0.003, respectively). We also analyzed the data with regard to HFPEF and HFREF, and this tendency was not changed ([Figure 2](#)).

On univariate analysis, age, hemoglobin, B-type natriuretic peptide (BNP), and glucose intolerance classification were associated with higher risk of MACCE. After adjusted multivariate Cox regression analysis, including all variables with $P < 0.1$ on univariate analysis, the presence of IGT (HR, 4.51; 95%CI: 1.41–14.47; $P=0.0011$) and DM (HR, 4.74; 95%CI: 1.58–14.23; $P=0.005$) were significantly associated with increased MACCE risk compared with the NGT group ([Table 3](#)). IFG, however, was not significantly related to increased MACCE risk. Age and BNP were also statistically significant on multivariate regression analysis.

Discussion

The most important findings of the present study were that the prevalence of IGT is high in patients with HF and that IGT, but not IFG, contributes equally to poor prognosis compared to DM even after adjustment for several risk factors.

The prevalence of glucose intolerance in patients with HF was reported to range from 23% to 43%,^{7,14–16} which is lower than that found in the present study. This wide range reflects the diverse criteria and methods used to identify patients with

glucose intolerance. Many studies investigating the prevalence of dysglycemia in HF used fasting or casual glucose levels or only HbA_{1c}. Fasting plasma glucose and HbA_{1c} have limited sensitivity for diagnosis of glucose intolerance, in particular IGT. For example, Egstrup et al reported that omitting OGTT would have misclassified 40% of newly diagnosed cases of diabetes, and by definition all patients with IGT among patients with HFREF.¹⁷ Some data suggest that HbA_{1c} measurement in addition to fasting glucose may be of no benefit for detecting IGT or DM in heart disease. In patients with coronary artery disease, HbA_{1c} was less strongly related to the 2-h OGTT glucose level than fasting plasma glucose. In addition, the areas under the receiver operating characteristic curve of fasting glucose and HbA_{1c} for detecting IGT or new DM were low (0.76 and 0.71, respectively) using OGTT as the gold standard.¹⁸

The prevalence and prognostic impact of IGT and DM have been reported in some studies in which diagnosis was made based only on HbA_{1c} and fasting glucose. The CHARM study, which included 2,412 patients with HF, showed that HbA_{1c} was an independent predictor of cardiovascular death, hospitalization for worsening HF, and total mortality in both diabetic and non-diabetic patients.⁹ In the Reykjavik study, IGT was shown to be an independent predictor of all-cause mortality to a similar degree to that of DM.¹⁹ In a recent study including only patients with HFREF (<45%) and IGT diagnosed previously on 75-g OGTT, HF patients with IGT tended to have a higher mortality rate than those without glucose intolerance. In the present study, IGT and DM contributed similarly to poor prognosis, consistent with these previous results. The diagnosis of IGT in the Reykjavik study, however, was done on 50-g OGTT, not 75 g as used in the present study. The European Guidelines on diabetes, pre-diabetes, and cardiovascular diseases recommend use of 75-g OGTT,²⁰ and this difference in methodology for diagnosis may have led to underestimation of the prevalence of DM and IGT. In the previous study by Egstrup et al, all patients had HFREF. Patients with HFPEF were included in the present study, and the results indicated a high prevalence and prognostic impact of glucose intolerance.

In the present study, IFG was not a predictor of poor prognosis, which is consistent with previous studies. Two meta-analyses showed that only post-prandial hyperglycemia, but not fasting hyperglycemia, is a good predictor of adverse cardiovascular events.^{21,22} Moreover, even among patients without HF, diastolic function evaluated on echocardiography was shown to be impaired in patients with DM or IGT, but not in those with IFG, compared to NGT.²³ This may have been why the prognosis of patients with IGT and HF was poorer than that of the other groups. The present study, however, excluded patients with atrial fibrillation; thus, taking into account the high prevalence of atrial fibrillation in HF, these results are not conclusive.

Although several studies have shown that IGT increases cardiovascular morbidity and mortality, it is still unknown as to whether medication for the pre-diabetic state would improve the prognosis. There have been no large-scale, randomized clinical trials addressing this issue, but some data have been reported indicating that intervention for the pre-diabetic state may improve the outcome of this population. Kim et al evaluated the prevalence of IGT in patients with dilated cardiomyopathy, and examined whether an α -glucosidase inhibitor could improve the cardiac function and symptoms. Their results showed that the α -glucosidase inhibitor improved glucose metabolism and cardiac function.²⁴ The STOP-NIDDM study showed that the rate of cardiovascular events was low in

IGT patients treated with acarbose in comparison with placebo controls.²⁵ Because previous studies have shown that postprandial elevated plasma glucose adversely affects endothelial function, inflammatory responses, and increases oxidative stress on the cardiovascular system,^{26–29} preventing progression from the pre-diabetic state to diabetes may be a promising strategy to reduce the morbidity and mortality rates in patients with HF. Further large-scale, prospective clinical trials are necessary to confirm this issue.

To our knowledge, this is the first report on the prevalence and prognostic impact of IGT in patients with congestive HF. We recommend that 75-g OGTT should be performed in all patients with HF to allow for precise risk stratification.

The present study had some limitations. First, this study was based on a small number of patients at a single center. The cohort in the present study included only patients with HF who required hospitalization, and thus the data described herein cannot be extrapolated to the whole HF population. We did not evaluate diastolic function on echocardiography because the subjects included a considerable number of patients with atrial fibrillation. Finally, the presence or absence of glucose intolerance was determined by the attending physician who also decided whether admission for treatment was required, and this may have affected the rate of readmission in the present study.

Conclusions

In patients with HF, IGT is a common comorbidity, and IGT contributes to poor prognosis in a similar fashion to DM as an independent factor. These findings suggest the importance of using OGTT to detect glucose intolerance and identify high-risk patients in this population.

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