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Relation of cardiac function to insulin resistance as evaluated by hyperinsulinemic-euglycemic clamp analysis in individuals with type 2 diabetes

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Keywords
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ABSTRACT

Aims: Whereas homeostasis model assessment of insulin resistance (HOMA-IR), an easily measured but limited index of insulin resistance, has been shown to correlate with impairment of cardiac function in individuals without diabetes, the pathological relevance of insulin resistance to the development of cardiac dysfunction in individuals with type 2 diabetes has remained unclear. Here we investigated the relation between left ventricular (LV) function as assessed by echocardiography and insulin resistance as evaluated by hyperinsulinemic-euglycemic clamp analysis, the gold standard for measurement of this parameter, in individuals with type 2 diabetes.

Methods: This retrospective study included 34 individuals with type 2 diabetes who underwent both hyperinsulinemic-euglycemic clamp analysis and echocardiography. Both the insulin sensitivity index (ISI) as determined by glucose clamp analysis as well as HOMA-IR were determined as measures of insulin resistance. The ratio of the peak early- to late-diastolic mitral inflow velocities (E/A) and the LV ejection fraction (LVEF) were determined as measures of diastolic and systolic function, respectively.

Results: The ISI was significantly correlated with both the E/A ratio and LVEF (correlation coefficients of 0.480 and 0.360, respectively), whereas HOMA-IR was not correlated with either cardiac parameter. Multivariate analysis revealed that ISI was an independent predictor for both a high log [E/A] ($P = 0.031$) and a high LVEF ($P = 0.045$).

Conclusions: Insulin resistance as evaluated by hyperinsulinemic-euglycemic clamp analysis may be causally related to LV diastolic and systolic dysfunction in individuals with type 2 diabetes.

INTRODUCTION

Heart failure has recently drawn increasing attention as an important cardiovascular complication of diabetes mellitus[1,2]. Individuals with diabetes often present with cardiac insufficiency in the absence of other underlying conditions such as coronary artery disease, arrhythmia, or valvular disease, suggesting that the diabetic condition itself can give rise to cardiac dysfunction[3,4].

In general, cardiac dysfunction thought to be caused by diabetes manifests initially as left ventricular (LV) diastolic dysfunction without a loss of ejection fraction and subsequently as LV systolic dysfunction[3,4]. Whereas the mechanisms responsible for the development of this condition remain unclear, several pathological factors including hyperglycemia, inappropriate activation of the renin–angiotensin–aldosterone system, the production of reactive oxygen species, altered energy metabolism in cardiomyocytes, and the generation of advanced glycation end products are thought to play a role[3,4].

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Insulin resistance, a characteristic of type 2 diabetes mellitus, has also been implicated in the development of heart failure associated with this disease. Homeostasis model assessment of insulin resistance (HOMA-IR) has thus been found to be correlated with the loss of LV diastolic function in individuals without diabetes[5–8] as well as in cohorts including both individuals with or without diabetes[9,10]. Whereas these studies are suggestive of the pathophysiologic relevance of insulin resistance to cardiac dysfunction, most of the study participants did not have diabetes. Moreover, although it is easy to measure, HOMA-IR reflects insulin resistance only under limited conditions[11,12]. It has thus remained unclear whether insulin resistance is actually related to cardiac dysfunction in individuals with diabetes.

We aimed to investigate the relation between cardiac function and insulin resistance in individuals with type 2 diabetes. To evaluate insulin resistance in the study participants, we adopted the hyperinsulinemic-euglycemic clamp method, which is the gold standard for measurement of insulin resistance in individuals with type 2 diabetes[13].

