Impact of Impaired Pancreatic β-Cell Function on Cardiovascular Prognosis in Heart Failure Patients Without Diabetes Mellitus

Taro Narumi, MD, PhD; Tetsu Watanabe, MD, PhD; Shigehiko Kato, MD, PhD; Harutoshi Tamura, MD, PhD; Satoshi Nishiyama, MD, PhD; Hiroki Takahashi, MD, PhD; Takanori Arimoto, MD, PhD; Tetsuro Shishido, MD, PhD; Masafumi Watanabe, MD, PhD

Background: Insulin resistance as assessed using homeostasis model assessment ratio (HOMA-R) is associated with latent myocardial damage in apparently healthy subjects in health check. Meanwhile, diabetes mellitus (DM) is an unfavorable prognostic risk factor in patients with heart failure (HF). We examined the impact of pancreatic β-cell dysfunction on clinical outcomes in HF patients without DM.

Methods and Results: This study enrolled 312 HF patients without DM. Pancreatic β-cell dysfunction was defined as HOMA-β<30%. A total of 108 patients (35%) had β-cell dysfunction. Plasma brain natriuretic peptide was higher in patients with pancreatic β-cell dysfunction compared with those without (625.2 vs. 399.0 pg/mL, P<0.001). On Kaplan-Meier analysis, a significantly higher cardiovascular events rate was observed in patients with pancreatic β-cell dysfunction (log-rank test, P=0.001), but there was no significant difference between patients with and without insulin resistance. On Cox hazard analysis, pancreatic β-cell dysfunction was independently associated with cardiovascular events after adjustment for confounding factors (HR, 1.58; 95% CI: 1.02–2.45), whereas insulin resistance was not associated with cardiovascular events.

Conclusions: Pancreatic β-cell dysfunction, but not insulin resistance, was associated with unfavorable outcome in HF patients without DM.

Key Words: Heart failure; Insulin resistance; Pancreatic β-cell function; Prognosis
Five patients undergoing chronic hemodialysis were excluded. Ninety-five patients with DM and 30 patients without the required data were also excluded. The remaining 339 patients were enrolled in the present study.

All subjects gave written informed consent prior to participation, and the protocol was approved by the institution’s Human Investigation Committee. The procedures were performed in accordance with the Helsinki Declaration.

Endpoints and Follow-up
The patients were prospectively followed for 1 year. The endpoints were cardiovascular events including deaths due to progressive HF, myocardial infarction, stroke, other vascular disease and sudden cardiac death, and re-hospitalization for worsening HF. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was confirmed by the attending physician. Two cardiologists, who were blinded to the blood biomarker data, reviewed the medical records and conducted telephone interviews to survey the incidence of cardiovascular events.10

| Table 1. Subject Baseline Characteristics |
|-----------------------------------------|
| n=312                                   |
| Age (years)                             |
| 72±13                                   |
| Male                                    |
| 175 (56)                                |
| Etiology                                |
| Hypertensive heart disease              |
| 58 (19)                                 |
| Ischemic heart disease                  |
| 58 (19)                                 |
| Dilated cardiomyopathy                  |
| 57 (18)                                 |
| Valvular heart disease                  |
| 46 (14)                                 |
| Other causes                            |
| 93 (30)                                 |
| Presentation profile                    |
| BMI (kg/m²)                             |
| 22.1±4.0                                |
| eGFR (ml/min/1.73m²)                    |
| 63.0±34.8                               |
| NYHA III/IV                             |
| 205 (66)                                |
| Blood biomarkers                        |
| Albumin (g/dL)                          |
| 3.4±0.6                                 |
| FPG (mg/dL)                             |
| 100.4±16.1                              |
| Insulin (µg/mL)                         |
| 5.1 (3.1–8.5)                           |
| Hemoglobin A1c (%) NGSP                 |
| 5.4 (5.1–5.7)                           |
| Total cholesterol (mg/dL)               |
| 162.3±40.5                              |
| Triglyceride (mg/dL)                    |
| 86.0±42.8                               |
| LDL-C (mg/dL)                           |
| 94.9±32.4                               |
| HDL-C (mg/dL)                           |
| 52.3±14.8                               |
| BNP (pg/mL)                             |
| 456.6 (215.4–942.4)                     |
| Echocardiography data                   |
| LVEDD (mm)                              |
| 54.3±10.6                               |
| LVEF (%)                                |
| 47.3±17.6                               |
| Medication                              |
| ACEI and/or ARB                         |
| 189 (61)                                |
| β-blockers                              |
| 181 (58)                                |

