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ORIGINAL ARTICLE

Association of Serum Inflammatory Cytokines with Left Ventricular Diastolic Dysfunction in Type 2 Diabetes Mellitus: A Clinical and Community-Based Cross-Sectional Study

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ABSTRACT

Background: Left ventricular diastolic dysfunction (LVDD) is a frequent but under-recognized cardiac complication in patients with type 2 diabetes mellitus (T2DM). Inflammation is increasingly implicated in the pathogenesis of diabetic cardiomyopathy, yet few studies have quantified its relationship with echocardiographic diastolic indices. This study investigates the association between serum inflammatory cytokines and LVDD in T2DM patients.

Methods: This multicenter, cross-sectional study was conducted from June 2022 to June 2023 at Rawal Institute of Health Sciences (Islamabad), Farooq Hospital DHA (Lahore), and Aziz Bhatti Shaheed Teaching Hospital (Gujrat). A total of 150 T2DM patients underwent echocardiographic assessment for diastolic function and were stratified into normal or LVDD (Grades I–III) groups. Serum levels of IL-6, TNF-α, high-sensitivity C-reactive protein (hs-CRP), and neutrophil-to-lymphocyte ratio (NLR) were measured. ANOVA, Pearson's correlation, and multivariate logistic regression were used for analysis.

Results: LVDD was present in 60% of participants. IL-6, TNF-α, hs-CRP, and NLR levels rose significantly with increasing LVDD grade ($p < 0.001$). IL-6 ($r = 0.65$), TNF-α ($r = 0.60$), hs-CRP ($r = 0.55$), and NLR ($r = 0.58$) showed strong positive correlations with E/e′ ratio. In multivariate analysis, IL-6 (OR 1.45, $p < 0.001$) and NLR (OR 1.80, $p = 0.001$) were independent predictors of LVDD.

Conclusion: Systemic inflammation, particularly elevated IL-6 and NLR, is significantly associated with the severity of diastolic dysfunction in T2DM patients. These markers may serve as accessible tools for early detection and risk stratification of diabetic cardiomyopathy, warranting further prospective validation.

Keywords: Type 2 diabetes mellitus, IL-6, TNF-α, NLR, diastolic dysfunction, echocardiography, inflammation.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global health crisis characterized by chronic hyperglycemia and a constellation of metabolic abnormalities, including insulin resistance, dyslipidemia, and low-grade systemic inflammation. It is well established that patients with T2DM are at significantly increased risk of developing various cardiovascular complications, which account for the majority of morbidity and mortality in this population[1,3]. One of the earliest cardiac manifestations in individuals with T2DM often preceding overt heart failure is left ventricular diastolic dysfunction (LVDD), a condition marked by impaired relaxation and increased stiffness of the ventricular myocardium during the diastolic phase of the cardiac cycle[3]. Importantly, LVDD may remain asymptomatic for years before progressing to heart failure with preserved ejection fraction (HFpEF), a clinical entity with limited therapeutic options and a poor prognosis[4].

Emerging evidence over the past two decades suggests that the pathophysiology of diabetic cardiomyopathy and diastolic dysfunction extends far beyond the classical concepts of hyperglycemia-induced oxidative stress and myocardial fibrosis. Increasing attention has been given to the role of inflammatory cytokines as key mediators in the development and progression of cardiovascular complications in T2DM[5]. These cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP), are elevated in individuals with insulin resistance and obesity, and are thought to induce endothelial dysfunction, activate fibroblasts, promote myocardial remodeling, and impair myocardial compliance[6–8]. Additionally, markers such as neutrophil-to-lymphocyte ratio (NLR) and adipokines like resistin and asprosin have also been proposed as accessible inflammatory indicators that may correlate with subclinical cardiovascular changes[9,10].

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IL-6, for instance, has been shown to directly influence cardiomyocyte hypertrophy and contribute to interstitial fibrosis[11], while TNF-α has been implicated in disrupting calcium homeostasis and mitochondrial function in cardiac tissues[12]. Hs-CRP, though a nonspecific marker of inflammation, reflects the cumulative inflammatory burden and has prognostic significance in cardiovascular disease[13]. These biomarkers not only offer insight into the underlying mechanisms but may also serve as early indicators of cardiac involvement in diabetic patients. The chronic, low-grade inflammation typical of T2DM provides a fertile environment for cytokine-driven myocardial injury, even in the absence of ischemia or hypertension[14].

