Patients With Dilated Cardiomyopathy Possess Insulin Resistance Independently of Cardiac Dysfunction or Serum Tumor Necrosis Factor-α

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SUMMARY

It has recently been reported that insulin resistance is prevalent in patients with dilated cardiomyopathy (DCM); however, it remains unclear whether insulin resistance is directly induced by DCM or if it is caused by congestive heart failure associated with DCM. We evaluated homeostasis model assessment insulin resistance (HOMA-R) in 14 patients with DCM in comparison with 9 patients with valvular heart diseases (VHD). We also measured the level of serum tumor necrosis factor (TNF-α) as a possible causative factor for inducing insulin resistance. Even after the adjustment for age, body mass index, and cardiac function, HOMA-R was significantly higher in patients with DCM than in those with VHD (\(P = 0.012\)) (mean ± SEM: 3.51 ± 0.59, and 0.80 ± 0.64, respectively). The serum TNF-α level tended to be higher in patients with DCM than in those with VHD; however, the difference was not significant. In conclusion, patients with DCM possess insulin resistance independently of the severity of cardiac dysfunction or serum TNF-α, suggesting that insulin resistance in patients with DCM may be closely associated with the pathogenic condition of DCM itself. (Int Heart J 2006; 47: 877-887)

Key words: Dilated cardiomyopathy, Heart failure, Insulin resistance, TNF-α

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilation and impaired contractility with intact coronary arteries. Patients with DCM suffer from congestive heart failure (CHF), lethal ventricular arrhythmias, and cardiogenic thromboembolism.1) On the other hand, insulin resistance is relatively unnoticed as a complication of DCM.2-4) Insulin resistance is frequently observed in patients with CHF with various etiologies.5,6) In the case of valvular heart diseases (VHD), accumulating evidence suggests that insulin resistance is a prog-
nostic factor and is related to the severity of CHF. However, it is not clear whether insulin resistance is directly associated with DCM or whether it is the consequence of CHF due to DCM. In addition, tumor necrosis factor (TNF-α), a well known cardioinhibitory and proinflammatory cytokine, may also play an important role in the pathogenesis of DCM, as well as in the other heart diseases predisposing CHF.

Therefore, the aim of this study was to clarify whether insulin resistance is directly associated with DCM per se or ascribed to CHF observed in DCM. For this purpose, we studied patients with DCM using a convenient insulin resistance marker, homeostasis model assessment resistance (HOMA-R), in comparison with not only the healthy controls but also patients with VHD who presented with cardiac dysfunction. We also measured serum TNF-α levels as a possible causative factor for inducing systemic insulin resistance as well as showing negative inotropic actions.

**METHODS**

*Subjects:* We enrolled 14 patients with DCM (9 men and 5 women; mean age, 57.9 ± 10.3 years; range, 43-75 years old) and 9 patients with VHD (7 men and 2 women; mean age, 66.4 ± 6.5 years; range, 57-76 years old) in the study. All patients were being treated at the outpatient clinic of the Department of Internal Medicine, Kyushu University Hospital. The clinical diagnosis of DCM was based on the criteria of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. All patients underwent coronary angiography, and those with coronary artery disease were excluded. Patients with specific cardiomyopathies caused by any metabolic or nutritional disorders or infectious diseases, such as viral myocarditis, were also excluded. One patient was excluded since his cardiac dysfunction was caused by hypertrophic cardiomyopathy in the dilated phase.

Among the patients with VHD, 4 had mitral regurgitation, 2 had aortic regurgitation, 1 had tricuspid regurgitation, and 2 had combined mitral and tricuspid regurgitation. At the time of study, the clinical condition was stable in all patients.

Among the DCM patients, 4 patients had been treated for diabetes mellitus at the time of the examination. Two patients had been treated with sulfonylurea drugs (one with glibenclamide and another with glimepiride). One patient had been treated with metformin, and two patients had been treated with voglibose. No patient had been treated with insulin or thiazolidinediones at the time of the examination. On the other hand, among the VHD patients, only one patient had
been treated for diabetes mellitus with a sulfonylurea drug (glibenclamide).

The severity of CHF was assessed according to the New York Heart Association (NYHA) functional classification. To assess cardiac function, transthoracic echocardiography (SONOS 5500, Phillips Medical Systems Co Bothel, WA, USA) was performed by experienced medical staff.

Healthy controls. Subjects who were admitted to the Hamanomachi Medical Health Center (Fukuoka, Japan) for a medical checkup were recruited as healthy controls. All underwent noninvasive cardiac examinations and an oral glucose tolerance test. Subjects with impaired glucose tolerance/diabetes mellitus or any cardiac symptoms were excluded from the study. Normal glucose tolerance was defined as a fasting blood glucose level of less than 6.1 mmol/L and a glucose level obtained 2 hours after the oral glucose administration of less than 7.8 mmol/L. The exercise loading electrocardiogram (ECG) test was performed to confirm normal performance status and to exclude coronary artery disease. Nine men and 6 women (mean age, 62.2 ± 8.0 years; range, 43-76 years old) showing normal glucose tolerance and normal cardiac function were eligible for enrollment in the control group.

