Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (9) Issue (12) (2024), (1- 4) **online: ISSN 2356–976x**

http://bjas.bu.edu.eg
Medical and Health Science

The early effect of dapagliflozin on diastolic function parameters in patients with mid range and reduced ejection fraction heart failure

Ahmed A.Mohammed, Elsayyed A.Eldarky, Ali I.Ateya and Hagar I.Allam
Cardiology Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
Email: Ahmed.Hasan21@fmed.bu.edu.eg

Abstract

Cardiovascular mortality and hospitalisation rates were greatest among heart failure (HF) patients with reduced ejection fraction (HFrEF) according to clinical trial data. Treatment of heart failure with sodium-glucose transporter-2 inhibitors (SGLT2i) has recently made significant strides [1]. Even in patients with HFrEF, LV diastolic dysfunction was a separate predictor of outcome [2]. It is essential to identify structural abnormalities using echocardiography since they have been linked to prognosis in HF and DM patients [3]. Both diabetic and non-diabetes patients with HF have had their risk of death and hospital readmission decreased by SGLT2is, according to large-scale randomised studies and meta-analyses [4]. These are part of the global guidelines for the treatment of heart failure (HF) at the intermediate assessment level [5]. Some theories suggest that SGLT2is exerts its cardioprotective effects by reversing cardiac remodelling [6] and restoring systolic and diastolic function [7].

Keywords: heart failure, sodium-glucose transporter-2 inhibitor, diastolic function.

1. Introduction

Heart failure is an expensive, progressive condition that poses a serious risk to people's lives, as well as their functional ability and quality of life [8]. Heart failure (HF) and diabetes mellitus (DM) have a similar pathophysiologic basis. Diastolic dysfunction is the most common kind of heart disease associated with type 2 diabetes and is thought to be the first functional impairment in cases of diabetes-related heart failure [9]. Left ventricular (LV) diastolic dysfunction is linked to death and heart failure in diabetic individuals [10]. Inflammation, oxidative stress, endothelial dysfunction, fibrosis, cardiac autonomic neuropathy, and changes in substrate utilisation are some of the pathophysiologic mechanisms that mechanistically explain how HF might progress. The new gold standard in treating both diabetes and heart failure, sodium-glucose cotransporter-2 inhibitors (SGLT2i), may reverse the pathophysiology of both diseases and improve HF outcomes [11]. This is because the interaction between the two disorders seems to be crucial.

2. Material and methods

- **Study Design:**

The coronary care unit at "Benha University hospital" will serve as the site of the single-center observational research.

- **Patients:**

The trial included one hundred patients who were on optimum guideline-directed medical treatment for symptomatic HF and had a baseline EF of less than 50%, whether they were diabetic or not.

- **Inclusion criteria:**

A group of adult male and female patients were brought to the hospital with a confirmed left ventricular ejection fraction (LVEF) less than 50% and a diagnosis of heart failure as per the ESC criteria.

Heart failure is a clinical syndrome that can be caused by a structural or functional cardiac abnormality. It is characterised by typical symptoms like shortness of breath, swelling of the ankles, and fatigue. Signs that may accompany these symptoms include elevated jugular venous pressure, pulmonary crackles, and peripheral oedema. Whether the patient is at rest or under stress, these abnormalities lead to a reduced cardiac output and elevated intracardiac pressures [2].

- **Exclusion criteria:**

The research did not include any patients who met these criteria:

- Cardiac arrhythmia.
- The condition of a rheumatic heart.
- End-stage kidney disease.
- Liver disease in its last stages.

- **Methods:**

The following data were collected:

A) Ethical considerations:

Everyone who took part in the study gave their informed permission. The Faculty of Medicine - Benha University's ethical committee for research involving human beings gave its approval to the project.

B) Patients Characteristics:

• General information on the population, including age, sex, and body mass index.