PARTICIPANTS AND METHODS

Study participants

This cross-sectional retrospective study was approved by the medical ethics committee of Kobe University Graduate School of Medicine (approval no. B190089, approved day August 20, 2020) and conformed to the provisions of the 1995 Declaration of Helsinki. The participants were recruited from individuals with type 2 diabetes aged between 20 and 90 years who attended Kobe University Hospital between January 2009 and March 2019, who had a fasting blood glucose concentration maintained below 130 mg/dL[14,15] to avoid the influence by glucose toxicity on insulin sensitivity, and who had undergone both transthoracic echocardiography and hyperinsulinemic-euglycemic clamp analysis within an interval of 60 days. Exclusion criteria were as follows: (1) Treatment with insulin, glucagon-like peptide 1 (GLP1) receptor agonists, thiazolidinediones, or sodium-glucose transporter 2 (SGLT2) inhibitors (subjects using GLP-1 receptor agonists[16,17], thiazolidinediones[18], and SGLT2 inhibitors[19] were excluded given that these drugs are thought to possess direct effects on cardiac function or body fluid volume); (2) comorbidity or past medical history of ischemic heart disease, valvular disease, arrhythmia, or symptomatic heart failure; (3) a diagnosis of cirrhosis, chronic obstructive lung disease, endocrine disease, or collagen disease; (4) treatment with drugs that affect glucose metabolism such as steroids or beta-blockers; (5) the presence of renal dysfunction (serum creatinine concentration of >1.3 mg/dL for men or >1.2 mg/dL for women); (6) pregnancy or breastfeeding; and (7) a judgment of inappropriateness for the study by the investigators. Participants of this study were made aware that the data were to be used for research purposes and that they could opt out if they objected to such use of their data.

Glucose clamp analysis

A hyperinsulinemic-euglycemic clamp was performed with the use of an artificial endocrine pancreas (STG-22 or −55; Nikkiso, Shizuoka, Japan) as described previously[20]. In brief, to achieve a blood glucose level of 90 mg/dL, we injected human regular insulin intravenously at a rate of 40 mU/m^2/min. The insulin sensitivity index (ISI) was obtained as: 100 × (mean glucose infusion rate [GIR] over the last 30 of the 120 min of the clamp [mg/kg/min])/(plasma glucose level at the end of the clamp [mg/dl] × serum insulin level at the end of the clamp [μU/mL]).

Metabolic parameters

The presence of hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥ 90 mmHg, or prescription of anti-hypertensive medications. HOMA-IR was calculated as fasting plasma glucose level [mg/dL] × fasting serum insulin level [μU/mL])/405 from a blood sample obtained on the glucose clamp. Other clinical information and laboratory data were collected from medical records.

Echocardiography

Echocardiography was performed for all participants by either an experienced sonographer or an experienced cardiologist with the use of an Aplio Artida, Aplio XG, Aplio 500 (Canon Medical Systems, Tochigi, Japan), or Vivid E9 (GE Medical Systems, Horton, Norway) echocardiography system. Standard LV measurements were obtained in accordance with the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[21]. The LV ejection fraction (LVEF) was evaluated by the biplane modified Simpson method. The pulse Doppler records were obtained from the apical four-chamber view at the level of the mitral valve in order to measure the peak early-diastolic mitral inflow velocity (E), the peak late-diastolic mitral inflow velocity (A), the E/A ratio, and the deceleration time. Diastolic function was assessed on the basis of the E/A ratio, which has been found to be associated with the onset of cardiac failure and the overall mortality rate[22,23].

Statistical analysis

Normality of data was evaluated with the Shapiro-Wilk test. Data are presented as the mean ± SD or the median (25–75% interquartile range) unless otherwise indicated. The relation between two variables was assessed with Pearson's correlation coefficient for normal distributions and with Spearman's rank correlation coefficient for nonnormal distributions. Natural logarithmic transformation was applied for nonnormally distributed data, and multivariate regression analysis was performed to identify potential independent predictors of cardiac function. Age, the presence of hypertension, and ISI were included as covariates. We selected age and the presence of hypertension as explanatory covariates given that both of them were prominent risk factors for asymptomatic left ventricular

dysfunction in patients with type 2 diabetes in a previous study[24]. All statistical analysis was performed with SPSS version 22.0 software. A P value of <0.05 was considered statistically significant.

RESULTS

Study subjects and their characteristics

From a total of 163 type 2 diabetic patients who underwent hyperinsulinemic-euglycemic clamp between January 2009 and March 2019, 78 and 38 patients were excluded because of the conflicting anti-diabetic medication and the absence of echocardiography data (Figure 1). From the remaining 47 patients, 13 were excluded for meeting the exclusion criteria (12 patients having concomitant diseases that might affect cardiac function and one patient taking a β blocker). Finally, 34 individuals were included in this study. The clinical parameters and laboratory data (Table 1) as well as the parameters of hyperinsulinemic-euglycemic clamp analysis and echocardiography (Table 2) of the study participants are shown.

