

Original Article

Clinical indicator analysis for myocardial injury induced by type 2 diabetes mellitus

Dan Liu^{1*}, Yu Yang^{1*}, Xinxin Bu², Jinrin Wang³, Jianling Du¹

¹Department of Endocrinology, The First Affiliated Hospital of Dalian Medical University, Dalian 116011, Liaoning, China; ²Department of Endocrinology, Jiangsu Province Hospital, Nanjing 210029, China; ³Department of Endocrinology, Shanghai Oriental Hospital, Shanghai 200120, China. *Equal contributors.

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Abstract: This study aimed to investigate the clinical indicators of myocardial injury induced by type 2 diabetes mellitus (T2DM). The study includes 23 patients with T2DM, also having myocardial injury, identified as the illness group (IG), and 46 T2DM patients, randomly assigned to the control group (CG). The IG was subdivided into the dysfunctional myocardial contraction group (DCG, n = 10; left ventricular ejection fraction [LVEF] < 50%) and the normal myocardial contraction group (NCG, n = 13; LVEF ≥ 50%). The disease course was independently associated with systolic dysfunction and defined as an LVEF < 50% (odds ratio [OR], 1.339; 95% confidence interval [CI], 1.032-1.737; P = 0.028). The triglyceride level was found to be an independent factor significantly associated with myocardial injury caused by T2DM (OR, 1.012; 95% CI, 1.002-1.022; P = 0.018). The thickness of the interventricular septum (IVS) was higher and the left ventricular fractional shortening was lower in patients of the DCG. The LVEF value was significantly correlated with the IVS thickness (r = -0.391, P = 0.001) and disease course (r = -0.261, P = 0.030). The disease course was a significant indicator of systolic dysfunction, indicating that along with the development of T2DM, myocardial injury exacerbates and finally leads to dysfunctional myocardial contraction. Every patient with T2DM has diastolic dysfunction to some degree, and systolic dysfunction and ventricular remodeling exist in patients with myocardial injury caused by T2DM. Elevated triglyceride levels in T2DM patients might promote the occurrence of diabetic myocardial injury.

Keywords: Diabetic, diastolic dysfunction, left ventricular ejection fraction, myocardial injury, systolic dysfunction, triglyceride

Introduction

Diabetic cardiomyopathy (DCM), which was first hypothesized by Rubler et al. in 1972 [1], is a specific cardiomyopathy that occurs in diabetic patients independent of other causes, such as hypertension or coronary artery disease [2]. Resulting from the disturbance in glucose metabolism, DCM is caused by microvascular disease and microcirculation dysfunction, as well as abnormalities in cardiac structure and function. DCM is initially characterized as diastolic dysfunction and decreased compliance, and finally as congestive heart failure [3-6], which seriously affects the quality of life and prognosis of patients with diabetes mellitus (DM).

A close correlation between diabetes mellitus (DM) and heart failure has been demonstrated

in many studies [7-9]. In the United Kingdom Prospective Diabetes Study, an increased prevalence of heart failure was recorded among patients with T2DM, correlating with levels of glycosylated hemoglobin (HbA1c) [5, 6]. Early diagnosis of DCM is difficult, because there is no definite criteria, and specific signs or symptoms may not appear until an advanced stage of the disease [10]. Moreover, myocardial biopsy and coronary computed tomography are not suitable for the clinical screening of DCM. Therefore, additional clinical evidence is required for the early diagnosis of DCM. The aims of this study were to compare the clinical and laboratory parameters between of T2DM patients without myocardial injury, and further investigate the clinical indicators of myocardial injury induced by T2DM.

Materials and methods

Subjects

All patients with T2DM having myocardial injury, admitted to the First Affiliated Hospital of Dalian Medical University from January 1, 2004 to December 31, 2013, were eligible for the retrospective study. Patients with T2DM who matched the previous group of patients with respect to age, sex, and disease course, and did not have acute or chronic complications, were enrolled as controls. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. Written informed consent was obtained from all participants.

Clinical and laboratory data collection

Demographic, clinical, and laboratory data collected during the hospital stay, including age, sex, disease course, and blood lipid profile, were analyzed to determine the indicators of myocardial injury induced by T2DM. Blood lipids included total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Laboratory data were collected on the day of the echocardiographic examinations.