All participants were questioned about smoking status, exercise habits, and medication that could affect insulin resistance. Immediately before commencement of the study, written informed consent was obtained from all participants. This study was conducted in accordance with the guidelines for experimentation on human beings and was approved by the Ethical Committee of Kyushu University.

Medical examination: The height and body weight of all participants were measured to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as body weight (kg) divided by height in meters square (m²). Following one night of fasting, blood samples were collected from an antecubital vein. The fasting blood sugar (FBS) concentration was measured by the hexokinase/glucose-6-phosphate dehydrogenase (HK-G6PDH) method (Shinotest, Tokyo). Serum insulin concentration was measured by immunoradiometric assay (Dinabot, Tokyo). Insulin resistance estimated by HOMA-R was calculated by using the following formula.\(^{15}\)

\[
\text{HOMA-R} = \frac{\text{FBS (mmol/L)} \times \text{fasting serum insulin (} \mu \text{U/mL)}}{22.5}
\]

In order to determine the serum TNF-\(\alpha\) level, blood samples were centrifuged immediately after collection at 4°C and stored at -80°C until measurement. The serum concentration of TNF-\(\alpha\) was measured by enzyme-linked immunosorbent assay (BML, Tokyo). The interassay coefficient of variation was 2.0%-3.2% and the intraassay coefficient of variation was 2.1%-5.9%.

Statistical analysis: The data were analyzed using SPSS 12.0 J for Windows (SPSS Japan, Tokyo). Analysis of variance (ANOVA) and analysis of covariance
(ANCOVA) were performed to compare the DCM, VHD, and control groups. Since the HOMA-R and TNF-α values showed a skewed distribution, they were transformed to a natural logarithm for statistical analysis and then back transformed for presentation. Fisher's exact test was performed for comparisons of categorical values. Pearson's correlation coefficients were used to assess the correlations between continuous variables, and Spearman's rank correlation coefficients were used for categorical variables. Statistical significance was accepted when $P$ was less than 0.05.

**RESULTS**

The characteristics of all subjects are shown in Table I. The DCM patients had higher FBS and HOMA-R values than the healthy control subjects. Although the FBS level in the DCM group was not significantly different from that in the VHD group, the fasting serum insulin level and HOMA-R were significantly greater in the DCM group than in the VHD group. In comparison with the VHD patients, the DCM patients were younger and had a lower left ventricular ejection fraction (LVEF). Angiotensin-converting enzyme (ACE) inhibitors were administered more frequently in the DCM patients than in the VHD patients (11/14 and 2/9, respectively; $P = 0.013$). No patient was administered thiazolidinediones. There was no significant difference between the 2 patient groups with respect to the administration of other medicines such as digitalis, furosemide, β-blockers, Ca-antagonists, warfarin, nitrate compounds, biguanides, and sulfonylureas. The prevalence of smoking was not significantly different between the 2 patient groups and healthy controls.

<table>
<thead>
<tr>
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<th>Control ($n=15$)</th>
<th>VHD ($n=9$)</th>
<th>DCM ($n=14$)</th>
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<tr>
<td>Men/Women$^a$</td>
<td>9/6</td>
<td>7/2</td>
<td>9/5</td>
</tr>
<tr>
<td>Mean age (years)$^b$</td>
<td>62.2 ± 1.9</td>
<td>66.4 ± 2.5*</td>
<td>57.9 ± 2.0</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)$^b$</td>
<td>23.6 ± 0.7</td>
<td>21.3 ± 0.9</td>
<td>23.4 ± 0.7</td>
</tr>
<tr>
<td>Diabetes mellitus$^a$</td>
<td>-</td>
<td>2/9</td>
<td>7/14</td>
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<tr>
<td>NYHA (I/II/III)$^a$</td>
<td>-</td>
<td>3/5/1</td>
<td>2/7/5</td>
</tr>
<tr>
<td>LVEF (%)$^b$</td>
<td>NA</td>
<td>64.9 ± 4.7***</td>
<td>34.9 ± 3.8</td>
</tr>
<tr>
<td>FBS (mmol/L)$^b$</td>
<td>5.1 ± 0.4**</td>
<td>5.9 ± 0.5</td>
<td>6.7 ± 0.4</td>
</tr>
<tr>
<td>Insulin (µU/L)$^b$</td>
<td>6.8 ± 1.5*</td>
<td>5.3 ± 2.0*</td>
<td>11.5 ± 1.6</td>
</tr>
<tr>
<td>HOMA-R$^{b,c}$</td>
<td>1.52 ± 0.51**</td>
<td>1.47 ± 0.66**</td>
<td>3.54 ± 0.53</td>
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</table>