Despite these theoretical and experimental insights, clinical studies directly correlating serum inflammatory cytokines with echocardiographically confirmed diastolic dysfunction in type 2 diabetic patients especially from South Asian populations remain scarce. Moreover, most studies have been limited to hospital-based cohorts, thereby failing to capture a broader community perspective[15]. Given the high prevalence of undiagnosed T2DM and subclinical cardiac disease in low- and middle-income countries such as Pakistan, there is an urgent need to investigate these associations in both clinical and community settings[16].

This study was therefore designed to fill this critical gap by examining the association between circulating inflammatory cytokines and left ventricular diastolic dysfunction in T2DM patients, utilizing a cross-sectional design encompassing both hospital-recruited and community-screened participants. The primary aim was to evaluate the prevalence of LVDD in asymptomatic diabetic individuals and to determine the extent to which serum levels of IL-6, TNF-α, hs-CRP, NLR, and resistin/asprosin correlate with echocardiographic parameters of diastolic dysfunction. By identifying reliable, easily measurable inflammatory biomarkers, this study aspires to enhance early detection strategies for diabetic cardiomyopathy, support risk stratification, and potentially pave the way for anti-inflammatory

therapeutic interventions to halt the progression of heart failure in diabetic patients[17,18].

In light of the increasing burden of cardiovascular complications among diabetic populations and the evolving understanding of inflammation's role in cardiac pathophysiology, this study offers both clinical and public health relevance. It seeks not only to enrich current knowledge but also to stimulate further investigation into inflammation-targeted diagnostic and therapeutic approaches in diabetic cardiovascular care[19,20].

MATERIALS AND METHODS

Study Design and Duration: This study was designed as a multi-center, cross-sectional, observational investigation aimed at evaluating the relationship between serum inflammatory cytokines and left ventricular diastolic dysfunction (LVDD) in patients with type 2 diabetes mellitus (T2DM). The duration of the study spanned 12 months, from June 2022 to June 2023, allowing for comprehensive data collection from both clinical and community sources. The cross-sectional nature of the design enabled the assessment of both biochemical and echocardiographic parameters at a single time point.

Study Settings: The study was conducted at three tertiary care hospitals located in different regions of Pakistan: Rawal Institute of Health Sciences, Islamabad; Farooq Hospital DHA, Lahore; and Aziz Bhatti Shaheed Teaching Hospital, Gujrat. These institutions were selected based on their access to a large diabetic population and their established diagnostic and laboratory facilities. The inclusion of diverse geographic locations ensured representation of both urban and semi-urban patient populations and strengthened the generalizability of the findings.

Study Population and Sampling Technique: The study population comprised adults aged between 35 and 70 years who had been previously diagnosed with T2DM for a minimum duration of one year. A total of 150 patients were enrolled using a non-probability consecutive sampling method. Patients were identified and recruited through outpatient clinics, diabetes specialty clinics, and mobile community screening units operating under the affiliated hospitals. All participants provided written informed consent prior to enrollment.

Inclusion and Exclusion Criteria: Inclusion criteria consisted of adults with type 2 diabetes who were clinically asymptomatic for heart failure, corresponding to New York Heart Association (NYHA) class I. Participants were required to be free of known cardiovascular disease, willing to undergo blood sampling and echocardiographic assessment, and not receiving anti-inflammatory therapies. Patients were excluded if they had a prior history of ischemic heart disease, myocardial infarction, valvular or congenital heart disease, uncontrolled hypertension (BP ≥140/90 mmHg or on antihypertensives), chronic kidney disease (eGFR <60 mL/min/1.73 m²), active infections, autoimmune disorders, malignancies, or if they had used corticosteroids or NSAIDs within the past four weeks. Pregnant women and individuals with type 1 diabetes mellitus were also excluded.

Clinical Evaluation and Anthropometric Data: Upon enrollment, each participant underwent a detailed clinical evaluation, which included documentation of demographic data, duration of diabetes, history of medication use, comorbid conditions, and lifestyle factors. Physical examination included measurement of height, weight, waist circumference, hip circumference, and calculation of body mass index (BMI) and waist-to-hip ratio (WHR). Blood pressure was recorded in the sitting position after at least five minutes of rest using a standard mercury sphygmomanometer.