Relation of insulin resistance and cardiac function

The relations between insulin resistance (HOMA-IR or ISI) and diastolic (E/A) or systolic (LVEF) cardiac function were investigated. In simple correlation analysis, ISI was significantly correlated with both E/A and LVEF (r = 0.480, P = 0.004, and r = 0.360, P = 0.037, respectively) (Figure 2a,b), whereas HOMA-IR was not correlated with either of these cardiac parameters (Figure 2c,d). ISI was not significantly correlated with other echocardiographic parameters including LV end-diastolic diameter (r = 0.128, P = 0.471), LV end-systolic diameter (r = 0.036, P = 0.841), interventricular septum thickness (r = –0.071, P = 0.690), LV posterior wall thickness (r = –0.042, P = 0.812), or E-wave deceleration time (r = 0.114, P = 0.520). In univariable regression analyses, age, diabetes duration, and eGFR were correlated with E/A (R = –0.653, P < 0.001, R = –0. 556, P < 0.002, and R = 0.435, P = 0.001), while BMI was correlated with LVEF (R = –0.465, P = 0.006) (Table S1). Multivariate linear regression analysis in which age,

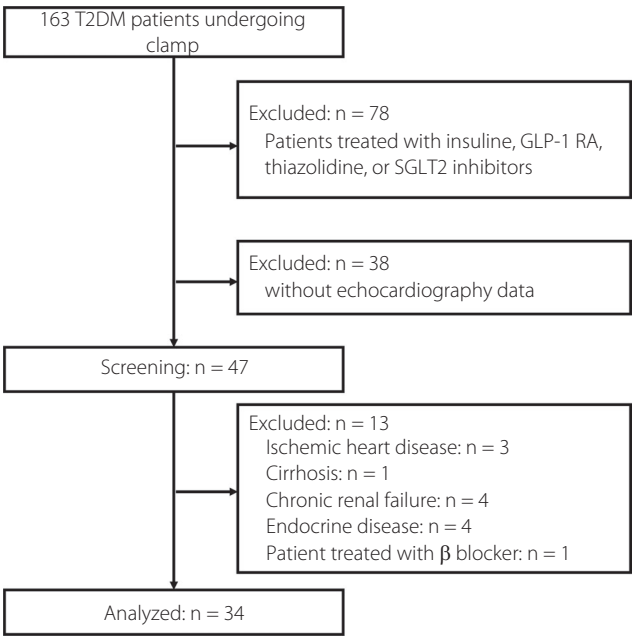

Figure 1 | Flow diagram of participant recruitment.

Table 1 | Clinical characteristics, laboratory data, and concurrent medications of the study participants (n = 34)

Clinical characteristics	
Male, *n* [%]	22 [64.7%]
Age (years)	54.5 ± 15.5
Body mass index (kg/m^2)	25.4 ± 4.8
Systolic blood pressure (mmHg)	123.4 ± 15.6
Diastolic blood pressure (mmHg)	70.4 ± 10.4
Heart rate (bpm)	73.5 ± 9.0
Duration of type 2 diabetes (years)	3.0 [1.0–10.0]
Family history of type 2 diabetes, *n* [%]	21 [61.8%]
Hypertension, *n* [%]	11 [32.4%]
Dyslipidemia, *n* [%]	14 [41.2%]
Smoker, *n* [%]	17 [50.0%]
Laboratory data	
Creatinine (mg/dL)	0.72 ± 0.18
eGFR (mL min^{-1} 1.73 m^{-2})	86.3 ± 22.0
Aspartate aminotransferase (U/mL)	21.5 [17.0–31.0]
Alanine aminotransferase (U/mL)	25.0 [17.0–41.0]
LDL-cholesterol (mg/dL)	105.6 ± 33.4
HDL-cholesterol (mg/dL)	43.5 [36.0–52.0]
Triglyceride (mg/dL)	144.0 [119.0–211.0]
Total cholesterol (mg/dL)	163.0 [147.0–206.0]
HbA_{1c} (%): on admission day	8.3 [6.9–9.5]
Fasting plasma glucose (mg/dL)	101.9 ± 18.1
Fasting immunoreactive insulin (μU/mL)	5.0 [3.8-9.3]
HOMA-IR	1.44 [0.97–2.07]
HOMA-β	62.8 [40.0–92.9]
Concurrent medications	
Metformin, *n* [%]	30 [88.2%]
DPP-4 inhibitor, *n* [%]	17 [50.0%]
Alpha-glucosidase inhibitor, *n* [%]	7 [20.6%]
Sulfonylurea, *n* [%]	4 [11.8%]
Glinide, *n* [%]	0 [0%]
ACE inhibitor or ARB, *n* [%]	9 [26.5%]
Calcium antagonist, *n* [%]	4 [11.8%]
Alpha-blocker, *n* [%]	0 [0%]
Diuretic, *n* [%]	0 [0%]
Statin, *n* [%]	14 [41.2%]