Echocardiography

Echocardiographic images were obtained using a Philips iE Elite ultrasound machine with a 3.5 MHz multi-frequency transducer. Conventional 2-dimensional echocardiographic examination measured the thickness of the left ventricular posterior wall (LVPW), thickness of the interventricular septum (IVS), left ventricular fractional shortening (LVFS), and left ventricular ejection fraction (LVEF). Early diastolic mitral annular velocity (E) and peak velocity of mitral annular motion, during atrial contraction (A), were measured with pulsed tissue Doppler, and the E/A ratio was calculated. Three consecutive cycles were recorded.

Diagnostic criteria

The diagnosis of T2DM was based on the diagnostic criteria accepted by the World Health Organization in 1999. The diagnostic criteria

for diabetic myocardial injury were as follows: (1) T2DM; (2) cardiac dysfunction; (3) myocardial hypertrophy (LVPW thickness > 12 mm and/or IVS thickness > 12 mm); (4) exclusion of the presence or history of hypertension, myocardial infarction, presence of stable or unstable angina pectoris, congenital heart disease, myocarditis, cardiomyopathy, pericardial disease, and valvular heart disease, among others; and (5) exclusion of integral or regional ventricular wall-movement abnormality, left ventricular hypertrophy, and valvular stenosis or insufficiency by ultrasonic cardiogram. Criterion (1) was the essential criterion. Patients who met criteria (1), (4), and (5) and criterion (2) or (3) were diagnosed as having diabetic myocardial injury and assigned to the illness group (IG) [10].

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Assumptions of normality and homogeneity of variance were first checked. Normally distributed data are presented as means \pm standard deviations (SD).

For normal distribution data, the differences between the results obtained in two groups were assessed by the Student's t-test for unpaired samples. For non-normal distribution data, The Kruskal-Wallis H test was used in comparison among multiple groups and two groups. Spearman's analysis was used to examine correlations. Multivariate binary logistic regression analyses were performed to investigate the independent indicators of myocardial injury induced by T2DM. A *P* value < 0.05 was considered statistically significant.

Results

Subjects

Twenty-three T2DM patients with myocardial injury were admitted to the hospital during the study period and enrolled in the IG (*n* = 23, **Table 1**), while 46 patients with T2DM, with matched age, sex, disease course, and without acute or chronic complications, were assigned to the control group (CG, *n* = 46). Based on the LVEF value, the IG was further subdivided into the following two groups: the dysfunctional myocardial contraction group (DCG, *n* = 10;

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Table 1. Clinical data of CG, DCG and NCG

| Parameters | CG (n = 46) | IG (n = 23) | | P value |
|---------------------------|---------------|---------------|-----------------|---------|
| | | NCG (n = 13) | DCG (n = 10) | |
| Gender (m/f) | 23/23 | 8/5 | 5/5 | 0.758 |
| Age (yr) | 61.87 ± 4.03 | 60.08 ± 4.27 | 60.00 ± 6.18 | 0.395 |
| Duration of diabetes (yr) | 10.96 ± 3.95 | 10.62 ± 4.15 | 16.90 ± 6.60*.# | 0.011 |
| BMI (kg/m ²) | 25.36 ± 1.53 | 25.36 ± 2.85 | 25.39 ± 1.47 | 0.977 |
| SBP (mmHg) | 133.59 ± 5.11 | 134.31 ± 1.80 | 132.60 ± 2.63 | 0.512 |
| DBP (mmHg) | 83.61 ± 4.19 | 84.23 ± 3.47 | 86.20 ± 3.94 | 0.169 |
| FPG (mmol/L) | 9.26 ± 1.02 | 9.17 ± 1.26 | 9.57 ± 1.86 | 0.842 |
| HbA1c (%) | 8.34 ± 0.19 | 8.49 ± 0.61 | 8.64 ± 0.57 | 0.473 |

Data are mean ± SD or number. IG: illness group, CG: control group, DCG: dysfunctional myocardial contraction group, NCG: normal myocardial contraction group. *P < 0.05, compared with CG. #P < 0.05, compared with NCG. P value, The Kruskal-Wallis H test was used to analyze differences among three groups.

