Echocardiographic Changes in Newly Diagnosed Type 2 Diabetes Mellitus Patients with and without Hypertension

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Background: Whether type 2 diabetes mellitus (T2DM) is independently associated with structural heart abnormalities is controversial because of confounders associated with T2DM. This study aimed to investigate echocardiographic features in patients with newly diagnosed T2DM, exploring changes in cardiac structure and function.

Material/Methods: This was a retrospective study of new T2DM cases treated at the Second People's Hospital Affiliated to Nanjing Medical University (Changzhou) in 2014–2016. In all, 128 T2DM cases were included (62 hypertensive and 66 non-hypertensive individuals). Controls were selected among individuals who underwent examination at the same department/period. Interventricular septal thickness (IVST), left ventricular end-diastolic diameter (LVEDD), posterior left ventricular wall thickness (PWTD), left ventricle mass (LVM), end-diastolic thickness of left ventricular posterior wall (Dd), aortic root diameter, left atrial diameter (LAd), left atrial diameter fraction-shortening values, and left ventricular ejection fraction (LVEF) were determined routinely.

Results: IVST, LVEDD, PWTD, Dd, LAd, and left atrial diameter fraction-shortening values were larger in patients with T2DM (all P<0.05 vs. controls). LVM was higher in T2DM patients (median, 57.12 vs. 54.77 g, P=0.001). There were no differences in aortic root diameter and EF (both P>0.05). Multivariable analysis showed that IVST (OR=1.33, 95% CI: 1.01–1.76, P=0.04), LAd (OR=1.16, 95% CI: 1.07–1.25, P<0.001), TcG (OR=1.34, 95% CI: 1.09–1.63, P=0.005), and HDL (OR=1.46, 95% CI: 1.02–2.08, P=0.04) were independently associated with hypertension in patients with T2DM.

Conclusions: Patients with newly diagnosed T2DM already display structural heart abnormalities. LAd and IVST are independently associated with hypertension in these patients, probably contributing to increased cardiovascular risk.

MeSH Keywords: Diabetes Mellitus, Type 2 • Echocardiography • Hypertension

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Background

Type 2 diabetes mellitus (T2DM) is an endocrine disorder characterized by hyperglycemia resulting from variable degrees of insulin resistance and deficiency [1]. Chronic hyperglycemia in diabetes can lead to multi-organ damage resulting in renal, neurologic, cardiovascular, and other serious complications [1]. The worldwide prevalence of T2DM was 9% in men and 7.9% in women in 2014 [2], but in China the prevalence rates of T2DM and prediabetes in 2013 were 10.9% and 35.7%, respectively [3], highlighting the seriousness of the epidemic. 

Cardiovascular disease (CVD) is the main cause of mortality among diabetic patients [4]. Epidemiological studies showed that more than 70% of patients with T2DM die of CVD, with 2–3 times higher CVD mortality than among non-diabetic individuals [4–6]. In China, T2DM is associated with increased mortality, especially in rural areas [7].

Early detection of potential CVD in diabetic patients can significantly reduce mortality from diabetic cardiovascular complications. Echocardiography allows determination of the morphological and functional characteristics of the heart and may indicate pathological changes that increase the risk of CVD [8]. Among the indicators, left ventricle hypertrophy (LVH) is a common finding in patients with hypertension, atherosclerosis, obesity, and/or dyslipidemia, but it remains controversial whether T2DM is independently associated with LVH since all the above conditions often coexist with T2DM [8,9]. The 3 main risk factors for increased left ventricle mass (LVM) are hypertension, insulin resistance (IR), and visceral adiposity [10]. LVH is dependent on body surface area and has been shown to predict short- and long-term CVD in patients with T2DM [11]. According to the ACCF/AHA guidelines, T2DM is considered to be a risk factor for heart failure that is independent of the other cardiovascular risk factors [12]. Hypertension in diabetic patients further increases the risks of CVD and death [13,14].

Therefore, the present study aimed to examine the echocardiographic features of patients with primary T2DM (newly diagnosed) and to explore changes in cardiac structure and function. The results could help understand the development of CVD in patients with T2DM and provide some clues and further research directions for the prevention of CVD in patients with T2DM.

