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ORIGINAL RESEARCH

Female is Associated with Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes

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Aim: Diabetic cardiomyopathy is a subset of heart disease that is directly associated with diabetes, and left ventricular diastolic dysfunction is the earliest sign. We aimed to investigate the association between sex differences and left ventricular diastolic function in patients with type 2 diabetes.

Methods: This was a cross-sectional study included patients with type 2 diabetes who visit the National Metabolic Management Center (MMC) at the First People's Hospital of Yunnan from 2018 to 2021. Patients with hypertension, history of heart disease or ejection fraction <50% were excluded from the study. Logistic regression was used to analyze their associations.

Results: A total of 1778 patients were included in the study. The study included 1205 (70%) males and 573 (30%) females. Compared with males, females had higher total cholesterol and LDL cholesterol levels but lower diastolic pressure, body mass index (BMI), visceral fat area, HbA1c, blood urea nitrogen (BUN), serum creatinine and triglyceride. Females had a relatively higher ejection fraction than males (68.17 ± 6.055 vs 67.5 ± 6.096, $P < 0.05$). More female patients than male patients in the age group of 45–60 years old had left ventricular diastolic dysfunction (female vs male, 54.5% vs 46.9%, $P < 0.05$). We also found that females were independently associated with left ventricular diastolic dysfunction, after adjusting for important clinical factors.

Conclusion: Left ventricular diastolic function might be worse in female patients with type 2 diabetes. Further study is needed to verify the underlying mechanism.

Keywords: type 2 diabetes, sex differences, left ventricular diastolic dysfunction

Introduction

According to the International Diabetes Federation (IDF) Diabetes Atlas in 2021, there are 537 million adults living with diabetes, and the number is predicted to rise to 643 million by 2030. Despite the control of glycemia, hypertension and/or hyperlipidemia, one person dies of diabetes every five seconds. Diabetes and its complications come with a huge burden.

Cardiovascular disease associated with diabetes confers the primary cause of death in patients with type 2 diabetes. Hopefully, the EMPA-Heart randomized clinical trial has proven that sodium-glucose cotransporter 2 (SGLT2) inhibitors with empagliflozin lower cardiovascular events in type 2 diabetes.[1] Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have also been shown to reduce stroke risk in type 2 diabetes.[2] The early detection of high-risk groups for cardiovascular disease gives us opportunity to initiate medications that are beneficial to the heart.

Physiologically, female sex hormones could be beneficial in cardiovascular diseases,[3] however, the benefit would disappear in patients with diabetes. Studies have shown that diabetic females were with more advanced carotid atherosclerosis[4] and higher rate of heart failure[5] than diabetic males when they were compared with their respective non-diabetic cohorts. Another study also confirmed that females with diabetes have higher hospital admission rates for acute myocardial incident compared with males.[6] A recent nationwide study observed that the relative rate of first-time cardiovascular complications related to diabetes was higher in females than in males.[7]

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Diabetic cardiomyopathy refers to a unique subset of heart diseases associated with diabetes. It is characterized by diastolic and systolic dysfunction, which is gradually unrelated to hypertension or primary heart diseases.[8] Left ventricular diastolic dysfunction is usually considered to be the earliest manifestation of diabetic cardiomyopathy. However, no study has focused on sex differences of diabetic cardiomyopathy, and whether female is a risk factor for the diabetic cardiomyopathy in the early stage remains unclear.

Therefore, in the current study, we aimed to investigate the association between sex difference and left ventricular diastolic function in patients with type 2 diabetes.

Method

Study Population

We performed a cross-sectional study. The study included patients with type 2 diabetes who visited the National Metabolic Management Center (MMC) at the First People's Hospital of Yunnan from 2018 to 2021. The diagnostic criteria for diabetes were based on the 1999 World Health Organization criteria and 2012 American Diabetes Association standards. Patients with (1) type 1 diabetes and other types of diabetes, (2) aged <18 and >80 years, (3) pregnancy, (4) a lack of echocardiography results, (5) a diagnosis of hypertension, (6) a history of heart disease and (6) an EF <50% were excluded from the study (Figure 1).

