ORIGINAL ARTICLE

Association between low cardiometabolic indexes and diastolic dysfunction in T2DM patients with HFpEF

Vina Yanti Susanti, PhD[1], Imam Manggalya Adhikara, PhD[2], Dhite Bayu Nugroho, PhD[2], Prenali Dwisthi Sattwika, MD[2], Vita Yanti Anggraeni, PhD[3], Andhika Widyaningsih, MD[4]

[1]Division of Endocrinology and Metabolic Disease, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital, [2]Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital, [3]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital, [4]Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital

ABSTRACT

Introduction: Dyslipidemia in metabolic syndrome characterized by low cardiometabolic indexes (TG/FBG, TG/HDL-C, and LDL-C/HDL-C) pose inherent risks for the development of diabetic cardiomyopathy. The tangible association between type 2 diabetes mellitus (T2DM) and Heart Failure with Preserved Ejection Fraction (HFpEF) initiated by diastolic dysfunction also has been widely studied. However, whether cardiometabolic indexes may be independently associated with left ventricular (LV) diastolic dysfunction in T2DM patients with HFpEF remained elusive. The aim of this study is to investigate the association between cardiometabolic indexes (TG/FBG, TG/HDL-C, and LDL-C/HDL-C) and diastolic dysfunction in T2DM patients with HFpEF.

Materials and Methods: In this cross-sectional study, we analyzed electronic medical records from October 2021 to January 2022 from Dr. Sardjito Hospital. A total of 55 T2DM patients with clinical HFpEF were enrolled. Baseline characteristics, clinical and laboratory variables, medication, and echocardiography data were obtained. Cardiometabolic indexes are presented as numeric data (median with IQR). Meanwhile, the diastolic function is presented as categorical data based on the echocardiographic parameters. Mann-Whitney analysis was performed. P-value <0.05 represent significant associations.

Results: In a cohort of 55 T2DM patients with HFpEF, subjects with diastolic dysfunction demonstrated significantly lower median values for TG/FBG (p=0.015), TG/HDL-C (p=0.003), and LDL-C/HDL-C (p=0.044) compared to those with normal diastolic function. These findings suggest a potential, albeit paradoxical, link between these cardiometabolic markers and impaired ventricular relaxation in this population.

Conclusion: TG/FBG, TG/HDL-C, and LDL-C/HDL-C were significantly associated with diastolic dysfunction. Optimal dyslipidemia control represented by high TG/FBG, TG/HDL-C, and LDL-C/HDL-C may become an appealing approach to prevent HFpEF progression in T2DM patients.

KEYWORDS:
Cardiometabolic indexes, diastolic dysfunction, T2DM, HFpEF

INTRODUCTION

Heart Failure with preserved Ejection Fraction (HFpEF) is now responsible for almost 50% of all heart failure cases. HFpEF is known to have many comorbidities burden, such as hypertension, diabetes mellitus, obesity, chronic kidney disease, chronic.[1] HFpEF has distinctive phenotype, not limited to diastolic dysfunction but rather resemble a systemic metabolic disorder with characterized as inflammation and microvascular dysfunction. These characteristics are the same as type 2 diabetes mellitus (T2DM) pathophysiology. T2DM can cause unique changes in myocardium and play role as independent classical risk factors of cardiovascular disease.[2–4] Diabetic cardiomyopathy is characterized with structural and functional abnormality, include diastolic dysfunction, myocardial, hypertrophy, interstitial fibrosis.[4] T2DM conditions can increase risk of heart failure two times and worsened it prognosis. Uncontrol T2DM can increased HF patient mortality up to 30-50%.[5]

Cardiometabolic syndrome is a combination of metabolic disorders and insulin resistance. This combination can cause cardiovascular disease (CVD) and be the most common global morbidity and mortality. T2DM and dyslipidemia increase the complication of CVD exponentially. Meanwhile the cardiometabolic indexes that have a role as cardiovascular complication predictors remain inconclusive.[6] Several cardiometabolic parameters have been researched such as triglyceride-fasting blood glucose index (TG/FBG), triglyceride-high density lipoprotein (TG/HDL), and low-density lipoprotein-high density lipoprotein (LDL/HDL). Cardiometabolic index ratio is better cardiovascular complication predictor than single metabolic parameter.[7]