Table 2. Blood lipid profile of CG and IG

| Blood Lipids | CG (n = 46) | IG (n = 23) | | P value |
|---------------|----------------|-----------------|-----------------|---------|
| | | NCG (n = 13) | DCG (n = 10) | |
| TG (mg/dl) | 156.41 ± 69.04 | 207.62 ± 72.66# | 200.10 ± 75.75# | 0.016 |
| TC (mg/dl) | 205.24 ± 49.17 | 183.92 ± 46.31 | 180.00 ± 65.54 | 0.287 |
| LDL-C (mg/dl) | 122.52 ± 29.52 | 111.23 ± 27.40 | 102.10 ± 37.77 | 0.191 |
| HDL-C (mg/dl) | 52.00 ± 8.84 | 54.46 ± 14.34 | 60.50 ± 31.93 | 0.770 |

Data are mean ± SD. IG: illness group, CG: control group, DCG: dysfunctional myocardial contraction group, NCG: normal myocardial contraction group. TG: triglyceride, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol. #P < 0.05, compared with CG. There is no difference between NCG and DCG. P value, The Kruskal-Wallis H test was used to analyze differences among three groups.

49.17 mg/dL, P > 0.05), LDL-C (107.26 ± 31.85 vs. 122.52 ± 29.52 mg/dL, P > 0.05), and HDL-C (57.09 ± 23.21 vs. 52.00 ± 8.84 mg/dL, P > 0.05) levels between the IG and CG (Table 2).

There were no significant differences between the DCG and NCG in the TG (207.62 ± 72.66 vs. 200.10 ± 75.75 mg/dL, P > 0.05), TC (180.00 ± 65.54 vs.

183.92 ± 46.31 mg/dL, P > 0.05), LDL-C (102.10 ± 37.77 vs. 111.23 ± 27.40 mg/dL, P > 0.05), and HDL-C (60.50 ± 31.93 vs. 54.46 ± 14.34 mg/dL, P > 0.05) levels (Table 2).

Echocardiography data of the CG, DCG, and NCG

IVS thickness (10.65 ± 1.72 vs. 9.52 ± 1.64 mm, P < 0.05), LVEF (49.26 ± 12.45 vs. 59.59 ± 3.75%, P < 0.05), LVFS (28.35 ± 6.38 vs. 33.80 ± 1.49%, P < 0.05), and the E/A ration (0.85 ± 0.13 vs. 0.92 ± 0.10, P < 0.05) were significantly different between the IG and CG. There was no significant difference in the LVPW thickness (11.30 ± 2.32 vs. 10.22 ± 1.35 mm, P = 0.136) between the IG and CG (Table 3).

The LVEF (36.40 ± 7.01% vs. 59.59 ± 3.75%, P < 0.05) and LVFS (21.55 ± 2.75% vs. 33.80 ± 1.49%, P < 0.05) were significantly lower in the DCG than in the CG. However, the IVS thickness (11.60 ± 1.78 vs. 9.52 ± 1.64 mm, P < 0.05) was higher in the DCG than in the CG. There

LVEF < 50%) and normal myocardial contraction group (NCG, n = 13, LVEF ≥ 50%) [10].

Clinical data of the CG, DCG, and NCG

There were no significant differences between the IG and CG in terms of age, sex, duration of diabetes, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG) level, and HbA1c level (Table 1).

The duration of diabetes was significantly longer in the DCG than in the NCG (16.90 ± 6.60 vs. 10.62 ± 4.15 years, P < 0.05). There were no differences between the DCG and NCG in terms of age, sex, BMI, SBP, DBP, FPG level, and HbA1c level (Table 1).

Lipid metabolism in the CG, DCG, and NCG

The TG levels were significantly higher in the IG than in the CG (204.35 ± 72.39 vs. 156.41 ± 69.04 mg/dL, P < 0.05). There were no differences in the TC (182.21 ± 54.13 vs. 205.24 ±

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Table 3. Echocardiographic data of CG, IG

| Group | E/A | LVPW (mm) | IVS (mm) | LVEF (%) | LVFS (%) |
|-------------|-------------|--------------|--------------|---------------|--------------|
| CG (n = 46) | 0.92 ± 0.10 | 10.22 ± 1.35 | 9.52 ± 1.64 | 59.59 ± 3.75 | 33.80 ± 1.49 |
| IG (n = 23) | 0.85 ± 0.13 | 11.30 ± 2.32 | 10.65 ± 1.72 | 49.26 ± 12.45 | 28.35 ± 6.38 |
| P value | 0.013 | 0.136 | 0.019 | 0.001 | 0.001 |

Data are mean ± SD. IG: illness group, CG: control group. LVPW: left ventricular posterior wall, IVS: interventricular septal, LVFS: left ventricular fractional shortening, LVEF: left ventricula ejection fraction, E/A: early diastolic mitral annular velocity (E)/peak velocity of mitral annular motion during atrial contraction (A).