Data are presented as *n* [%], mean ± SD, or median [25–75% interquartile range]. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LDL, low density lipoprotein.

Table 2 | Glucose clamp and echocardiographic data for the study participants (n = 34)

Glucose clamp data	
GIR (mg/kg/min)	6.7 ± 2.2
ISI	0.072 ± 0.028
Echocardiographic data	
LV end-diastolic diameter (mm)	45.6 ± 5.7
LV end-systolic diameter (mm)	28.7 ± 5.1
Interventricular septum thickness (mm)	9.50 ± 1.55
LV posterior wall thickness (mm)	9.76 ± 1.18
E (cm/s)	59.2 ± 14.4
A (cm/s)	65.1 ± 16.2
E/A ratio	0.97 [0.77–1.17]
E-wave deceleration time (ms)	228.7 ± 59.1
LV ejection fraction (%)	65.8 ± 3.7

Data are the mean ± SD or median [25–75% interquartile range]. A, peak late-diastolic mitral inflow velocity; E, peak early-diastolic mitral inflow velocity; GIR, glucose infusion rate; ISI, insulin sensitivity index; LV, left ventricular.

Table 3 | Multivariable analyses with cardiac function

	Log (E/A)	LVEF
Age	−0.015 ± 0.003	0.086 ± 0.038
	P < 0.001*	P = 0.030*
HT	−0.072 ± 0.097	−1.745 ± 1.202
	P = 0.463	P = 0.157
ISI	387.9 ± 171.2	4414.1 ± 2112.6
	P = 0.031*	P = 0.045*

Data are shown β ± SE. A, peak late-diastolic mitral inflow velocity; E, peak early-diastolic mitral inflow velocity; HT, hypertension; ISI, insulin sensitivity index; LVEF, left ventricular ejection fraction; SE, standard error. *P < 0.05.

the presence of hypertension and ISI are assigned to covariates revealed that ISI was an independent predictor both for log [E/A] (P = 0.031) and LVEF (P = 0.045) (Table 3). Younger age was also independently correlated with greater log [E/A] (P < 0.001) and LVEF (P = 0.030).

DISCUSSION

We have here shown that insulin resistance as evaluated by the hyperinsulinemic-euglycemic clamp, but not by HOMA-IR, was inversely correlated with both LV diastolic and systolic function in individuals with type 2 diabetes. Multivariate analysis revealed that a high ISI was predictive of both a high E/A and a high LVEF after adjusting by the age and the presence of hypertension. Whereas one small study showed a correlation between LV diastolic function and insulin sensitivity determined by the clamp method[25], this previous study neither examined LV systolic function nor adjusted relevant cofounders. Our study is thus the first to demonstrate a relation between insulin sensitivity and both LV diastolic and systolic function with the use of glucose clamp analysis in subjects with type 2 diabetes.

We found that HOMA-IR was not correlated with cardiac function, even though it has previously been shown to be correlated with diastolic[5–9] and systolic[10] function. Although the differences between our findings and those of these previous studies may be due to the small sample size of our study or to the differences in ethnicity of the study participants, they may also be attributable to the inadequacy of HOMA-IR as a