Data given as mean±SD, n (%), or median (IQR). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; H-FABP, heart-type fatty binding protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NGSP, National Glycohemoglobin Standardization Program; NYHA, New York Heart Association.

Results

Beta-Cell Dysfunction and Insulin Resistance
Pancreatic β-cell function was estimated using HOMA-β: HOMA-β (%)=(fasting insulin×360)/(fasting plasma glucose−63). Pancreatic β-cell dysfunction was defined as HOMA-β <30%.11 Insulin resistance was also evaluated using HOMA-R. HOMA-R=fasting insulin×fasting plasma glucose/405. Insulin resistance was defined as HOMA-R >2.5.11

Statistical Analysis
Data are presented as mean±SD. In the case of non-normal distribution, the data are presented as median (IQR). Unpaired Student’s t-test and the chi-squared test were used for comparison between 2 groups of continuous and of categorical variables, respectively. Mann-Whitney U-test was used for non-normally distributed data. Comparison of data between 3 groups was performed using 1-way analysis of variance (ANOVA) followed by Bonferroni post-hoc analysis. Univariate and multivariate analysis with Cox proportional hazard regression were used to determine significant predictors of cardiovascular events. Multivariate analysis was adjusted for factors that were significant on univariate analysis. Plasma brain natriuretic peptide (BNP) was converted to the logarithm in Cox proportional hazard regression analysis. Cumulative overall and event-free survival rates were computed using the Kaplan-Meier method and were compared using log-rank test. P<0.05 was considered statistically significant. All statistical analysis was performed using JMP version 10 (SAS Institute, Cary, NC, USA).

Beta-Cell Dysfunction Status
Subjects were divided into 2 groups according to the presence of pancreatic β-cell dysfunction. The prevalence of pancreatic β-cell dysfunction increased with New York Heart Association (NYHA) functional class (II, 21%; III, 37%; and IV, 51% respectively, P<0.001; Figure 1A). Moreover, HOMA-β decreased with increasing NYHA functional class (P<0.001; Figure 1B).

The patients with pancreatic β-cell dysfunction were older than those without. Body mass index (BMI), serum albumin, and triglyceride were lower, and plasma BNP was higher in patients with pancreatic β-cell dysfunction compared with those without (median, 625.2 vs. 399.0 pg/mL, P<0.001; Figure 1C; Table 2).

We previously reported that serum heart-type fatty acid-binding protein (H-FABP) as a marker of myocardial damage is associated with prognosis in patients with HF.12 Serum H-FABP was higher in patients with pancreatic β-cell dysfunction compared with those without (median, 14.1 vs. 7.1 ng/mL, P<0.001; Figure 2A). There was no significant difference, however, in serum H-FABP between patients with and without insulin resistance (Figure 2B).
Pancreatic Function and Cardiovascular Prognosis

Figure 1. (A) Prevalence of pancreatic β-cell dysfunction and (B) homeostasis model assessment-β vs. New York Heart Association (NYHA) functional class in heart failure patients without diabetes mellitus. (A, B) P<0.001 for both. (C) Plasma brain natriuretic peptide (BNP) vs. presence of pancreatic β-cell dysfunction: median BNP; (+) 625.2 pg/mL vs. (−) 399.0 pg/mL (P<0.001).