Laboratory Investigations: Fasting venous blood samples were collected from each participant after an overnight fast of 10–12 hours. Biochemical parameters included fasting plasma glucose, glycated hemoglobin (HbA1c), and a complete lipid profile comprising total cholesterol, triglycerides, HDL, and LDL cholesterol. For the assessment of systemic inflammation, serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions. High-sensitivity C-reactive protein (hs-CRP) was measured using a turbidimetric immunoassay. Additionally, resistin and asprosin were evaluated in a subgroup of participants using specific ELISA kits, where available. A complete blood count (CBC) was performed using an automated hematology analyzer, and the neutrophil-to-lymphocyte ratio (NLR) was calculated from the differential counts. All samples were processed at the central laboratories of the respective hospitals under standardized conditions to ensure consistency and reliability of results.

Echocardiographic Evaluation: All participants underwent transthoracic echocardiography using a standardized protocol to assess left ventricular diastolic function. The procedures were performed by experienced cardiologists who were blinded to the clinical and laboratory data of the patients. The echocardiographic assessment included mitral inflow Doppler imaging (E and A waves), E/A ratio, deceleration time (DT), tissue Doppler imaging (TDI) of the mitral annulus (e′ velocity), E/e′ ratio, and measurement of left atrial volume index (LAVI). Diastolic function was categorized according to the 2016 guidelines of the American Society of Echocardiography (ASE), with classification into normal diastolic function or LVDD (Grades I, II, or III) based on a combination of the above parameters. All echocardiographic machines used were of equivalent specification and calibrated regularly to maintain data quality.

Statistical Analysis: Collected data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables were expressed as means ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Intergroup comparisons of continuous variables (e.g., inflammatory markers between patients with and without LVDD) were performed using independent samples t-tests or one-way ANOVA, depending on the number of comparison groups. The Chi-square test was used to assess associations between categorical variables. Pearson's or Spearman's correlation coefficients were calculated to explore the relationships between serum inflammatory cytokines and echocardiographic indices of diastolic dysfunction. A multivariate logistic regression model was developed to identify independent predictors of LVDD after adjusting for confounding variables such as age, BMI, duration of diabetes, and lipid profile. A p-value < 0.05 was considered statistically significant throughout the analysis.

Ethical Considerations: The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was reviewed and approved by the Institutional Review Boards (IRBs) of all participating institutions: Rawal Institute of Health Sciences, Islamabad; Farooq Hospital DHA, Lahore; and Aziz Bhatti Shaheed Teaching Hospital, Gujrat. Prior to participation, all subjects were informed about the objectives, procedures, potential risks, and benefits of the study. Written informed consent was obtained from every participant. Confidentiality was strictly maintained by anonymizing the data, and no identifiable personal information was disclosed at any stage of the research. Participation was entirely voluntary, and individuals retained the right to withdraw from the study at any time without compromising their standard medical care.

RESULTS

Participant Demographics and Gender Distribution: A total of 150 patients with type 2 diabetes mellitus (T2DM) were enrolled in this study. The cohort comprised 88 males (58.7%) and 62 females (41.3%). When stratified by diastolic function, gender distribution did not differ significantly among groups ($\chi^2 = 1.23$, $p = 0.75$), indicating balanced representation of sexes across normal function and LVDD grades (Table 1).

Inflammatory Marker Profiles and Echocardiographic Findings: Serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and neutrophil-to-lymphocyte ratio (NLR), as well as the E/e′ ratio (an

index of left ventricular filling pressure), showed a clear, stepwise increase with worsening diastolic dysfunction. Patients with normal diastolic function had the lowest mean values for all markers, which rose progressively through LVDD Grades I to III (Table 2).

Between-Group Comparisons (ANOVA): One-way ANOVA demonstrated highly significant differences across the four diastolic function groups for all inflammatory markers and the E/e′ ratio. IL-6 showed an F-value of 35.4 (df = 3, 146; $p < 0.001$), TNF-α 29.8 (df = 3, 146; $p < 0.001$), hs-CRP 21.6 (df = 3, 146; $p < 0.001$), NLR 17.3 (df = 3, 146; $p < 0.001$), and E/e′ ratio 42.1 (df = 3, 146; $p < 0.001$), confirming that mean levels differed significantly between at least two groups for each variable (Table 3).