Material and Methods

Study design and participants

This retrospective study included patients with newly diagnosed T2DM treated at the Department of Endocrinology of the Second People’s Hospital Affiliated to Nanjing Medical University (Changzhou) between January 2014 and December 2016. A total of 128 patients with newly diagnosed T2DM were assessed in this study (Figure 1), including 62 hypertensive and 66 non-hypertensive individuals. Control subjects were selected from among individuals who underwent a routine examination in the same department during the same period. This study was approved by the Research Ethics Committee of the Second People’s Hospital Affiliated to Nanjing Medical University (Changzhou). The need for individual consent was waived by the committee. All data were handled and anonymized based on ethical and legal standards.

Inclusion criteria for the T2DM group were: 1) new diagnosis of T2DM according to the 1999 WHO diabetes diagnostic criteria and classification standards [15]; 2) no diagnosis of heart diseases such as valvular heart disease, ischemic heart disease, cardiomyopathy, congestive heart failure, renal failure, chronic lung disease, severe anemia, and hemoglobin diseases, as determined by routine tests based on standard indications; and 3) no cancer. Inclusion criteria for controls were: 1) glycated hemoglobin (HbA1c) <6.5%; 2) fasting plasma glucose (FPG) <6.0 mmol/L; 3) no hypertension, T2DM, or dyslipidemia; 4) no diagnosis of heart diseases such as valvular heart disease, ischemic heart disease, cardiomyopathy, congestive heart failure, renal failure, chronic lung disease, severe anemia, and hemoglobin diseases, as determined by routine tests based on standard indications; and 5) no cancer. The controls were matched for age and sex with T2DM patients.

Measurements and data collection

All subjects routinely underwent blood sampling in the fasting state between 06:00 and 07:30 in the morning. Blood lipids, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL), were measured on a Cobas c702 system.
Echocardiography was performed using a Philips iE33 Doppler echocardiography system equipped with a real-time three-dimensional probe X3-1 (frequency of 1–3 MHz) (Philips, Best, the Netherlands). Images of the left ventricle were taken in the short axis of the great artery, the long axis of the left ventricle, the short axis views of various levels, and standard apical 4-chamber and 2-chamber sections in the resting state; 3–5 cardiac cycles were measured continuously to obtain average readings. Interventricular septal thickness (IVST), left ventricular end-diastolic diameter (LVEDD), posterior left ventricular wall thickness (PWTD), LVM, end-diastolic thickness of left ventricular posterior wall (Dd), aortic root diameter, left atrial diameter (LAd), left atrial diameter fraction-shortening values, and left ventricular ejection fraction (LVEF) were determined routinely [16]. A senior technician collected all the images and another technician recorded and analyzed the data. LVM was derived according to the following formula:

$$LVM = 0.8 \times 1.04 \left[ (LVST + PwT + LVDd)^3 - LVDd^3 \right] + 0.6.$$  

**Statistical analysis**

All statistical analyses were performed with SPSS 19.0 (IBM, Armonk, NY, USA). Continuous data are presented as mean±standard deviation or median (inter-quartile range, IQR) based on distribution determined by the Kolmogorov-Smirnov test and analyzed by the t test or the Wilcoxon rank-sum test, as appropriate. Categorical data are presented as frequencies and percentages and were analyzed by the chi-square test or Fisher’s exact test, as appropriate. Multivariable logistic regression was used with variables selected by the stepwise forward method (entry, 0.05; exclusion, 0.10). Two-sided P <0.05 was considered as being statistically significant.

**Results**

**Characteristics of the subjects**

Patients with T2DM had a mean age of 54.3±12.9 years and the mean age of controls was 55.7±10 years, and the proportions of males were 61.7% and 61.2%, respectively (both P<0.05). BMI, HbA1c, TC, TG, and LDL levels were higher in the T2DM group when compared with controls, while HDL and creatinine levels were lower (all P<0.05). Among the 128 T2DM patients, there were 62 and 66 hypertensive and non-hypertensive individuals, respectively (Figure 1). Non-hypertensive patients were further compared with controls. As shown in Table 1, age (50.09±13.3 years vs. 55.71±10.54 years; p=0.0008), male proportion (42% vs. 66%, p=0.0006), creatinine (75.02±15.86 µmol/L vs. 79.97±13.39 µmol/L; p=0.0178), and HDL (1.36±0.44 mmol/L vs. 1.49±0.36 mmol/L; p=0.0219) were lower in T2DM patients without hypertension compared with controls, while BMI (25.33±4.2 kg/m² vs. 23.4±3.09 kg/m²; p<0.001), HbA1c (11.77±3.53% vs. 5.85±0.65%; p<0.001), and triglycerides (1.96±1.32 mmol/L vs. 1.50±1.23 mmol/L; p=0.0121) were higher.