The patient's ejection fraction (EF), NYHA class (found in Table 1), and the presence or absence of

risk factors including smoking, type 2 diabetes, hypertension, dyslipidaemia, or ischaemic heart disease are all details to be noted throughout the admission process.

There are a number of abnormalities that can be found on an electrocardiogram (ECG), including ischaemic changes, abnormal or normal QRS complex, signs of chamber hypertrophy, and sinus or non-sinus rhythm.

C)Section C: Research

• Laboratory tests for C-reactive protein, glucose, urea, cholesterol, triglycerides, HDL, LDL, and cardiac enzymes (troponin and CK-MB).

2D echocardiography studies evaluating left ventricular systolic performance using the modified Simpson method ((LVEDV - LVESV) / LVEDV) * 100).In the apical 4-chamber, pulsed wave Doppler was used to assess peak (E), late (A), and the E/A ratio across the mitral valve. The E/E′ ratio was calculated by utilising tissue Doppler imaging (TDI) to measure the early diastolic (E') and late diastolic (A') heart velocities. The tissue Doppler strain rate was calculated by using TDI data to compute the regional velocity gradient.

Follow up after 1 month:

After adding dapagliflozin to OMT, the patient underwent echocardiography again to evaluate diastolic function measures.

D) Statistical analysis:

We will use the appropriate tool to statistically analyse and tabulate all of the data.

3. Results

All one hundred patients who were ultimately considered had a history of heart failure with a moderately decreased or reduced ejection fraction, and they were all hospitalised to the cardiology department. A mean age of 58.30 ± 12.24 years old was recorded for the patients. Table 2 shows that the majority of the patients were male (65%), with a body mass index (BMI) ranging from 24.10 to 29.50 kg/m2. Concerning co-morbidities, 60% of patients had diabetes, 45% had hypertension, and 41% had dyslipidaemia. Among those who took part, 38 percent smoked cigarettes. After just one month of starting GDMT for heart failure, adding dapagliflozin greatly improved diastolic function parameter.

Table (1) Natriuretic peptides cutoffs for acute heart failure diagnosis

	BNP (ng/L)	NT-proBNP (ng/L)			MR-proANP (ng/L)
Chronic heart failure					
Heart failure unlikely	< 35	< 125			
“Grey area”	35–150	125–600			
Heart failure likely	> 150	> 600			
Acute heart failure		Age < 50	Age 50–75	Age > 75	ق
Heart failure unlikely	< 100	< 300	< 300	< 300	
“Grey area”	100–400	300–450	300–900	300–1800	< 120
Heart failure likely	> 400	> 450	> 900	> 1800	

Table (2) Demographic data and risk factors in all studied patients

Age (years)		**Mean±SD**	58.30±12.24
		(Range)	(41.00 - 79.00)
Gender		**Male**	65 (65.0%)
Count (%)		**Female**	35 (35.0%)
Body mass index (Kg/m^2)		**Mean±SD**	27.00±1.43
		(Range)	(24.10 - 29.50)
Risk factors	**Diabetes mellitus**	**Yes**	60 (60.0%)
	Count (%)	**No**	40 (40.0%)
	Hypertension	**Yes**	45 (45.0%)
	Count (%)	**No**	55 (55.0%)
	Dyslipidemia	**Yes**	41 (41.0%)
	Count (%)	**No**	59 (59.0%)
	Smoking	**Yes**	38 (38.0%)
	Count (%)	**No**	62 (62.0%)

4. Discussion

In modern medicine, heart failure (HF) ranks high among the most prevalent and consequential clinical issues. Mortality and morbidity rates from HF remain high, despite substantial advancements in patient care and therapy in the last several years. Heart failure (HF) problems and mortality are more common in patients with diabetic mellitus (DM) [12].

Dysfunction of the left ventricle during diastole occurs as a result of increased myocardial stiffness and interstitial myocardial proliferation [13].The progression of diastolic dysfunction is associated with an increased risk of HF. It doesn't matter what

the left ventricular ejection fraction is; diastolic dysfunction guarantees death from HF [14].