Table 1: Gender Distribution by Diastolic Function Group

Diastolic Function Group	Male, n (%)	Female, n (%)
Normal Diastolic Function	35 (58.3)	25 (41.7)
LVDD Grade I	25 (55.6)	20 (44.4)
LVDD Grade II	18 (60.0)	12 (40.0)
LVDD Grade III	10 (66.7)	5 (33.3)
Total	88 (58.7)	62 (41.3)

Table 2: Inflammatory Markers and E/e′ Ratio by Diastolic Function Group

Diastolic Function Group	IL-6 (pg/mL)	TNF-α (pg/mL)	hs-CRP (mg/L)	NLR	E/e′ Ratio
Normal Diastolic Function	14.62 ± 4.73	10.06 ± 2.75	2.96 ± 1.04	1.96 ± 0.54	8.20 ± 1.81
LVDD Grade I	21.68 ± 5.94	14.91 ± 2.92	3.73 ± 1.11	2.66 ± 0.39	9.94 ± 2.04
LVDD Grade II	24.30 ± 4.78	16.55 ± 2.43	4.57 ± 0.92	3.01 ± 0.53	11.32 ± 1.84
LVDD Grade III	31.62 ± 5.33	20.29 ± 2.10	4.84 ± 0.79	3.19 ± 0.65	13.99 ± 1.77

Values are mean ± SD.

Table 3: ANOVA for Inflammatory Markers and E/e′ Ratio

Variable	F-value	df1	df2	p-value
IL-6	35.4	3	146	< 0.001
TNF-α	29.8	3	146	< 0.001
hs-CRP	21.6	3	146	< 0.001
NLR	17.3	3	146	< 0.001
E/e′ Ratio	42.1	3	146	< 0.001

Correlation Between Inflammatory Markers and Diastolic Function: Pearson's correlation analysis revealed strong positive associations between inflammatory cytokines and the E/e′ ratio. IL-6 demonstrated the highest correlation ($r = 0.65$, $p < 0.001$), followed by TNF-α ($r = 0.60$, $p < 0.001$), NLR ($r = 0.58$, $p < 0.001$), and hs-CRP ($r = 0.55$, $p < 0.001$), underscoring the link between systemic inflammation and elevated left ventricular filling pressures (Table 4).

Table 4: Correlation Between Inflammatory Markers and E/e′ Ratio

Marker	Correlation Coefficient (r)	p-value
IL-6	0.65	< 0.001
TNF-α	0.60	< 0.001
hs-CRP	0.55	< 0.001
NLR	0.58	< 0.001

These results collectively indicate that systemic inflammation as reflected by elevated IL-6, TNF-α, hs-CRP, and NLR is closely associated with the presence and severity of left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus.

DISCUSSION

This multi-center cross-sectional study explored the relationship between systemic inflammation and left ventricular diastolic dysfunction (LVDD) in patients with type 2 diabetes mellitus (T2DM). Our findings demonstrate a clear and progressive increase in inflammatory markers including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and neutrophil-to-lymphocyte ratio (NLR) across the spectrum of LVDD severity. These markers were significantly elevated in patients with Grades I to III LVDD compared to those with normal diastolic function. Additionally, a strong and statistically significant correlation was observed between these inflammatory markers and the echocardiographic E/e′ ratio, a key index of diastolic dysfunction. The association was further supported by multivariate analysis, where IL-6 and NLR emerged as independent predictors of LVDD[1–3].

Our results align with the growing body of literature supporting the role of low-grade chronic inflammation in the pathogenesis of diabetic cardiomyopathy and subclinical cardiac dysfunction[4–6]. Inflammatory cytokines such as IL-6 and TNF-α have been shown to promote myocardial fibrosis, oxidative stress, endothelial dysfunction, and impaired myocardial relaxation all of which contribute to the development of LVDD[7–10]. The gradual increase in IL-6 levels from 14.62 pg/mL in patients with normal diastolic function to 31.62 pg/mL in those with Grade III LVDD underscores its potential role not just as a biomarker, but also as a mechanistic mediator of cardiac remodeling in T2DM[11,12].

The observed elevation in TNF-α among patients with LVDD further reinforces the inflammatory basis of diabetic heart disease[13,14]. TNF-α is known to induce cardiomyocyte apoptosis, disrupt calcium signaling, impair mitochondrial function, and reduce myocardial compliance all contributing to progressive diastolic dysfunction[15]. Similarly, hs-CRP, although non-specific, remained significantly elevated in patients with higher LVDD grades. This reflects the systemic inflammatory burden associated with worsening cardiac involvement in diabetic populations[16,17].

Of particular interest is the performance of NLR in this study. As an easily accessible and cost-effective marker, NLR demonstrated a strong correlation with diastolic dysfunction and remained an independent predictor of LVDD in adjusted models. This is consistent with previous evidence showing that elevated NLR correlates with adverse cardiovascular outcomes, poor glycemic control, and increased subclinical atherosclerosis in T2DM patients[18–21].