This study protocol conformed with the Declaration of Helsinki and was approved by the Ethics Committee of the First People's Hospital of Yunnan Province. The approval ID number is KHLL2021-KY012.

All the participants have provided informed consent.

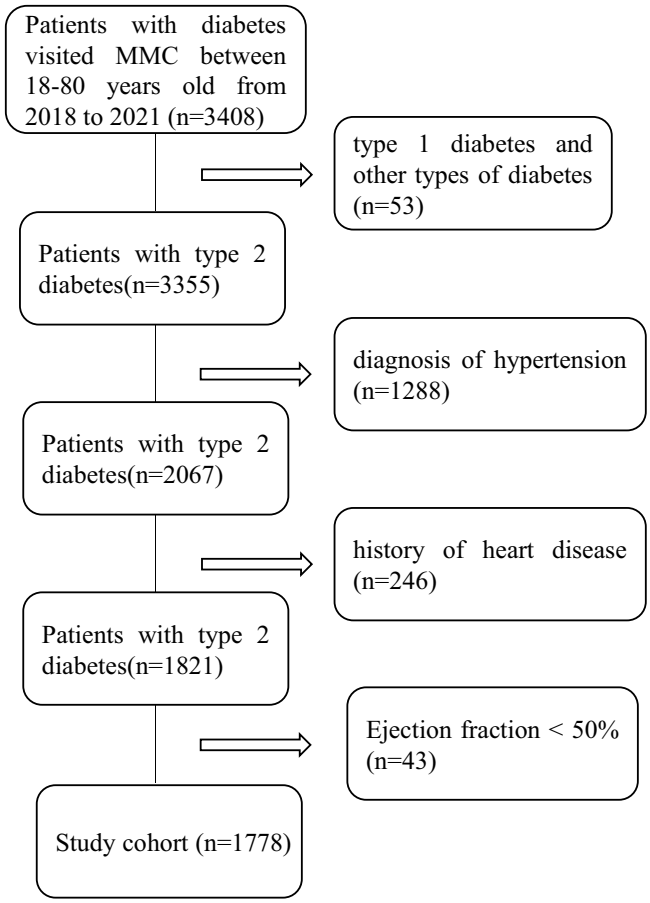

Figure 1 Flowchart of study participants.
Abbreviation: MMC, Metabolic Management Center.

Clinical Parameters and Evaluation of Left Ventricular Diastolic Function

Clinical parameters including age, sex, hypertension, duration of diabetes, liver and kidney function, etc., were collected from the electronic records of our hospital.

Evaluation of left ventricular diastolic function with normal ejection fraction was accomplished by professional cardiac sonographers in our hospital according to Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography in 2016.[9] Briefly, we diagnosed left ventricular diastolic function if the following four conditions satisfy greater than two: (1) average E/e' >14; (2) septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s; (3) tricuspid regurgitation velocity >2.8 m/s; (4) left atrium volume index >34mL/m^2.

Statistical Analysis

Data are presented as mean ± standard deviation (normal distribution) or median and interquartile range (skewed distribution). Differences between groups were analyzed using the Student's *t*-test, the Mann–Whitney test, the rank sum test or the chi-square test, as appropriate. Univariable and multivariable logistic regressions were employed to assess the association between clinical parameters and left ventricular diastolic dysfunction.

Results

Clinical Characteristics of the Study Cohort

A total of 1778 patients were included in the study, and baseline clinical characteristics are presented in Table 1. Briefly, the mean age of patients was 50.0 ± 10.89 years old, the mean diabetic duration was 87.7 ± 72.2 months, and the mean HbA1c was 10.0 ± 2.68%. The mean serum albumin was 40 ± 4.33 g/L, the mean serum creatinine was 64 ± 15.8 μmol/