Table 2. Subject Characteristics vs. Pancreatic β-Cell Dysfunction

| Age (years) | Normal pancreatic β-cell function (n=204) | Pancreatic β-cell dysfunction (n=108) | P-value |
|-------------|------------------------------------------|--------------------------------------|---------|
| Male        | 69±13                                    | 77.5±11.6                            | <0.001  |
| Etiology    |                                          |                                       | 0.705   |
| Hypertensive heart disease | 31                                       | 27                                   | –       |
| Ischemic heart disease   | 33                                       | 25                                   | –       |
| Dilated cardiomyopathy  | 44                                       | 13                                   | –       |
| Valvular heart disease  | 31                                       | 15                                   | –       |
| Other causes   | 65                                       | 28                                   | –       |
| Presentation profile |                                          |                                       |         |
| BMI (kg/m²)   | 23.0±4.0                                 | 20.2±3.3                             | <0.001  |
| eGFR (mL/min/1.73 m²) | 62.1±25.9                               | 64.7±47.2                            | 0.533   |
| NYHA III/IV  | 119 (58)                                 | 86 (80)                              | <0.001  |
| Blood biomarkers |                                          |                                       |         |
| Albumin (g/dL) | 3.5±0.6                                  | 3.2±0.6                              | <0.001  |
| FPG (mg/dL)    | 99.4±15.2                                | 102.1±17.7                           | 0.188   |
| Insulin (µU/mL) | 6.9 (4.8–10.6)                          | 2.6 (1.9–4.0)                        | <0.001  |
| Hemoglobin A<sub>1c</sub> (%) NGSP | 5.4 (5.1–5.7)  | 5.4 (5.1–5.7)                      | 0.985   |
| Total cholesterol (mg/dL) | 162.0±42.1                             | 162.9±37.5                           | 0.873   |
| Triglyceride (mg/dL)   | 90.3±46.7                                | 77.9±32.8                            | 0.015   |
| LDL-C (mg/dL)  | 94.7±34.6                                | 95.3±28.0                            | 0.881   |
| HDL-C (mg/dL)  | 52.0±14.6                                | 53.0±15.1                            | 0.561   |
| BNP (pg/mL)    | 399.0 (180.6–783.8)                      | 625.2 (305.5–1,252.8)               | <0.001  |
| Echocardiography data |                                          |                                       |         |
| LVEDD (mm)     | 54.8±11.0                                | 53.3±9.8                             | 0.223   |
| LVEF (%)       | 47.0±18.4                                | 48.1±15.9                            | 0.597   |
| Medication    |                                          |                                       |         |
| ACEI and/or ARB | 129 (63)                                 | 60 (56)                              | 0.188   |
| β-blockers    | 121 (59)                                 | 60 (56)                              | 0.523   |

Data given as mean± SD, n (%) or median (IQR). Abbreviations as in Table 1.
Beta-Cell Dysfunction and Cardiac Events

There were 90 cardiovascular events (29%), consisting of 25 cardiovascular deaths and 65 rehospitalizations for worsening HF during the follow-up period. On Kaplan-Meier analysis, significantly higher cardiac event rates were observed in patients with pancreatic β-cell dysfunction (log-

Serum BNP, HOMA-β and HOMA-R

HOMA-β ($r=-0.26$, $P<0.001$) was negatively correlated with log-BNP (Figure 3A), but there was no correlation between HOMA-R and log-BNP (Figure 3B).
Table 3. Unadjusted and Adjusted HR for Cardiovascular Events

|                      | Unadjusted HR | 95% CI     | P-value | Adjusted HR† | 95% CI     | P-value |
|----------------------|---------------|------------|---------|--------------|------------|---------|
| Age (10-year increase) | 1.26          | 1.06–1.49  | 0.009   | 1.15         | 0.96–1.37  | 0.129   |
| Gender (male)         | 1.12          | 0.74–1.71  | 0.583   | 1.25         | 0.82–1.91  | 0.296   |
| NYHA functional class (II/IV) | 1.01          | 0.65–1.58  | 0.960   | –            | –          | –       |
| Log-BNP (1-SD increase) | 1.47          | 1.18–1.83  | <0.001  | 1.35         | 1.08–1.69  | 0.009   |
| LVEF (10% increase)   | 0.98          | 0.87–1.10  | 0.698   | –            | –          | –       |
| Pancreatic β-cell dysfunction | 1.97          | 1.30–2.98  | 0.001   | 1.58         | 1.02–2.45  | 0.039   |
| Insulin resistance    | 1.44          | 0.81–2.54  | 0.212   | –            | –          | –       |

†After adjustment for age, gender, and log-serum BNP. Abbreviations as in Table 1.