**Echocardiography parameters**

Table 1 shows the echocardiography parameters of the subjects. IVST, LVEDD, Dd, LVESD, left atrial diameter, and left atrial diameter fraction-shortening values were greater in patients with T2DM when compared with controls (all P<0.05). LVM was higher in the T2DM group (57.12±6.33 vs. 54.77±5.35 g, P<0.001). There were no significant differences in aortic root diameter or EF (both P>0.05). Non-hypertensive patients were further compared with control patients. As shown in Table 1, LVM (143.96±33.09 g vs. 157.04±29.49 g; p=0.005) was lower in T2DM patients without hypertension compared with controls, while IVST (9.27±0.92 mm vs. 9.6±1.08 mm; p=0.0422), LVEDD (48.86±3.77 mm vs. 47.37±4.19 mm; p=0.0123), left ventricular end-systolic diameter (33.05±3.15 mm vs. 31.88±3.72 mm; p=0.0257), and left atrial diameter (37.53±3.65 mm vs. 36.07±3.90 mm; p=0.0092) were higher.

**Characteristics of patients with T2DM according to hypertensive status**

There were significant differences between the non-hypertension and hypertension groups in age (50.1±13.3 years vs. 58.7±10.9 years; p<0.001), uALB/uCr (ACR; 9.7 vs. 15; p=0.002), IVST (9.27±0.92 mm vs. 9.6±1.08 mm; p=0.0422), and left atrial diameter (38 [35, 40] mm vs. 38 [37, 41.25] mm; p=0.003). Patients with primary diabetes and hypertension were older age, had greater interventricular septum thickness and left atrial diameter, and had higher microalbuminuria compared with the non-hypertensive group (Table 2).

**Factors associated with T2DM in non-hypertensive patients**

Table 3 summarizes univariable and multivariable analyses of various factors in normotensive patients with T2DM. Univariable analysis showed that age, sex, BMI, creatinine, TG, HDL, IVST, LVEDD, LVESD, and left atrial diameter were associated with normotensive T2DM patients. Multivariable analysis of these parameters revealed that age (OR=0.971, 95% CI: 0.944–1.000 0.049), male sex (OR=0.161, 95% CI: 0.072–0.358; P<0.001), BMI (OR=1.163, 95% CI: 1.049–1.289; P=0.004), and FPG were determined by an enzymatic colorimetric assay (Glucose HK Gen.3, Roche Diagnostics, Basel, Switzerland). FPG was determined by high-performance liquid chromatography (HPLC) (HLC-723G8, TOSOH, Yamaguchi, Japan).
creatinine (OR=0.944, 95% CI: 0.918–0.972; P<0.001) were associated with diabetes in non-hypertensive patients, independently from each other.

Factors associated with hypertension in patients with T2DM

Table 4 shows the univariable and multivariable analyses of various factors in hypertensive patients with T2DM. Univariable analysis showed that BMI, IVST, LVEDD, end-diastolic thickness of the left ventricular posterior wall, LVESD, left atrial diameter, left atrial diameter fraction-shortening, creatinine, TC, TG, LDL, and HDL had associations with hypertension in patients with newly diagnosed T2DM patients (all P<0.05). These parameters were entered into multivariable analysis, and IVST (OR=1.33, 95% CI: 1.01–1.76, P=0.04), left atrial diameter (OR=1.16, 95% CI: 1.07–1.25, P<0.001), TGs (OR=1.34, 95% CI: 1.09–1.63, P=0.005), and HDL (OR=1.46, 95% CI: 1.02–2.08, P=0.04) were independently associated with hypertension in patients with T2DM (Table 4).