Values are mean ± SEM BMI indicates body mass index; DCM, dilated cardiomyopathy; FBS, fasting blood sugar; HOMA-R, homeostasis model assessment insulin resistance; LVEF, left ventricular ejection fraction; and VHD, valvular heart disease. Fisher's exact test$^a$ and analysis of variance (ANOVA)$^b$ were used under log-transformation for analysis$^c$. * $P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus DCM.
After adjustment for age and BMI (Figure 1), the DCM patients also had significantly higher FBS, insulin and HOMA-R than the healthy control subjects. In addition, the DCM patients had higher serum insulin and HOMA-R than the VHD patients.

Figure 2 shows the correlation between HOMA-R and NYHA classification. Spearman's rank correlation was 0.42 ($P = 0.04$) for all patients, 0.45 ($P = 0.23$) for the DCM patients, and 0.38 ($P = 0.32$) for the VHD patients. The parameters of cardiac function assessed by means of echocardiography (ie, LVEF and left ventricular systolic/diastolic diameters) had no significant correlation with HOMA-R.

To clarify the specificity of insulin resistance in the DCM patients, further analysis was confined to the patients with relatively mild cardiac dysfunction, ie, those with NYHA class I and II (Table II). The DCM patients showed higher serum insulin levels ($P = 0.049$) and HOMA-R ($P = 0.040$) than the VHD patients. After adjustment for age, BMI, and LVEF, almost the same results were obtained (HOMA-R: for DCM, $3.51 \pm 0.59$ and for VHD, $0.80 \pm 0.64$; $P = 0.012$).

We further investigated the contribution of serum TNF-α to the difference in the insulin resistance observed among the patients with DCM and VHD. Table III shows the comparison of TNF-α between the 2 patient groups. The level of TNF-α was slightly higher in the DCM patients than in the VHD patients (19.7 ±
Figure 2. Correlation between NYHA classification and HOMA-R. Spearman's rank correlation coefficient is 0.42 ($P = 0.04, n = 23$). DCM indicates dilated cardiomyopathy; HOMA-R, homeostasis model assessment insulin resistance; and VHD, valvular heart disease.

Table II. Characteristics of Patients in NYHA Class I and II

<table>
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<tr>
<th></th>
<th>VHD ($n = 8$)</th>
<th>DCM ($n = 9$)</th>
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<tr>
<td>Men/Women</td>
<td>7/1</td>
<td>8/1</td>
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<tr>
<td>Age (years)</td>
<td>65.8 ± 2.7*</td>
<td>55.2 ± 2.6</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.1 ± 0.9</td>
<td>22.9 ± 0.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1/8</td>
<td>5/9</td>
</tr>
<tr>
<td>NYHA (I/II)</td>
<td>3/5</td>
<td>2/7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>64.8 ± 4.1**</td>
<td>37.1 ± 5.6</td>
</tr>
<tr>
<td>FBS (mmol/L)</td>
<td>5.7 ± 0.7</td>
<td>7.1 ± 0.6</td>
</tr>
<tr>
<td>Insulin (µU/L)</td>
<td>4.8 ± 1.6*</td>
<td>9.4 ± 1.5</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>1.27 ± 0.59*</td>
<td>3.09 ± 0.55</td>
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</table>

Values are mean ± SEM BMI indicates body mass index; DCM, dilated cardiomyopathy; FBS, fasting blood sugar; HOMA-R, homeostasis model assessment insulin resistance; LVEF, left ventricular ejection fraction; and VHD, valvular heart disease. Fisher's exact test and analysis of variance (ANOVA) were used under log-transformation for analysis. *$P < 0.05$, **$P < 0.01$ versus DCM.
Figure 3. Correlation between TNF-α and HOMA-R. Pearson's correlation coefficient is 0.35 ($P = 0.098$, $n = 23$). DCM indicates dilated cardiomyopathy; HOMA-R, homeostasis model assessment insulin resistance; TNF-α, tumor necrosis factor alpha; and VHD, valvular heart disease.

<table>
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<th>Table III. Serum Concentration of TNF-α</th>
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<tr>
<td>TNF-α (pg/mL)</td>
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<tr>
<td>Adjusted for age and BMI</td>
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</table>

Values are mean ± SEM and log transformed for analysis. BMI indicates body mass index; DCM, dilated cardiomyopathy; and VHD, valvular heart disease.

2.1 and 15.4 ± 2.7 pg/mL, respectively), although the difference was not significant ($P = 0.46$), even after adjustment for age and BMI ($P = 0.35$).