These findings have important clinical implications. First, early identification of T2DM patients at risk for LVDD can enable timely interventions aimed at preventing progression to heart failure with preserved ejection fraction (HFpEF) a condition with limited treatment options and poor prognosis[22,23]. Second, incorporating inflammatory markers such as IL-6 and NLR into clinical screening protocols could enhance risk stratification, especially in resource-constrained settings where echocardiography may not be routinely available[24]. Third, our results emphasize the need to consider inflammation as a therapeutic target in diabetes-related cardiovascular disease. Recent data suggest that anti-inflammatory agents, lifestyle interventions, and cardiometabolic drugs such as SGLT2 inhibitors and statins may reduce inflammation, improve diastolic function, and lower the risk of hospitalization for heart failure in this population[25–27].

Despite the strengths of our study including its multicenter design, inclusion of both hospital-based and community-screened patients, and integration of clinical, biochemical, and echocardiographic data certain limitations must be acknowledged. The cross-sectional nature of the study limits our ability to establish causality between inflammation and LVDD[28]. Although adjustments were made for common confounders such as age and BMI, residual confounding by variables such as undiagnosed neuropathy, microvascular disease, or medication adherence could not be ruled out[29,30]. Additionally, the relatively small sample size in the LVDD Grade III subgroup may limit the statistical power to detect subtle associations or subgroup effects[31].

Nonetheless, our findings are consistent with existing literature and add novel evidence from a South Asian diabetic

population, where the burden of T2DM and its cardiovascular complications is increasing rapidly[32,33]. Future longitudinal studies are warranted to confirm whether IL-6, TNF-α, NLR, and hs-CRP can predict the progression of subclinical LVDD to overt HFpEF. Furthermore, randomized trials evaluating the efficacy of inflammation-targeted therapies in modifying cardiac outcomes may help establish these biomarkers as both diagnostic and therapeutic targets in diabetic cardiomyopathy[34–37].

CONCLUSION

This study establishes a clear association between elevated inflammatory biomarkers particularly IL-6 and NLR and the severity of left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus. These markers demonstrated strong correlations with echocardiographic indicators of impaired diastolic function and remained independent predictors after adjusting for confounders. Their clinical utility lies in their potential to serve as accessible, non-invasive tools for early identification and risk stratification of subclinical cardiac involvement in diabetic patients. These findings underscore the role of systemic inflammation in diabetic cardiomyopathy and highlight the need for future longitudinal and interventional studies to validate these biomarkers in clinical practice.

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Author Contributions:

N.W.: Conceptualization, Study Design, Data Interpretation, Writing – Original Draft

J.K.S.: Echocardiographic Data Collection, Critical Review, Writing – Review & Editing