Discussion

Whether T2DM is independently associated with structural heart abnormalities is controversial because of confounding factors associated with T2DM. Therefore, the aim of the present study was to investigate and analyze the echocardiographic features of patients with newly diagnosed primary T2DM, and to explore the changes in cardiac structure and functions. The results suggested that patients with newly diagnosed T2DM already display some structural heart abnormalities, especially those with hypertension. LAd and IVST were independently associated with hypertension in these patients, probably contributing to increased cardiovascular risk.
Table 2. Clinicodemographic indicators and cardiac ultrastructure between the hypertension and non-hypertension subgroups of patients with T2DM.

| Indicators                                      | No hypertension (n=66) | Hypertension (n=62) | P     |
|------------------------------------------------|-----------------------|---------------------|-------|
| Age (years)                                    | 50.1±13.3             | 58.7±10.9           | <0.001* |
| uALB/uCRE (ACR) (mg/g)                         | 9.7 (6,15)            | 15 (8.15,34.83)     | 0.002* |
| HbA1c (%)                                      | 11.8 (10.07,12.8)     | 10.85 (9.67,12.33)  | 0.065 |
| 25 hydroxy vitamin D (nmol/L)                  | 30.49±11.82           | 29.21±13.59         | 0.650 |
| Creatinine (µmol/L)                            | 74.71±15.65           | 74.75±20.20         | 0.989 |
| Total cholesterol (mmol/L)                     | 4.77±1.01             | 4.93±1.18           | 0.426 |
| Triglycerides (mmol/L)                         | 1.53 (1.16,2.26)      | 1.68 (1.19,3.22)    | 0.327 |
| High-density lipoprotein (mmol/L)              | 1.36±0.45             | 1.35±0.31           | 0.904 |
| Low-density lipoprotein (mmol/L)               | 3.04±0.84             | 3.23±0.88           | 0.224 |
| Serum calcium (mmol/L)                         | 2.31±0.15             | 2.34±0.12           | 0.264 |
| Serum phosphorus (mmol/L)                      | 1.16±0.27             | 1.16±0.27           | 0.973 |
| Interventricular septal thickness (mm)         | 9 (9,10)              | 9 (9,10)            | 0.002* |
| Left ventricular end-diastolic diameter (mm)   | 49.5 (47.0,51.25)     | 48 (47,51.25)       | 0.981 |
| Left diastolic thickness of left ventricular posterior wall (mm) | 9 (8,10)              | 9 (8,10)            | 0.099 |
| Left ventricular mass (g)                      | 58.35±6.06            | 58.09±4.77          | 0.789 |
| Left ventricular end-systolic diameter (mm)    | 33 (31,35)            | 33 (32,35)          | 0.511 |
| Aortic root diameter (mm)                      | 29 (28,31)            | 30.5 (29,33)        | 0.146 |
| Left atrial diameter (mm)                      | 38 (35,40)            | 38 (37,41.25)       | 0.003* |
| Left atrial diameter fraction-shortening (%)   | 32.32±3.18            | 31.66±2.79          | 0.217 |
| EF (%)                                         | 60.21±4.49            | 59.53±3.95          | 0.366 |

BMI – body mass index; EF – ejection fraction. * P values <0.05 are considered statistically significant.

There are many complications caused by T2DM, among which diabetic CVDs are the most serious [17]. Patients with T2DM have a 5-fold higher risk of death due to CVD or stroke compared with the general population, which is associated with significant social and economic burdens [18]. Cardiac diastolic and systolic dysfunction is common in diabetic patients and is independent of coronary artery disease and hypertension [19]. Structural changes in the heart may be present even when the electrocardiogram (ECG) is normal [20]. Therefore, early detection and intervention play important roles in the prevention and development of CVDs in patients with T2DM.

Diabetic cardiomyopathy is a primary myocardial lesion independent of coronary artery disease, hypertension, and valvular disease, and is associated with T2DM [9,21–23]. Measuring LVM can accurately diagnose early diabetic cardiomyopathy [9,21–23]. Most primary and secondary heart diseases are prone to increased LVM. When the load reaches a certain threshold, it leads to LVH and degeneration, as well as thickening of ventricular septal and left ventricular wall, resulting in increased LVM [24]. In addition, increases in LVM early in the course of T2DM might influence the risk of CVD.