Table 4. Echocardiographic data of CG, DCG and NCG

| Parameters | CG (n = 46) | IG (n = 23) | | P value |
|------------|--------------|--------------|----------------------------|---------|
| | | NCG (n = 13) | DCG (n = 10) | |
| LVPW (mm) | 10.22 ± 1.35 | 10.92 ± 2.36 | 11.80 ± 2.30 | 0.171 |
| IVS (mm) | 9.52 ± 1.64 | 9.92 ± 1.32 | 11.60 ± 1.78* [#] | 0.009 |
| LVFS (%) | 33.80 ± 1.49 | 33.58 ± 0.89 | 21.55 ± 2.75* [#] | 0.000 |
| E/A ratio | 0.92 ± 0.10 | 0.89 ± 0.11 | 0.79 ± 0.13 [#] | 0.014 |
| LVEF (%) | 59.59 ± 3.75 | 59.15 ± 1.77 | 36.40 ± 7.01* [#] | 0.000 |

Data are mean ± SD. DCG: dysfunctional myocardial contraction group, NCG: normal myocardial contraction group, LVPW: left ventricular posterior wall, IVS: interventricular septal, LVFS: left ventricular fractional shortening, LVEF: left ventricula ejection fraction, E/A: early diastolic mitral annular velocity (E)/peak velocity of mitral annular motion during atrial contraction (A). **P* < 0.05, compared with CG. [#]*P* < 0.05, compared with NCG. *P* value, The Kruskal-Wallis H test was used to analyze differences among three groups.

was a significant difference in the E/A ratio between the DCG and CG (0.79 ± 0.13 vs. 0.92 ± 0.10, *P* < 0.05), and the E/A ratios were below the normal level in both the DCG and CG (Table 4).

The LVEF (36.40 ± 7.10% vs. 59.15 ± 1.77%, *P* < 0.05) and LVFS (21.55 ± 2.75% vs. 33.58 ± 0.89%, *P* < 0.05) were also lower in the DCG than in the NCG. The IVS thickness (11.60 ± 1.78 vs. 9.92 ± 1.32 mm, *P* < 0.05) was higher in the DCG than in the NCG. There were no significant differences in the LVPW thickness and E/A ratio between the DCG and NCG (Table 4).

In addition, Spearman's analysis showed that the LVEF was significantly correlated with the IVS thickness (*r* = -0.391, *P* = 0.001) and disease course (*r* = -0.261, *P* = 0.030) (Figure 1).

Determination of clinical indicators associated with myocardial injury

Clinical and laboratory variables, including age, sex, duration of diabetes, SBP, DBP, BMI; and TG, TC, LDL-C, HDL-C, FPG; and HbA1c levels were entered into a multivariate binary logistic regression. The TG level was identified as an independent factor, significantly associated with myocardial injury caused by T2DM (OR, 1.012; 95% CI, 1.002-1.022; *P* = 0.018). The disease course was independently associated with systolic dysfunction, defined as an LVEF < 50% (OR, 1.339; 95% CI, 1.032-1.737; *P* = 0.028) (Tables 5 and 6).