TG/FBG index significantly associated with heart failure, acute myocardium infarct, and stroke progressivity.[8–10] Meanwhile the TG/HDL index has been strongly associated with insulin resistance, central obesity, and increasing CVD risk.[11] TG/HDL index was independent variable of all-cause and CVD mortality in peritoneal dialysis patients.[12] On the other hand, LDL/HDL index associated with risk of coronary artery disease (CAD), diastolic dysfunction, and other cardiovascular complications.[13-14]

Cardiometabolic index (TG/FBG, TG/HDL, and LDL/HDL) represent dyslipidemia and glycemic control which are

This article was accepted: 16 June 2025
Corresponding Author: Vina Yanti Susanti
Email: vinayantisusanti@ugm.ac.id

associated with cardiovascular complications.10 Meanwhile to our knowledge, there are just a few studies on the association between cardiometabolic index and left ventricular diastolic dysfunction as the initial sign of heart failure progressivity. Therefore, this study aimed to investigate the association between cardiometabolic index and diastolic dysfunction in T2DM patients with HFpEF.[1]

MATERIALS AND METHODS

This study is a cross-sectional study that was conducted from October 18, 2021, to January 31, 2022 at Dr. Sardjito Hopital. This study aimed to assess the association between cardiometabolic index and diastolic dysfunction in T2DM patients with HFpEF. All echocardiographic examinations were carried out using standard echocardiography tools (Vivid™) by the resident cardiologist on duty and the reading evaluation was carried out by a cardiology consultant specialist. Cardiometabolic parameters (TG, FBG, LDL, and HDL) examination was carried out using the standard method of blood venous which was checked when patients were routinely visit at the endocrinology clinic of Dr. Sardjito Hospital using a glucose one touch Point of Care Testing (POCT) examination so that it was recorded in laboratory symmetric data and medical records at Dr. Sardjito Hospital. The research subjects were patients who were routinely monitored at Dr. Sardjito Hospital. Inclusion criteria were all T2DM patients with clinical heart failure based on the Framingham criteria15 with LVEF > 50% . While the exclusion criteria were: (1) History of coronary heart disease; (2) History of heart surgery or congenital heart disease; (3) Severe renal impairment as indicated by estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73m^2 or undergoing renal replacement therapy; (4) Comorbid malignancy, chronic liver disease (5) Severe heart valve disorders; and (6) non-paroxysmal atrial fibrillation. Diagnosis of T2DM using the PERKENI criteria.[16]

This study received ethical approval from the Medical and Health Research Ethics Committee (MHREC) at Universitas Gadjah Mada – Dr. Sardjito General Hospital. Approval number KE/FK/0643/EC/2021 was issued on 11 June 2021, valid for one year, covering the study protocol, subject information, and informed consent forms. MHREC maintains oversight of the study in accordance with international and national guidelines.

Continuous variables were expressed as median and interquartile range (IQR), while categorical variables were presented as counts and percentages. Comparison of cardiometabolic indexes between the diastolic function groups was performed using the Mann–Whitney U test. The differences in medians along with p-values and 95% confidence intervals (CI) were reported to determine statistical significance. A p-value of less than 0.05 was considered statistically significant. Boxplots were used to illustrate the distribution of each cardiometabolic index (TG/FBG, TG/HDL-C, LDL-C/HDL-C) between groups. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, New York, USA).

RESULTS

A total of 55 eligible subjects with mean age 62.72 ± 8.27 years old are included in this study, which dominantly suffer T2DM for 5-10 years (62%). The subjects of this study were also dominated with hypertension (80%) and grade 1 obesity (47%). The mean of FBG is 137.16 ± 49.34. Meanwhile the mean of lipid profiles (TG, HDL, and LDL) are 145.96 ± 75.16, 46.93 ± 13.04, and 112.53 ± 37.45, respectively. Of the 55 subjects enrolled, 78% exhibited echocardiographic findings consistent with normal diastolic function. However, those with diastolic dysfunction had significantly lower cardiometabolic index values. As illustrated in Figure 1, the TG/FBG ratio (Panel A), TG/HDL-C ratio (Panel B), and LDL-C/HDL-C ratio (Panel C) were all significantly reduced in subjects with diastolic dysfunction compared to those with normal diastolic function (p=0.015, 0.003, and 0.044, respectively). These findings suggest a potential association between lower cardiometabolic index values and impaired ventricular relaxation. Other baseline characteristics of the subjects are presented in Table I.