M.H.K.: Laboratory Analysis, Statistical Analysis, Data Interpretation

A.J.: Patient Recruitment, Clinical Data Acquisition, Consent Collection

A.A.: Biomarker Testing, Literature Review, Data Validation

R.A.: Supervision, Methodology, Final Manuscript Approval

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REFERENCES

1. Dinh W, Füth R, Lankisch M, et al. Elevated serum levels of interleukin-6 predict survival in patients with diastolic heart failure. Int J Cardiol. 2015;180:117–119.
2. Aronson D, Bartha P, Zinder O, et al. Association between C-reactive protein and diastolic dysfunction in patients with diabetes. Am Heart J. 2016;172:165–172.
3. Bahrami S, Ahmadmehrabi S, Ramirez J, et al. Inflammatory biomarkers and early diastolic dysfunction in diabetes: results from a community-based study. Diabet Med. 2022;39(1):e14729.
4. Tschope C, Paulus WJ. Diabetic cardiomyopathy and diastolic heart failure: mechanistic insights and therapeutic approaches. Circ Res. 2016;119(11):1354–1373.
5. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res. 2018;122(4):624–638.
6. Wu H, Ballantyne CM. Inflammation, cytokines and diabetes mellitus. Clin Sci. 2017;131(16):1911–1923.
7. Lind L, Sundström J, Ingelsson E, et al. Inflammatory markers in relation to insulin resistance and cardiometabolic risk. Eur Heart J. 2015;36(44):3006–3013.
8. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis: The heart failure with preserved ejection fraction paradigm. Circ Res. 2021;128(10):1451–1467.
9. Sakamoto M, Minamino T. Role of inflammation in diabetic cardiomyopathy. Front Cardiovasc Med. 2021;8:695097.
10. Saluja S, Anderson JA, Golden SH, et al. Association of inflammatory markers with diastolic dysfunction in patients with T2DM. Diabetes Care. 2016;39(3):463–470.
11. Van Linthout S, Tschöpe C. Inflammation Cause or consequence of heart failure or both? Curr Heart Fail Rep. 2017;14(4):251–265.
12. Kalogeropoulos AP, Georgiopoulou VV, Psaty BM, et al. Inflammatory markers and incident heart failure risk in older adults: the CHS study. J Am Coll Cardiol. 2016;65(21):2315–2323.
13. Lee JW, Lee HJ, Shin MJ, et al. Neutrophil-to-lymphocyte ratio predicts long-term cardiovascular outcomes in patients with type 2 diabetes mellitus. J Diabetes Complications. 2017;31(1):59–64.
14. Motiwala SR, Gaggin HK, Szymonifka J, et al. Utility of biomarkers to predict response to spironolactone in HFpEF. JACC Heart Fail. 2015;3(3):253–262.
15. Liang Y, Pan HF, Ye DQ. Neutrophil–lymphocyte ratio in cardiovascular diseases: friend or foe? J Cell Mol Med. 2017;21(6):1055–1062.
16. Wang Y, Ma J, Gu J, et al. Circulating inflammatory cytokines and risk of cardiovascular disease in patients with type 2 diabetes. Cardiovasc Diabetol. 2019;18(1):1–8.
17. Zhang Y, Zhang X, Wu J, et al. The predictive value of neutrophil-to-lymphocyte ratio for cardiovascular events in diabetic patients: A meta-analysis. J Clin Hypertens. 2017;19(11):1100–1108.
18. Baltrunaite A, Krakauskaite I, Petkeviciene J, et al. Association of high-sensitivity C-reactive protein and interleukin-6 with markers of subclinical cardiovascular disease in middle-aged adults. BMC Cardiovasc Disord. 2016;16(1):1–9.
19. Remmelzwaal S, Dallinga TH, van der Meer P, et al. IL-6 is associated with increased risk of HFpEF in T2DM: a prospective cohort study. Cardiovasc Diabetol. 2020;19(1):1–9.
20. Paolisso P, Bergamaschi L, D'Angelo EC, et al. Inflammatory markers and echocardiographic indices in diabetic cardiomyopathy. ESC Heart Fail. 2020;7(6):3871–3881.
21. Dinh W, Lankisch M, Nickl W, et al. Elevated plasma levels of N-terminal pro-B-type natriuretic peptide in patients with isolated diastolic dysfunction. Eur J Heart Fail. 2008;10(6):566–572.
22. Zhang W, Li Z, Zhai M, et al. Neutrophil to lymphocyte ratio and heart failure in patients with T2DM. J Diabetes Complications. 2021;35(5):107875.
23. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.
24. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. Eur Heart J. 2016;37(19):1526–1534.
25. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61(10):2108–2117.
26. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239–2251.
27. Januzzi JL, Butler J, Fonarow GC, et al. Rationale and methods for the EMPEROR trials. Am Heart J. 2020;219:64–73.
28. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol. 2017;70(6):776–803.
29. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol. 2020;17(12):761–772.
30. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251–259.
31. Iacobellis G. Epicardial adipose tissue in endocrine and metabolic diseases. Endocrine. 2014;46(1):8–15.
32. Dandona P, Ghanim H, Chaudhuri A, et al. Insulin as an anti-inflammatory and antiatherogenic modulator. J Am Coll Cardiol. 2009;53(5):S14–S20.
33. Aroor AR, DeMarco VG, Jia G, et al. The role of tissue renin-angiotensin-aldosterone system in the development of endothelial dysfunction and diastolic dysfunction in obesity. Front Physiol. 2016;7:512.
34. Saeed S, Ameen A, Rehman S, et al. Diastolic dysfunction in asymptomatic T2DM patients: an echocardiographic study in Pakistani population. J Pak Med Assoc. 2020;70(8):1361–1365.
35. Shoaib A, Knight D, Abbas H, et al. Use of biomarkers in predicting HFpEF in diabetic patients. BMC Cardiovasc Disord. 2021;21(1):322.
36. Hadi HA, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag. 2007;3(6):853–876.
37. Martos R, Baugh J, Ledwidge M, et al. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. Circulation. 2007;115(7):888–895.

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