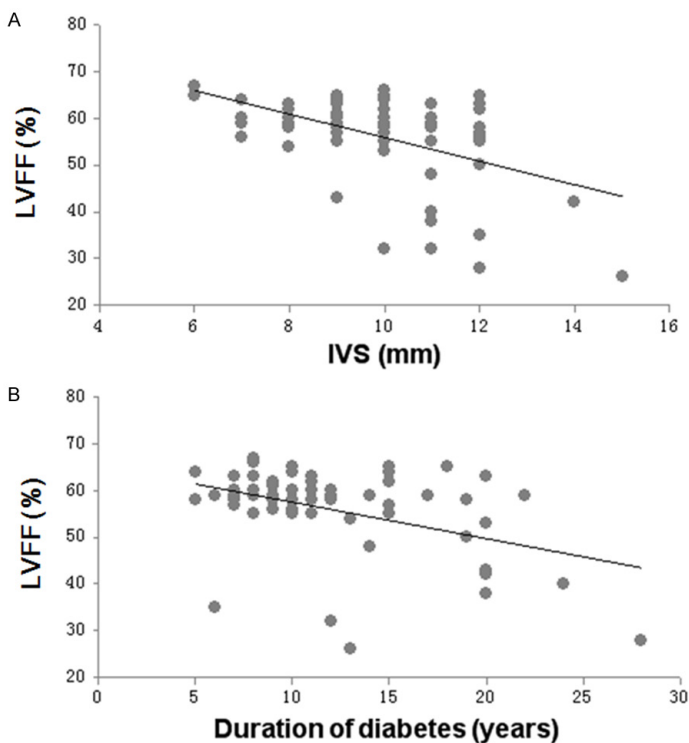


Figure 1. Results of spearman's correlation analysis. There was a significant correlation between the LVFF and the thickness of IVS (A) and between the LVFF and the duration of diabetes (B). LVFF: left ventricula ejection fraction; IVS: interventricular septal. *r* = Spearman's correlation coefficient.

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Table 5. Multivariate logistic regression analysis of clinical and laboratory variables associated with myocardial injury

| | OR | 95% CI | P |
|---------------------------|-------|-------------|-------|
| Gender | 0.526 | 0.143-1.929 | 0.332 |
| Age (yr) | 0.895 | 0.770-1.042 | 0.153 |
| Duration of diabetes (yr) | 1.065 | 0.924-1.228 | 0.384 |
| TG (mg/dl) | 1.012 | 1.002-1.022 | 0.018 |
| TC (mg/dl) | 0.993 | 0.973-1.013 | 0.487 |
| LDL-C (mg/dl) | 0.986 | 0.954-1.020 | 0.416 |
| BMI (kg/m ²) | 1.040 | 0.733-1.473 | 0.828 |
| SBP (mmHg) | 0.981 | 0.840-1.145 | 0.809 |
| DBP (mmHg) | 1.115 | 0.926-1.341 | 0.250 |
| FPG (mmol/L) | 1.298 | 0.713-2.362 | 0.393 |
| HbA1c (%) | 1.442 | 0.665-3.129 | 0.354 |

Clinical and laboratory variables included age, gender, duration of diabetes, TG, TC, LDL-C, BMI, SBP, DBP, FPG and HbA1c. OR, odds ratio; CI, confidence interval.

Table 6. Multivariate logistic regression analysis of clinical and laboratory variables associated with systolic dysfunction defined as the LVEF < 50%

| | OR | 95% CI | P |
|---------------------------|-------|-------------|-------|
| Gender | 0.972 | 0.108-8.766 | 0.980 |
| Age (yr) | 1.058 | 0.825-1.357 | 0.657 |
| Duration of diabetes (yr) | 1.339 | 1.032-1.737 | 0.028 |
| TG (mg/dl) | 1.007 | 0.991-1.023 | 0.417 |
| TC (mg/dl) | 0.995 | 0.961-1.030 | 0.765 |
| LDL-C (mg/dl) | 0.978 | 0.916-1.044 | 0.504 |
| HDL-C (mg/dl) | 1.093 | 0.978-1.222 | 0.116 |
| BMI (kg/m ²) | 0.836 | 0.486-1.439 | 0.519 |
| SBP (mmHg) | 0.907 | 0.647-1.273 | 0.572 |
| DBP (mmHg) | 1.360 | 0.966-1.914 | 0.078 |
| FPG (mmol/L) | 1.598 | 0.567-4.508 | 0.375 |
| HbA1c (%) | 1.848 | 0.363-9.401 | 0.459 |

Clinical and laboratory variables included age, gender, duration of diabetes, TG, TC, LDL-C, HDL-C, BMI, SBP, DBP, FPG and HbA1c. LVEF, left ventricular ejection fraction; OR, odds ratio; CI, confidence interval.

Discussion

Our study provides data on the clinical indicators of myocardial injury in patients with T2DM and demonstrates that the duration of diabetes is a significant indicator of systolic dysfunction. Although there was no difference in the disease course between the patients of the IG and CG, the course of the disease in patients of the DCG was longer than that in the patients of

the NCG, indicating that the development of the disease may exacerbate myocardial injury and finally lead to systolic dysfunction. This finding was consistent with that of previous studies [5, 6, 10, 11]. Non-enzymatic action exerts a long-term effect on myocardial cells. Accumulation of advanced glycation end-products and interstitial fibrosis will increase the stiffness of the myocardium [12-14] and impair systolic and diastolic function.