Association between Cardiometabolic Indexes (TG/FBG, TG/HDL, and LDL/HDL) and Diastolic Dysfunction

The comparison of cardiometabolic index values between subjects with normal diastolic function and those with diastolic dysfunction is illustrated in Figure 1. In Panel A, subjects with diastolic dysfunction had significantly lower TG/FBG ratios compared to those with normal diastolic function (median [IQR]: 0.62 [0.38–0.86] vs. 1.00 [0.75–1.41]; p = 0.015). In Panel B, TG/HDL-C was also markedly lower in the diastolic dysfunction group (1.54 [1.16–1.88] vs. 2.82 [2.03–4.11]; p=0.003). Similarly, Panel C shows that LDL-C/HDL-C was significantly reduced in patients with diastolic dysfunction (1.87 [1.18–2.27] vs. 2.40 [1.89–3.23]; p=0.044). These findings demonstrate a consistent pattern: patients with diastolic dysfunction had significantly lower cardiometabolic index values across all three ratios, suggesting a potential link between lower cardiometabolic burden and the presence of subclinical cardiac dysfunction in T2DM patients with HFpEF. The complete result of bivariate analysis is presented in Table II.

DISCUSSION

This cross-sectional study demonstrated a large proportion (78%) of patients in this T2DM-HFpEF cohort were categorized as having normal diastolic function based on echocardiographic parameters. This apparent paradox may reflect the limitations of current diastolic dysfunction grading criteria, particularly in distinguishing early or subclinical forms of dysfunction in patients with T2DM. It is also possible that diastolic function was assessed during a compensated phase, where structural and functional abnormalities may not be overt. Furthermore, the diagnosis of HFpEF relies not only on echocardiographic parameters but also on clinical presentation, natriuretic peptide levels, and comorbidities, as highlighted in the HFA-PEFF diagnostic algorithm. Therefore, echocardiographic classification alone may underestimate diastolic dysfunction in some clinically diagnosed HFpEF cases.

Table I: Baseline characteristics of the participants

Parameters	Overall (n = 55)
Demographics	
Age (years), mean ± SD	62.7 ± 8.3
> 60 years, n (%)	35 (63%)
Female, n (%)	34 (62%)
Diabetes Mellitus Duration, n (%)	
< 5 years	7 (13%)
5–10 years	34 (62%)
> 10 years	14 (25%)
Hypertension, n (%)	44 (80%)
Anthropometric Data	
Body weight (kg), mean ± SD	64.9 ± 13.1
Height (cm), mean ± SD	157.6 ± 6.9
Body Mass Index (kg/m²), mean ± SD	26.0 ± 4.4
< 18.5 (underweight), n (%)	3 (5%)
18.5–22.9 (normal weight), n (%)	8 (15%)
23.0–24.9 (overweight), n (%)	10 (18%)
25.0–29.9 (grade 1 obesity), n (%)	26 (47%)
≥ 30 (grade 2 obesity), n (%)	8 (15%)
Blood Pressure	
Systolic blood pressure (mmHg), mean ± SD	138.1 ± 23.2

Table II: Association between TG/FBG, TG/HDL-C, and LDL-C/HDL-C and diastolic dysfunction

Index	Normal median [IQR]	Diastolic dysfunction median [IQR]	p-value	95% CI
TG/FBG	1.00 [0.75–1.41]	0.62 [0.38–0.86]	0.015	–0.89 to –0.07
TG/HDL-C	2.82 [2.03–4.11]	1.54 [1.16–1.88]	0.003	–2.63 to –0.48
LDL-C/HDL-C	2.40 [1.89–3.23]	1.87 [1.18–2.27]	0.044	–1.47 to –0.01