Table 1 Baseline Characteristics

Parameters	Total (1778)	Male (1205)	Female (573)	p
Age (years)	50.0±10.89	49.2±10.74	51.7 ±10.99	0.000
Diastolic pressure (mmHg)	73±8.5	74±8.7	72±8.2	0.000
Systolic pressure (mmHg)	116±12.6	116±12.4	117±12.9	0.431
Body mass index (kg/m^2)	24.51±3.441	24.68±3.339	24.17±3.623	0.003
Visceral fat area (cm^2)	85.14±39.867 (n=1672)	87.34±41.531 (n=1143)	80.36±35.582 (n=529)	0.000
Subcutaneous fat area (cm^2)	173.10±62.514 (n=1658)	173.24±61.22 (n=1134)	172.79±65.286 (n=524)	0.894
Family history of diabetes	549(30.9)	354(29.4)	195(34.0)	0.047
Diabetic duration (months)	87.7±72.2 (n=1369)	86.7±70.4 (n=905)	89.7±75.7 (n=464)	0.465
HbA1c (%)	10.0±2.68	10.1±2.69	9.8±2.65	0.012
Serum glucose (mmol/L)	8.6±3.680	8.7±3.77	8.5±3.49	0.461
ALT (U/L)	21(15,32)	22(16,33)	18(13,28)	0.000
AST (U/L)	18(15,24)	18(15,24)	18(14,23)	0.116
Serum albumin (g/L)	40±4.33	40±4.4	39±4.0	0.000
Blood urea nitrogen (mmol/L)	5.41±2.44	5.6±2.73	5.1±1.61	0.000
Serum creatinine (umol/L)	64±15.8	70±14.4	53±11.4	0.000
Uric acid (umol/L)	355±95.3	371±93.9	321±89.3	0.000
Triglyceride (mmol/L)	1.70(1.12,2.74)	1.75(1.13,2.87)	1.62(1.06,2.52)	0.010

(*Continued*)

Table 1 (Continued).

Parameters	Total (1778)	Male (1205)	Female (573)	p
Total cholesterol (mmol/L)	4.8±1.30	4.8±1.32	4.9±1.25	0.031
HDL cholesterol (mmol/L)	1.0±0.28	1.0±0.28	1.1±0.25	0.000
LDL cholesterol (mmol/L)	2.8±0.90	2.8±0.87	2.9±0.96	0.019
ACR (mg/g)	12(2.7,69.4)	11(2.7, 64.4)	13(2.6,76.3)	0.551
Smoke	726(40.8)	709(58.8)	17(3.0)	0.000
Drink	673(55.9)	621(51.5)	52(9.1)	0.000
Left atrium diameter (mm)	33.27±5.348	33.74±5.246	32.28±5.430	0.000
Interventricular septum thickness (mm)	10.22±3.270	10.47±3.625	9.67±2.254	0.000
Left ventricular end-diastolic diameter (mm)	43.45±7.023	44.36±6.960	41.54±6.773	0.000
Left ventricular end-systolic diameter (mm)	27.52±4.93	28.25±4.729	26.00±4.995	0.000
Left ventricular posterior wall thickness (mm)	9.49±3.046	9.61±2.343	9.26±4.154	0.060
Aortic root inner diameter (mm)	24.41±4.658	25.32±4.851	22.59±3.733	0.000
Ejection fraction (%)	67.41±6.103	67.5±6.096	68.17±6.055	0.000
Left ventricular diastolic function	877(49.3)	565(46.9)	312(54.5)	0.003

Note: Data presented as mean ± SD or median (range).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-to-creatinine ratio.

L, and the median of albumin-to-creatinine ratio (ACR) was 12 (2.7, 69.4) mg/g. There were 1205 (70%) male and 573 (30%) female in the cohort. Compared with male, female was older, had the higher total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, but female had lower diastolic pressure, body mass index (BMI), visceral fat area, HbA1c, blood urea nitrogen (BUN), alanine aminotransferase (ALT), serum creatinine and triglyceride. More males were smokers and drinkers, but more females have a family history of diabetes. There was no difference of systolic pressure, subcutaneous fat area, diabetic duration, aspartate transaminase (AST) and ACR between male and female.