DCM is usually characterized by varying degrees of systolic and diastolic dysfunction in the left ventricle, and diastolic dysfunction occurs in the early stage [15]. However, the early stage of DCM with diastolic dysfunction is easily overlooked because of the lack of obvious clinical manifestations. Ultrasonic cardiography has played an important role in the diagnosis of DCM as the main diagnostic method. The E/A ratio is used to evaluate the left ventricular diastolic function. The E/A ratio was < 1 in both the IG and CG and it further decreased in the DCG in this study, which was consistent with the findings of previous studies [13-16], indicating that left ventricular diastolic dysfunction exists even when DCM has not been diagnosed. In our study, the mean of duration was longer than 10 years, supporting the concept that diastolic dysfunction may appear in patients with T2DM, having their glucose levels under control and without other diabetic complications [16].

Systolic dysfunction, unlike diastolic dysfunction, is always accompanied by obvious clinical manifestations and indicators such as LVEF and LVFS. In this study, LVEF and LVFS of IG declined compared with CG. The LVEF was significantly correlated with the disease course. The IVS thickness were higher in patients of the IG than in patients of the CG, and the IVS thickness was higher in patients of the DCG than in patients of the NCG, after systolic dysfunction was present, indicating that diabetic myocardial injury is complicated by left ventricular hypertrophy. There is much interest in the association of hyperglycemia and insulin resistance with left ventricular hypertrophy and cardiac structure alteration. Previous clinical and animal research showed that the thickness of the LVPW and IVS, left atrial diameter, and left ventricular mass index are increased in patients with T2DM [17-19], and may be associated with collagen metabolism disorders, fibrosis in myocardial cells, intersti-

tial remodeling, and ventricular hypertrophy induced by DM [20]. Our results indicate that systolic dysfunction and ventricular hypertrophy exist in patients with myocardial injury caused by T2DM. Therefore, regular monitoring of the IVS thickness will help assessing left ventricular hypertrophy. The IVS thickness, which was significantly correlated with the LVEF, is possibly a more significant indicator of systolic dysfunction and prognosis in patients with DCM. In addition, the LVFS decreased with the decrease of LVEF, so the LVFS could be utilized to evaluate systolic function as well as the LVEF.

In our study, multivariate logistic regression analysis identified the TG level as an independent factor, significantly associated with myocardial injury caused by T2DM, supporting the concept that lipid metabolism disorders may promote the occurrence of diabetic myocardial injury in patients with T2DM. Lipid oxidation increases with increasing energy supply in the myocardium when insulin is deficient or insulin sensitivity decreases; consequently, TGs and free fatty acids accumulate in myocardial cells [21, 22]. Previous studies demonstrated that fatty acid oxidation affects the distribution of calcium ion, and then inhibits the activity of the enzymatic system of myocardial cells [17-20, 23]. Meanwhile, intramyocardial lipid accumulation could cause myocardial injury such as cell hypertrophy and apoptosis, interstitial fibrosis, left ventricular hypertrophy, and LVFS reduction [19, 24]. Our result that elevated TG levels in patients with T2DM may be associated with myocardial injury induced by T2DM, is consistent with those of previous studies [19, 20].

In conclusion, our study indicates that the duration of diabetes is a significant indicator of systolic dysfunction. Diastolic dysfunction precedes systolic dysfunction, and every patient with T2DM may have diastolic dysfunction to some degree, suggesting that such patients, with a prolonged duration of diabetes, should undergo regular ultrasonic cardiographic examinations to detect abnormal diastolic function and diabetic myocardial injury, as early as possible. Monitoring of the IVS thickness will help assessing left ventricular hypertrophy, and the IVS thickness is possibly a more significant indicator of systolic dysfunction and prognosis in patients with DCM. Elevated TG levels in patients with T2DM might promote the occurrence of diabetic myocardial injury, suggesting

that a lower TG level will help reduce the occurrence of DCM in patients with T2DM. Additional large, multicenter, prospective studies are required to validate our findings.

Disclosure of conflict of interest

None.

Address correspondence to: Jianling Du, Department of Endocrinology, The First Affiliated Hospital of Dalian Medical University, No. 222 Zhongshan Road, Dalian 116011, Liaoning, China. Tel: +86 18098875615; E-mail: danliudoc@126.com

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