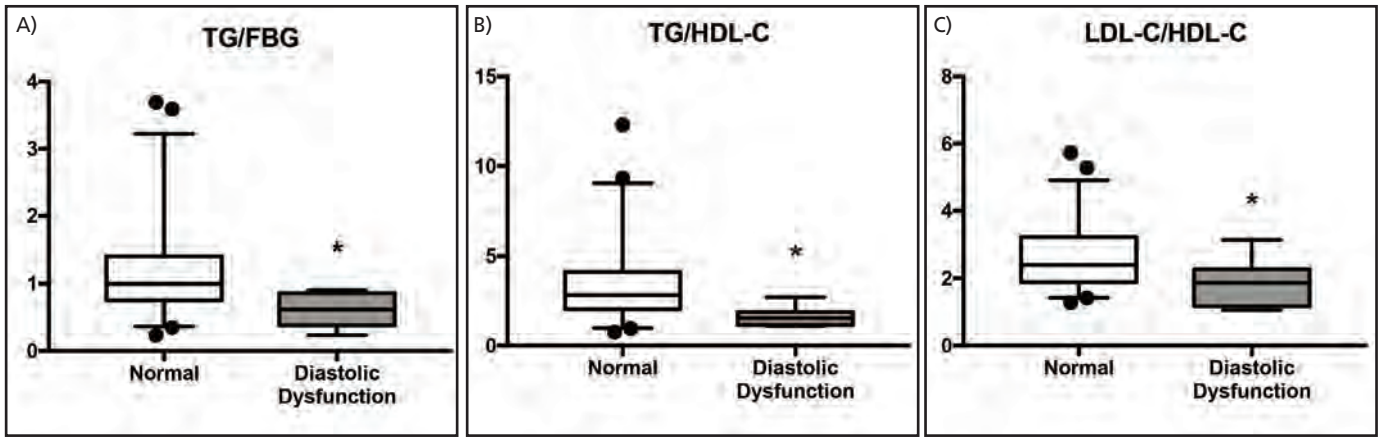

Fig. 1: Distribution of cardiometabolic indexes according to diastolic function status. (A) Triglyceride-to-fasting blood glucose (TG/FBG) ratio; (B) Triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio; (C) Low-density lipoprotein-to-high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio. In each plot, the median, interquartile range (IQR), and outliers are shown. Comparisons were made between normal and abnormal diastolic function groups using the Mann–Whitney U test.

Our studies found that there is association between TG/FBG and diastolic dysfunction with p-value 0.015, CI 95% -0.89 to -0.07. TG/FBG was a reliable predictor for metabolic syndrome, including BMI, HbA1c, blood pressure, insulin resistance etc. Recent study also showed that TG/FBG index was strongly associated with greater risk of developing HFpEF. TG/FBG play a role as reliable biomarker to identify asymptomatic HFpEF patients.[17-18] On the other hand, recent studies proved that TG/FBG also significantly associated with other CVD, such as CAD, stroke, and lower limb vascular stenosis.[19-20]

The other parameter which uses TG and FBG as its component is Triglyceride-glucose index (TyG). TyG suggested as a reliable and valuable predictor for risk stratification and prognostic indicator in CHF patients. Increasing TyG value correlated significantly with increasing mortality incidence in CHF patients. The predictive implication of TyG index mainly found in HFmrEF and HFpEF patients.[21] TyG index also can be an independent and causal risk factor for HF incident. Based on some recent studies the TyG index were well correlated with insulin resistance. Insulin resistance contribute to abnormal circulating free

fatty acids and triglycerides, increasing proinflammatory molecules, and maladaptive activation of renin-angiotensin-aldosterone system which cause cardiac dysfunction.[22]

TG/HDL-C index represents the cardiovascular events and part of the cardiometabolic index which is a novel indicator for abdominal fat and strongly correlated with hypertension, hyperuricemia, diabetes, arterial stiffness, and CVD assessment. TG/HDL-C can detect LVH, metabolic disorders, and myocardial infarction.[23-24] TG/HDL-C known as atherogenic index of plasma which is associated with coronary artery disease risk and outcomes.[25] TG/HDL-C index has positive association with metabolic syndrome and insulin resistance which is also the positive risk factor of diastolic dysfunction.[26-27] This study found that there is significant association between the TG/HDL-C index with diastolic dysfunction (p-value 0.0003, CI 95% -2.63 to -0.48). Similar result was also found in a study done by Khedr et al in a T1DM patient. There is positive association between TC/HDL and TG/HDL index with diastolic complication in T1DM patients with p-value 0.016 and 0.028, respectively. HDL, TC/HDL, and TG/HDL can predict diastolic dysfunction only in female patients.[14]