In terms of cardiac characteristics, females had significantly shorter left atrium diameter, ventricular septal thickness, left ventricular end-diastolic and systolic diameter, and aortic root inner diameter compared with males. The differences might contribute to physiological differences. Females had relatively higher ejection fraction than males (68.17 ± 6.055 vs 67.5 ± 6.096, $P < 0.05$), but there was no difference of left ventricle posterior wall thickness between male and female.

The Association Between Clinical Factors and Left Ventricular Diastolic Dysfunction

First, we used the univariable logistic regression to analyze important clinical factors which might be associated with left ventricular diastolic dysfunction (Table 2). We found that female, the older, higher blood pressure, higher visceral/subcutaneous fat area, family history of diabetes, longer diabetic duration, lower HbA1c, higher BUN, and serum creatinine were all associated with left ventricular diastolic dysfunction.

Then, we used multivariable logistic regression to adjusted confounding factors (Table 3). We found that females were still associated with left ventricular diastolic dysfunction when adjusted age, diastolic/systolic pressure, BMI, visceral/subcutaneous fat area, diabetic duration, HbA1c, family history of diabetes, smoking, drinking, serum albumin, ALT, AST, BUN, serum creatinine, ACR, uric acid, triglyceride, total cholesterol and HDL/LDL cholesterol (Figure 2).

Table 2 Univariate Logistic Regression

Parameters	HR	95%	P value
Female	1.354	1.109–1.653	0.003
Age (years)	1.128	1.114–1.143	0.000
Diastolic pressure (mmHg)	1.022	1.011–1.033	0.000
Systolic pressure (mmHg)	1.024	1.017–1.032	0.000
Body mass index (kg/m^2)	1.019	0.992–1.047	0.177
Visceral fat area (cm^2)	1.004	1.002–1.007	0.001
Subcutaneous fat area (cm^2)	1.002	1.001–1.004	0.002
Family history of diabetes	1.430	1.168–1.752	0.001
Diabetic duration (months)	1.005	1.004–1.007	0.000
HbA1c (%)	0.891	0.859–0.923	0.000
Serum glucose (mmol/L)	0.992	0.967–1.017	0.522
ALT (U/L)	0.995	0.991–0.0999	0.024
AST (U/L)	0.997	0.990–1.004	0.405
Serum albumin (g/L)	1.006	0.984–1.027	0.615
Blood urea nitrogen (mmol/L)	1.151	1.085–1.221	0.000
Serum creatinine (umol/L)	1.012	1.006–1.018	0.000
Uric acid (umol/L)	1.001	1.000–1.002	0.253
Triglyceride (mmol/L)	1.004	0.975–1.033	0.811
Total cholesterol (mmol/L)	1.001	0.932–1.076	0.973
HDL cholesterol (mmol/L)	1.337	0.950–1.881	0.096
LDL cholesterol (mmol/L)	0.993	0.896–1.101	0.893
ACR (mg/g)	1.000	1.000–1.000	0.432
Smoke	0.885	0.732–1.070	0.206
Drink	0.963	0.795–1.166	0.699
Left atrium diameter (mm)	1.049	1.029–1.070	0.000
Interventricular septum thickness (mm)	1.024	0.990–1.059	0.170
Left ventricular end-diastolic diameter (mm)	0.988	0.975–1.002	0.082
Left ventricular end-systolic diameter (mm)	0.984	0.965–1.003	0.099
Left ventricular posterior wall thickness (mm)	1.076	1.029–1.124	0.001
Aortic root inner diameter (mm)	1.018	0.997–1.039	0.088
Ejection fraction (%)	0.994	0.979–1.009	0.452

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-to-creatinine ratio.