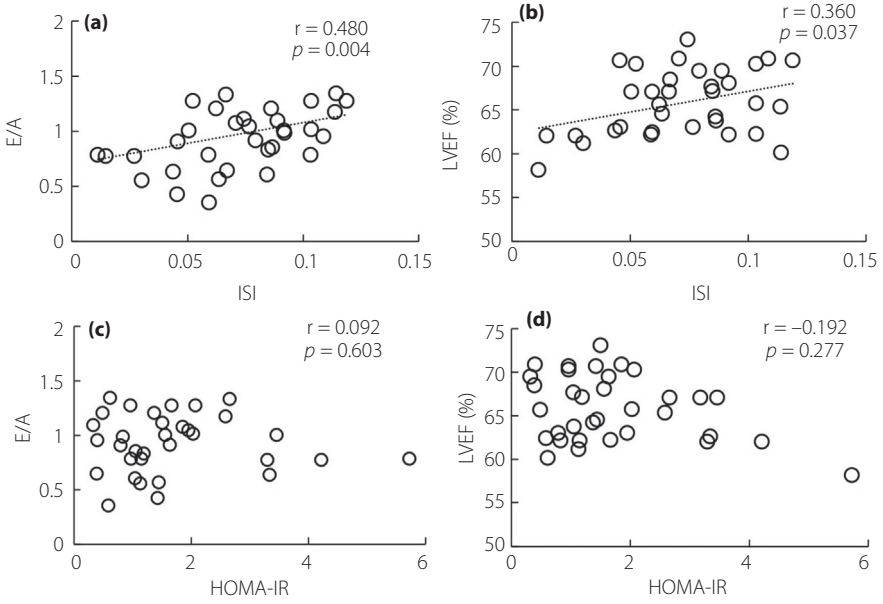

Figure 2 | Correlation analysis for ISI and either E/A (a) or LVEF (b) as well as for HOMA-IR and either E/A (c) or LVEF (d).

parameter reflecting insulin resistance. One of the assumptions of HOMA-IR is that fasting glucose and insulin concentrations reflect the normal insulin secretary response[26]. Although this readily calculated index is well correlated with the clamp-derived ISI in individuals with normal glucose tolerance, it has limitations for evaluation of insulin resistance in those with a lower body mass index, a lower β-cell function, or a higher fasting glucose level[27]. Indeed, the relation between HOMA-IR and the clamp-derived index in individuals with impaired glucose tolerance was weaker than that apparent in those with normal glucose tolerance[28]. HOMA-IR is thus not appropriate as a measure of insulin resistance in persons with established type 2 diabetes[11,12].

Several mechanisms for how insulin resistance might give rise to cardiac dysfunction, or diabetic cardiomyopathy, have been proposed. Insulin resistance impairs glucose disposal in the myocardium by inducing a switch in energy substrate from glucose to free fatty acids. This change in energy substrate requires a greater oxygen consumption to generate ATP by β-oxidation, resulting in an increased generation of reactive oxygen species and a concomitant decrease in the efficiency of energy transduction for contraction of the myocardium[29,30] In addition, several lipid metabolites, such as ceramide and diacylglycerol, whose abundance is increased in the insulin-resistant state show myocardial toxicity and may induce myocardial dysfunction, apoptosis, and fibrosis[31,32]. Moreover, insulin resistance has been shown to promote myocardial fibrosis by stimulating fibrous tissue deposition and extracellular matrix synthesis in a manner dependent on the overexpression of transforming growth factor–β1[33]. In addition to insulin resistance, the development of diabetic cardiomyopathy has been attributed to various factors such as persistent hyperglycemia, cardiac autonomic abnormalities, changes in the renin–angiotensin–aldosterone system, and oxidative stress[3,4,34]. Further studies are thus necessary to clarify the detailed mechanisms underpinning the development of this condition.

Limitations of our study include its retrospective nature, cross-sectional design, and relatively small sample size. Given that this is a retrospective study, we did not calculate the sample size and statistical power before the initiation of the study. Post-hoc analyses, however, revealed that the statistical power of the correlation between ISI and E/A ($r = 0.48$, $n = 34$) was 0.9 whereas that between ISI and LVEF ($r = 0.36$, $n = 34$) was 0.68. The evaluation of diastolic function with E/A, which we utilized in this study, sometimes leads to 'pseudo-normal', in particular, in the evaluation for elderly subjects. LV diastolic function is graded by a combination of parameters including the LA volume index, TR velocity, E/e', and E/A[35]. It is intriguing to investigate whether the clinical grade determined by those parameters is related to insulin resistance.

In conclusion, our study is the first to suggest that insulin resistance as evaluated by glucose clamp analysis is associated with LV diastolic and systolic dysfunction in individuals with type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Univariate regression analysis between the cardiac function and the related factors (n = 34)