Discussion

In the present study, we have clearly demonstrated that pancreatic β-cell dysfunction but not insulin resistance on HOMA was associated with unfavorable outcomes in HF patients without DM.

While the insulin level is high, hepatic glucose production is suppressed, and fasting blood sugar and post-prandial blood sugar are maintained in the normal range, and there are no symptoms. Hepatic insulin resistance is accompanied by skeletal muscle insulin resistance, and pancreatic dysfunction. The overwork of pancreatic β-cell function does not last long, and exhaustion leads to impairment of insulin secretion. Hepatic glucose production starts to increase simultaneously with the lowering pancreatic β-cell function, leading to blood sugar elevation. In this manner, the understanding of pancreatic β-cell function has shed new light on the pathological background of DM development.

DM is one of the most common risk factors for the development of cardiovascular disease. Acute myocardial infarction patients with DM have severe left ventricular systolic dysfunction and mortality due to HF compared with those without. Iribarren et al reported that HF patients with DM had severe mortality and frequent rehospitalization rate compared with those without. Insulin resistance is also a known risk factor for the development of cardiovascular disease and HF. We previously reported that insulin resistance is associated with latent and ongoing myocardial damage in apparently healthy subjects in community-based health check. Insulin resistance was also reported to be associated with the development of HF in a community-based cohort. This indicates that insulin resistance plays a role in the early stage of development of HF. Also, in HF patients, hyperinsulinemia based on insulin resistance induces chronic adipose tissue inflammation and development of the catabolic state. Remarkable enhancement of insulin signaling promotes the myocyte aging process, which worsens cardiac function and aggravates HF.

In the present study there was no association between insulin resistance on HOMA-R and prognosis in HF patients without DM. Although pancreatic β-cell dysfunction assessed on HOMA-β was correlated with log-BNP, insulin resistance was not correlated with log-BNP. Insulin resistance as assessed on HOMA-R did show a trend, but this was not statistically significant due to the limited number of patients analyzed and the short follow-up period (1 year). HOMA-R and HOMA-β are convenient tools for the assessment of systemic insulin resistance and secretion, respectively. Of course, they are indirect indicators, but are worthwhile in daily medical practice for patients with HF.

Before the onset of DM, hyperinsulinemia based on sustained insulin resistance leads to pancreatic β-cell dysfunction and hyperinsulinemia. Myocardial ischemia due to HF changes aerobic metabolism to anaerobic metabolism in myocytes. Insulin plays a key role in the uptake of glucose. Anaerobic metabolism in myocytes uses glucose in mitochondria and produces adenosine triphosphate. In this study, BMI was significantly lower in patients with pancreatic β-cell dysfunction compared with those without. Given that Asian patients with DM are more prone to insulin resistance, with a poorer insulin secretory potential than Western patients, it was possible that Japanese patients with HF are likely to show pancreatic β-cell dysfunction, which may be associated with lower BMI. Berry and Clark suggested that several inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α, are elevated in patients with HF, and induce chronic inflammation and metabolic disorder, which promote a catabolic state. HOMA-R and HOMA-β are convenient tools for the assessment of systemic insulin resistance and secretion, respectively. Thus, hyperinsulinemia based on pancreatic β-cell dysfunction worsens cardiac function. The present study has shown that pancreatic β-cell dysfunction, but not insulin resistance, provides important information in HF patients without DM.

Conclusions

Pancreatic β-cell dysfunction was associated with unfavorable outcomes in HF patients without DM. Future research is required to investigate the association between the state of HF and cardiometabolic dysfunction.

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The authors declare no conflicts of interest.

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