Table 3 Multivariate Logistic Regression

Parameters	HR	95%	P value
Female	1.548	1.014–2.363	0.043
Age (years)	1.147	1.125–1.170	0.000
Diastolic pressure (mmHg)	1.030	1.008–1.052	0.006
Systolic pressure (mmHg)	0.994	0.980–1.009	0.448
Body mass index (kg/m^2)	1.074	0.992–1.163	0.076
Visceral fat area (cm^2)	0.996	0.992–1.001	0.141
Subcutaneous fat area (cm^2)	1.004	1.000–1.008	0.049
Diabetic duration (months)	1.000	0.998–1.003	0.628
HbA1c (%)	0.979	0.923–1.039	0.485
Family history of diabetes	1.327	0.991–1.779	0.058
Smoke	1.147	0.819–1.606	0.425
Drink	0.996	0.730–1.359	0.978
Serum albumin (g/L)	1.037	1.000–1.076	0.052
ALT (U/L)	1.002	0.989–1.015	0.790
AST (U/L)	0.998	0.978–1.018	0.823
Blood urea nitrogen (mmol/L)	1.021	0.958–1.088	0.530
Serum creatinine (umol/L)	1.006	0.994–1.017	0.332
ACR (mg/g)	1.000	1.000–1.000	0.632
Uric acid (umol/L)	1.001	0.999–1.002	0.461
Triglyceride (mmol/L)	1.080	0.970–1.203	0.160
Total cholesterol (mmol/L)	0.880	0.653–1.185	0.399
HDL-cholesterol (mmol/L)	0.836	0.408–1.714	0.625
LDL cholesterol (mmol/L)	1.157	0.828–1.617	0.394

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-to-creatinine ratio.

Sex Difference of Left Ventricular Diastolic Dysfunction in Different Age Groups

In the above analysis, we found age was an important factor associated with left ventricular diastolic dysfunction; thus, we analyzed the incidence of it in different age groups. The incidence of left ventricular diastolic dysfunction had no difference between male and female (female vs male, 16.5% vs 13.8%, $P > 0.05$) in patients less than 45 years old or more than 60 years old (female vs male, 80.2% vs 80.0%,$P > 0.05$). However, more females were with the left ventricular diastolic dysfunction than males in patients in age group of 45–60 years old (female vs male, 54.5% vs 46.9%, $P < 0.05$) (Figure 3).

Discussion

In the current study, we found that females were independently associated with left ventricular diastolic dysfunction in our cohort with type 2 diabetes, even after adjusting for important clinical confounding factors. More females were with the left ventricular diastolic dysfunction than males in patients in age group of 45–60 years old.

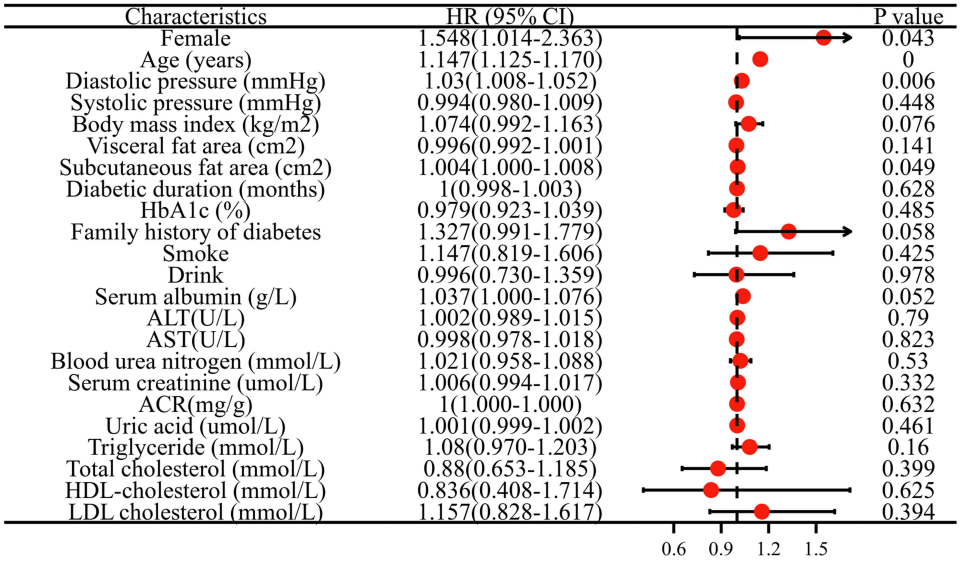

Figure 2 The association between clinical factors and left ventricular diastolic dysfunction determined by multivariate logistic analysis.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-to-creatinine ratio; HR, hazard ratio; CI, confidence interval.