Mechanism of association between TG/HDL-C and diastolic dysfunction remains unclear. There is some speculation of its mechanism. First, TG/HDL-C represent insulin resistance (IR). Higher IR associated with left ventricular diastolic dysfunction. The changes of myocardial diastolic function are already present in subclinical T2DM.[27–29] Secondly, TG/HDL-C also represent metabolic syndrome. Metabolic syndrome associated with high pro-inflammatory cytokines level.[30] Thirdly, decreasing HDL-C and increasing TG can elevate myocellular lipid accumulation and trigger lipoapoptosis which can cause diastolic dysfunction. Low HDL-C concentration also causes arterial stiffness and increasing myocardiocytes hypertrophy which can induce diastolic dysfunction.[26]

In this study the LDL/HDL was significantly associated with diastolic dysfunction The similar result was consistent with previous study (p-value 0.044, CI 95% -1.47 to -0.01). High LDL-C/HDL-C associated with increased HbA1c, decreased eGFR, CHD, and left ventricular hypertrophy in elderly.[31] One of the most important things in left ventricular hypertrophy pathophysiology is myocardial fibrosis which is clinically manifested by diastolic dysfunction.[32] Increasing LDL and decreasing HDL are two components of dyslipidemia which significantly correlated with diastolic dysfunction. The severity of diastolic dysfunction was also significantly correlated with LDL level. Oxidized LDL in the blood inhibit the function of HDL and also cause endothelial dysfunction and cardiomyocytes apoptosis. On the other hands, dyslipidemia induce alterations in myocardial lipid metabolism, increase inflammation, and oxidative stress which ultimately lead to cardiac lipotoxicity and diastolic dysfunction.[32-33]

About 30-60% T2DM patients, either with normal or abnormal glycemic control, have dyslipidemia, specifically high TG, high LDL, and low HDL.[34] In T2DM patients, dyslipidemia tends to be the main factor in the CVD. CVD risk also associated with HbA1c levels, every 1% increase in absolute HbA1C levels increasing the CVD risk about 18%. Poor glycemic index can increase the FBG, TC, TG, and TC/HDL-C.[35] T2DM patients can experienced diabetic myocardial dysfunction with main features impaired in left ventricular diastolic function. The glycemix control level (HbA1C) and duration of T2DM also strongly correlated with diastolic dysfunction.[31,36] Persistent hyperglycemias induce abnormal lipid metabolism, systemic inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system (RAAS), and myocardial microvasculopathy. Those complex mechanism led to diastolic dysfunction which can cause heart failure.[31]

All of cardiometabolic indexes analyzed in this study, either TG/FBG, TG/HDL, or LDL/HDL are easily calculated, cheap, and commonly available parameters in most laboratories.In this study all of those indexes are significantly associated with diastolic dysfunction in T2DM patient with HFpEF. This result indicates that there is probability of cardiometabolic indexes as diastolic dysfunction predictor in T2DM patients with HFpeF.

This study has several limitations that should be acknowledged. First, the cross-sectional design prevents any inference of causality between cardiometabolic indexes and diastolic dysfunction. Second, the relatively small sample size from a single center may limit the generalizability of our findings to broader populations with T2DM and HFpEF. Third, the reliance on echocardiographic parameters alone to define diastolic dysfunction may underestimate subclinical abnormalities, particularly in patients with preserved ejection fraction. Additionally, the potential influence of medications, glycemic control variability, and unmeasured confounding factors (e.g., natriuretic peptides or left atrial strain) could not be fully accounted for in the analysis. Future prospective studies with larger and more diverse cohorts are warranted to validate these findings.

CONCLUSIONS

This study showed that lower cardiometabolic indexes characterized by TG/FBG, TG/HDL-C, and LDL-C/HDL-C were significantly associated with diastolic dysfunction in T2DM patients with HFpEF. These findings suggest that these easily calculated lipid ratios could serve as potential biomarkers for identifying T2DM patients at risk for diastolic dysfunction. Further prospective research is warranted to validate these associations and clarify their underlying mechanisms and clinical utility.

CONFLICT OF INTEREST

All the authors declare that there are no conflicts of interest.

ACKNOWLEDGMENT

We thank the patients and their families who contributed to these studies. We are also grateful to the many staff members and those who provided excellent technical support and assistance throughout the study.

FUNDING
This study received no external funding.

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