Many studies have confirmed that 90% of patients with T2DM, but without evidence of CVDs, have left diastolic dysfunction [21,25,26], supporting the heart function results observed in this study. Indeed, significant differences were observed between the T2DM and control groups in IVST, LVEDD, Dd, LVM, and left atrial diameter. Nevertheless, the exact mechanisms leading to left ventricular diastolic dysfunction in diabetic patients are not clear [23,27]. Among the suggested hypotheses, IR and myocardial cell metabolism, cardiac renin-angiotensin system and sympathetic nervous system activation, oxidative stress, cardiac microvascular endothelial cell proliferation, myocardial cell volume hypertrophy, myocardial deposition of glycoproteins, collagen fibers, TGs, cholesterol, and...
myocardial interstitial fibrosis are possible culprits [22,28–30]. Those changes may participate in myocardial stiffness, myocardial degeneration, interventricular septum and left ventricular posterior wall thickening, which increase left ventricular mass index, lower ventricular diastolic compliance, and reduce diastolic energy supplied by ventricular diastole, leading to decreased left ventricular diastolic function [22,28–30].

The study observed the well-known disturbances in glucose and lipid metabolism commonly found in T2DM [1,17,25]. Those changes may play prominent roles in myocardial remodeling in diabetic patients, as supported by Bhuiyan et al. [31]. Indeed, the latter authors observed strong correlations between left ventricular diastolic dysfunction, duration of diabetes, HbA1c levels, obesity, and microcirculation, and emphasized that diabetes, although asymptomatic, eventually leads to cardiovascular events with microcirculatory disturbances. Patil et al. [32] pointed out that increased calcium accumulation in the heart and impaired calcium homeostasis may be involved in diabetic cardiac function changes. These authors found that cardiac TG levels were significantly increased in ob/ob mice. High glucose and high lipid levels play a direct role in the activation of myocardium peroxisome proliferator, which activates the receptor α (PPARα) signaling pathway, resulting in myocardial energy metabolism, mainly from glucose oxidation and increased oxidative stress [33,34].

Subgroup analysis in the present study showed that T2DM patients with hypertension were older and had higher Dd and urinary microalbuminuria compared with non-hypertensive patients. Those results are consistent with previous findings that diabetes, obesity, hypertension, and left atrial enlargement are significantly associated [35]. Hypertension and early onset of T2DM can decrease left ventricular diastolic and systolic functions, which suggests that heart diseases caused by diabetes may be more serious than hypertension since diabetic patients have worse overall cardiac function [36–38]. Hypertension is considered the most important factor in promoting the occurrence and development of left ventricular hypertrophy [39]. It was previously believed that left ventricular hypertrophy is a structural change in the heart during sustained high blood pressure, but recent

Table 3. Univariable and multivariable analyses of factors associated with patients who were newly diagnosed T2DM without hypertension.

|                             | Univariable analysis | Multivariable analysis |
|-----------------------------|----------------------|------------------------|
|                            | OR 95% CI  P         | OR 95% CI  P          |
| Age (years)                 | 0.957 0.932–0.983   | 0.971 0.944–1.000   |
| Sex, male (n, %)            | 0.363 0.201–0.653   | 0.161 0.072–0.358   |
| BMI (kg/m²)                 | 1.21 1.099–1.331     | <0.001* 1.163 1.049–1.289 |
| Creatinine (µmol/L)         | 0.975 0.955–0.996   | 0.019 0.944 0.918–0.972   |
| Uric acid (µmol/L)          | 1.001 0.997–1.005   | 0.505            |
| Total cholesterol (mmol/L)  | 1.223 1.010–1.463   | 0.182            |
| Triglycerides (mmol/L)      | 1.299 1.043–1.618   | 0.019            |
| High-density lipoprotein (mmol/L) | 0.374 0.160–0.874 | 0.023            |
| Low-density lipoprotein (mmol/L) | 1.444 0.974–2.140 | 0.067            |
| Interventricular septal thickness (mm) | 1.331 1.008–1.758 | 0.044            |
| Left ventricular end-diastolic diameter (mm) | 1.099 1.020–1.184 | 0.014            |
| End-diastolic thickness of left ventricular posterior wall (mm) | 1.337 0.974–1.835 | 0.072            |
| Left ventricular end-systolic diameter (mm) | 1.104 1.012–1.205 | 0.026            |
| Aortic root diameter (mm)   | 1.003 0.903–1.113   | 0.96            |
| Left atrial diameter (mm)   | 1.108 1.024–1.198   | 0.011            |
| Left atrial diameter fraction-shortening (%) | 0.95 0.877–1.029 | 0.205            |
| EF (%)                      | 0.986 0.944–1.031   | 0.548            |