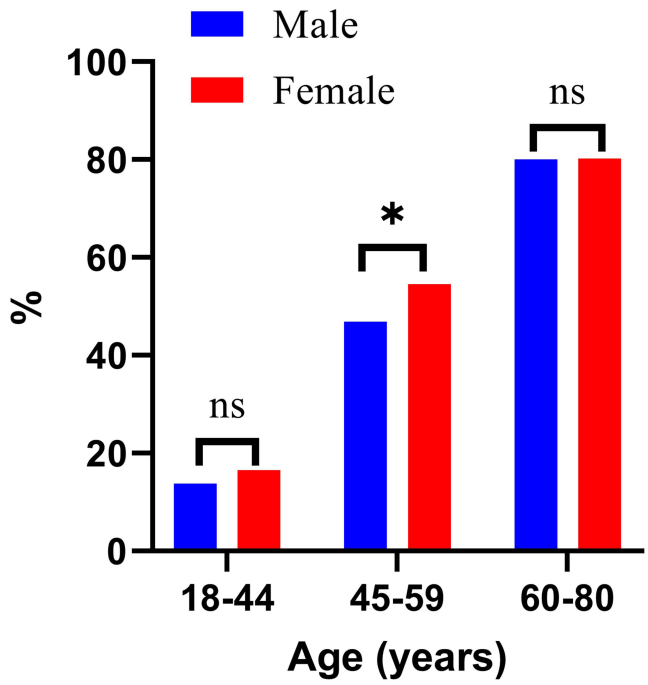

Figure 3 The sex difference of left ventricular diastolic dysfunction in different age groups.
Note: *P < 0.05.
Abbreviation: ns, not statistically significant.

Lifestyle changes and obesity increase the susceptibility to diabetes. The incidence of diabetes has increased dramatically, with one in ten people living with diabetes worldwide (https://diabetesatlas.org/). Cardiovascular disease is one of the serious macrovascular complications that causes high mortality of patients with type 2 diabetes. Well-controlled lipid and

glycemic levels have decreased the prevalence of cardiovascular disease. However, the incidence of heart failure remains high even after adjusting for common risk factors such as age, hypertension, and hypercholesterolemia in diabetes.[10] The estimated prevalence of heart failure in type 2 diabetic reached 22%.[11] Recent decades, diabetic cardiomyopathy has been considered as a significant mediating mechanism in the development of heart failure. Diabetic cardiomyopathy is defined as left ventricular dysfunction and cardiac structural maladaptation associated with diabetes independent of established risk factors such as coronary artery disease, hypertension, or valvular heart disease.[12] It is characterized by gradual diastolic and systolic dysfunctions. A recent study from the UK Biobank involving 3984 patients also indicated diabetic cardiomyopathy affected the heart globally.[13] It is important to slow down the progression of diabetic cardiomyopathy at the beginning. The EMPA-HEART cardioLink-6 randomized clinical trial[1] and DAPA-LVH trial[14] have both found that empagliflozin and dapagliflozin were able to be beneficial for left ventricular function. Moreover, DELIVER and EMPEROR-preserved studies recently found dapagliflozin and empagliflozin reduced composite cardiovascular death or first hospitalization for heart failure.[15] Therefore, identifying patients at high risk of diabetic cardiomyopathy, especially in left ventricular diastolic dysfunction and preserved ejection fraction stage, and giving them appropriate therapy timely are significant.