Figure 3 shows the correlation between serum TNF-α level and HOMA-R. Pearson's correlation coefficient was 0.35 ($P = 0.098$) for all patients, 0.30 ($P = 0.29$) for the DCM patients, and 0.27 ($P = 0.36$) for the VHD patients.
DISCUSSION

Insulin resistance is frequently observed in CHF with various etiologies, and CHF per se is known as a predictor of diabetes mellitus. In particular, recent studies have reported a high prevalence of insulin resistance in patients with DCM or animal models of DCM. However, these reports did not indicate whether insulin resistance is proportional to the severity of CHF. In addition, the cause of insulin resistance in patients with DCM has not been clarified.

In the present study, we compared the patients with DCM not only with healthy people but also with patients with cardiac disease other than DCM. In this setting, patients with ischemic heart disease (IHD) were carefully excluded because of the potential insulin resistance in IHD. We recruited VHD patients with a NYHA classification comparable to that of patients with DCM. Thus, we attempted to clarify the causal relationship between DCM and insulin resistance by comparing the insulin resistance level of DCM with that of VHD. This kind of dual controlled study design is important for the purpose of this study.

Even after adjustment for age, BMI, and cardiac function, the DCM patients showed higher HOMA-R than the VHD patients (Table II). Cardiovascular agents, such as ACE inhibitors, α₁-blockers or β-blockers, are reported to improve insulin sensitivity. In the present study, no significant differences were observed with respect to the use of cardiovascular drugs between the 2 patient groups, with the exception of ACE inhibitors, which were administered more frequently to the DCM patients than the VHD patients. Although adjustment for drug administration was not conducted in this study, such adjustment would have more clearly indicated the prevalence of insulin resistance in the DCM patients. HOMA-R has been used as a simple but clinically useful and reliable parameter; our findings are consistent with those from a recent study in which a more accurate but complicated evaluation of insulin resistance was performed. Thus, our results have provided additional evidence for insulin resistance in patients with DCM. In population-based studies, insulin resistance and the associated metabolic disorders precede the cardiac dysfunction and vice versa. These epidemiologic studies suggest that improvements in insulin sensitivity and glycemic control may be a new therapeutic or preventive strategy for the management of CHF, including DCM.

Although the mechanisms underlying insulin resistance in patients with DCM remain to be studied, one possible explanation is reduced LVEF leading to the impaired peripheral circulation and the subsequent poor distribution of glucose to the skeletal muscle. However, in the present study, no significant correlation was observed between HOMA-R and LVEF in all patients enrolled. After adjustment for LVEF, the insulin resistance was greater in the selected patients.
with DCM relative to those with VHD. These observations indicate that cardiac dysfunction is unlikely to be a primary cause of insulin resistance in DCM.

Initially, we hypothesized that serum TNF-α could be a causative factor of insulin resistance in DCM. TNF-α is regarded as one of the key cytokines causing insulin resistance in obese or diabetic patients. Additionally, this cytokine is involved in the pathogenesis of CHF of various etiologies. Although the contribution of TNF-α to the insulin resistance in the DCM patients was not evident in the present study due in part to the limited number of patients (Figure 3), serum TNF-α levels in the DCM group were slightly higher than those in the VHD group (Table III). Levine, et al. have reported elevated circulating levels of TNF-α in CHF, and this level is proportional to the severity of CHF. Recently, Sutsota, et al. also have reported higher serum levels of TNF-α in CHF patients with NYHA class III and IV than in those with NYHA class II. Torre-Amione, et al. have reported that TNF-α is expressed in the failing human heart, which is related to the elevated circulating level of TNF-α in the end stage CHF. Tsutamoto, et al. have also demonstrated that the transcardiac increase in TNF-α is related to the hemodynamics of DCM. Though we excluded one patient with dilated-phase hypertrophic cardiomyopathy (DHCM) in the present study, Zen, et al. have reported elevated levels of TNF-α in DHCM patients and suggested a possible detrimental effect of TNF-α in HCM patients. This line of evidence implies that TNF-α provides a possible etiologic link between the insulin resistance and CHF in patients with DCM.

From a genetic perspective, there has been accumulating evidence for the genomic anomaly in a large number of patients with familial DCM, ie, inherited gene defects are involved in 20%-35% of patients with DCM. Therefore, there may be unknown genetic factors that could explain the coexistence of DCM and insulin resistance, at least in a small fraction of patients with DCM.

**Conclusions:** We have demonstrated the characteristic existence of insulin resistance in patients with DCM, which is independent of cardiac dysfunction or the serum TNF-α level. Our findings will contribute to clarifying the pathogenesis of DCM and to treating patients with DCM.

**ACKNOWLEDGEMENT**

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**REFERENCES**