BMI – body mass index; EF – ejection fraction. * P values <0.05 are considered statistically significant.
studies have shown that genetic factors, neuroendocrine factors, and metabolic status play important roles in the occurrence and development of left ventricular remodeling [39]. Some hypotheses have been proposed, including stimulation and hypertrophy of cardiomyocytes by angiotensin II, high insulin levels, the sympatho-adrenal nervous system, and endothelin [39,40]. Nevertheless, since those mechanisms are usually found together in patients with T2DM, it is difficult to determine the exact individual contribution of each one. Diabetes mellitus combined with hypertension can aggravate left ventricular structural changes and increase the risk of left ventricular hypertrophy.

The present study had limitations. The sample size was small and from a single center. This was a retrospective study, and no follow-up was performed to correlate the structural and functional heart changes with outcomes over time. Blood parameters of inflammation and oxidative stress were not measured either. Finally, all subjects were Chinese, and the specific genetic and environmental characteristics of those patients might limit the generalizability of our results to other populations.

### Conclusions

Patients with newly diagnosed T2DM already display structural heart abnormalities, especially those with hypertension. LAD and IVST were independently associated with hypertension in the newly diagnosed T2DM patients in subgroup analysis. Early diabetes with primary hypertension is associated with changes in cardiac structure.

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### Conflict of interests

None.

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**Table 4.** Univariable and multivariable analyses of factors associated with hypertension in patients with newly diagnosed T2DM.

| Factor                                | Univariable analysis | Multivariable analysis |
|---------------------------------------|----------------------|------------------------|
|                                       | OR       | 95% CI     | P   | OR       | 95% CI     | P   |
| Age (years)                           | 0.989    | 0.970–1.009| 0.284|          |           |      |
| Sex, male (n,%                       | 0.977    | 0.610–1.566| 0.924|          |           | 5*   |
| BMI (kg/m²)                           | 1.205    | 1.116–1.301| <0.001*     |\
| Interventricular septal thickness (mm)| 1.699    | 1.341–2.153| <0.001*     |\
| Left ventricular end-diastolic diameter (mm)| 1.068    | 1.009–1.130| 0.024*     |\
| End-diastolic thickness of left ventricular posterior wall (mm)| 1.608    | 1.235–2.094| <0.001*     |\
| Left ventricular end-systolic diameter (mm)| 1.138    | 1.057–1.225| 0.001*     |\
| Aortic root diameter (mm)             | 1.047    | 0.964–1.139| 0.276|          |           | 5*   |
| Left atrial diameter (mm)             | 1.155    | 1.081–1.234| <0.001*     |\
| Left atrial diameter fraction-shortening (%)| 0.918    | 0.860–0.981| 0.012*     |\
| EF (%)                                | 0.969    | 0.932–1.008| 0.114|          |           | 5*   |
| Uric acid (µmol/L)                    | 1.000    | 0.997–1.003| 0.960|          |           |      |
| Creatinine (µmol/L)                   | 0.981    | 0.966–0.996| 0.013*     |\
| Total cholesterol (mmol/L)            | 1.281    | 1.017–1.614| 0.035*     |\
| Triglycerides (mmol/L)                | 1.423    | 1.169–1.732| <0.001*     |\
| Low-density lipoprotein (mmol/L)      | 0.271    | 0.131–0.564| <0.001*     |\
| High-density lipoprotein (mmol/L)     | 1.625    | 1.189–2.220| 0.002*     |\

BMI – body mass index; EF – ejection fraction. * P values <0.05 are considered statistically significant.
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