There are many risk factors associating with diabetic cardiomyopathy, such as BMI,[16] diabetic duration,[17] and insulin resistance states[18] in patients with type 1 diabetes. Obesity women with gestational diabetes mellitus have lower biventricular even in post-partum.[19] In our current study, based on type 2 diabetes, we just included patients with normal left ventricular systolic function and found that the higher level of BMI is independently associated with left ventricular diastolic dysfunction. Besides, we found that the older, higher diastolic pressure, and larger subcutaneous fat area also increase the risk for it. Mounting evidence suggests that females have the higher risk for cardiovascular disease.[8,20] The Framingham Heart Study indicated that diabetes independently increases the risk of heart failure in men by 2-fold and in women by of 5-fold, comparison with age-matched non-diabetic groups.[5] However, there is no study focus on a gender discrepancy of left ventricular diastolic dysfunction in type 2 diabetes. In our study, we found that females were independently associated with the left ventricular diastolic dysfunction, which is regarded as the early stage of diabetic cardiomyopathy.

In addition, we generally believe that the risk of heart disease in pre-menopausal females is lower than in males of the same age because the protective effect of estrogen. However, this protective effect is lost in patients with type 2 diabetes. When we stratified patients by age groups, we found the incidence of left ventricular diastolic dysfunction was same in patients with 18–44 years old and 61–80 years old groups, but the incidence was significantly higher in female with 45–60 years old than male. We speculated it might be associated with hormone fluctuations in perimenopause or menopause. The results remind us to screen the diabetic cardiomyopathy for this group of patients more carefully at an early stage and give them the most appropriate therapy in a timely manner.

The underlying mechanisms of sex differences in diabetic cardiomyopathy are complex and have not yet been studied thoroughly. There are several factors that may contribute to it. First and foremost is the role of sex steroid hormones. It is well documented that estrogen and progesterone have protective effect on glucose homeostasis and metabolic disorder.[21] Estrogen and its receptors are also could inhibit vascular injury and[22] have effect on endothelial cell growth and smooth muscle differentiation,[23] which are beneficial on cardiovascular.[24] The most direct evidence is hormone replacement therapy (HRT) of estrogens which protect cardiovascular disease in study.[25] However, these protective effects might disappear during the perimenopause and menopause periods and even would play a harmful role. Clarifying the issue can provide evidence of the HRT for females with diabetes who are perimenopause and menopause. There are other contributors of sex differences such as lifestyle. A study showed that testosterone and exercise can promote neoangiogenesis in rats with diabetes, which is associated with the increased expression of VEGF-A and SDF-1a to protect heart.[26]

In the current cross-sectional study (even in MMC at the First People's Hospital of Yunnan), we also found that the number of males was almost as twice as females, and males have significantly the higher BMI, triglyceride, and larger visceral fat area. In recent years, sex differences in diabetes have been addressed in many studies. However, it has not been fully understood and reached a consensus. Most epidemiological evidence shows that diabetes is more prevalent in males. According to a national cross-sectional study of China, the prevalence was also higher in males than females.[27] The underlying mechanisms are complicated, lifestyle including smoking or drinking, sex steroid hormones, energy expenditure, response for medications, and metabolic features all play important roles in the susceptibility of diabetes. In

males, the main metabolic characteristics include the higher skeletal muscle mass, visceral adiposity, and ectopic fat, but females are usually characterized with the higher total fat mass, subcutaneous adiposity, and higher peripheral insulin sensitivity.[28]

There are several limitations of the study. First, cause and effect cannot be well illustrated in a cross-sectional study, and prospective study is needed in future. Second, we decided to use real-world data to diminish the selective bias, but there are much more males than females in our cohort. This may relate to sex difference of incidence of type 2 diabetes or influenced by behavioral and environmental factors. Third, cardiovascular magnetic resonance is the most advanced way to evaluate cardiac function; however, there are few patients who would accept the examination because of it is expensive, and we would continue to collect results of the examination. Last, in order to study the diabetic cardiomyopathy, we excluded patients with hypertension and cardiovascular disease history. Therefore, the study sample is small.

Conclusion

Left ventricular diastolic function might be worse in female patients with type 2 diabetes. Further study is needed to verify the underlying mechanism.

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Disclosure

Yiting Wang and Yikun Zhou are co-first authors for this study. The authors report no conflicts of interest in this work.

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