A new family of drugs called sodium-glucose cotransporter type 2 inhibitors (SGLT2i) have recently emerged to treat type 2 diabetes. When it comes to reducing the risk of cardiovascular events in HF patients, dapagliflozin is only one of many SGLT2is that have demonstrated potential. This holds true regardless of whether the patients also have type 2 diabetes. In fact, they are recommended at level IA by worldwide criteria for the treatment of heart failure patients [15].

How this therapeutic benefit is attained is still a mystery. On its own, the weight loss and blood pressure reductions associated with SGLT2i cannot explain the advantage, nor can hypoglycemia, fewer atherosclerotic events, better renal function, or the other benefits. The effects of SGLT2i on many inflammatory pathways, such as oxidative stress, fibrosis, and circulating cytokines, have been demonstrated to contribute to diastolic dysfunction [16]. There is conflicting evidence from the same body of research on the relationship between left ventricular structural and functional improvement and reduced HF hospitalisations [17].

Inhibitors of SGLT2 have shown promise in a number of areas, including endothelial dysfunction, aortic stiffness, visceral adipocyte hypertrophy, and epicardial fat deposition [18]. It is possible that these procedures will improve LV diastolic function.

In the DAPA-HF trial, dapagliflozin significantly reduced CV mortality and HFrEF patients' deterioration, marking a huge advance in the HF area. Researchers utilised the Kansas City Cardiomyopathy Questionnaire Score (KCCQ) with the main composite end point to gain a better understanding of the effects of SGLT2i on symptoms, physical function, and quality of life. Incorporating dapagliflozin into the treatment plans of HFrEF patients led to an improvement in their health condition and a marked reduction in the incidence of clinical deterioration requiring medication intensification [19].

Our results are consistent with those of another study showing that diabetic patients with symptomatic HFrEF had an improvement in echocardiographic indicators of diastolic function after 30 days of dapagliflozin medication [20]. The ratios of E/A and E/E' were enhanced for greater precision.

Our results were in line with those of [21], which showed that dapagliflozin considerably improved left ventricular diastolic function in non-diabetic outpatients with HFrEF or HFmrEF. A substantial drop in the E, E′, and E/e′ indices (corresponding P values of 0.045, 0.039, and 0.022, respectively) was associated with this finding.

5. Conclusion

Patients with HFrEF and HFmrEF who were already receiving pharmacological treatment based on current guidelines had a considerable improvement in classical diastolic echocardiographic measures after adding SGLT2 inhibition with dapagiflozin to their regimen for one month.

6. Limitations

We need further studies with larger patient populations and performed at different sites to draw valid conclusions about the effect of SGLT2 inhibitors on diastolic and systolic function markers.

References

[1] Mie K. Eickhoff, Flemming J. Olsen, Marie Frimodt-Møller, et al. Effect of dapagliflozin on cardiac function in people with type 2 diabetes and albuminuria – A double blind randomized placebo-controlled crossover trial, Journal of Diabetes and its Complications, Volume 34, Issue 7, 2020, 107590, ISSN 1056-8727.

[2] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27):2129–2200.

[3] Yamanaka, S.; Sakata, Y.; Nochioka, K.; et al. Prognostic impacts of dynamic cardiac structural changes in heart failure patients with preserved left ventricular ejection fraction. Eur. J. Heart Fail. 2020, 22, 2258–2268.

[4] Lopaschuk, G.D.; Verma, S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. JACC Basic. Transl. Sci. 2020, 5, 632–644.

[5] McDonagh T.A., Metra M., Adamo M., et al. 2023 focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023; 44 (37): 3627-3639.

[6] Zhang, N.; Wang, Y.; Tse, G.; et al. Effect of sodium-glucose cotransporter-2 inhibitors on cardiac remodelling: A systematic review and

meta-analysis. Eur. J. Prev. Cardiol. 2022; 28, 1961–1973.

[7] Pascual-Figal DA, Zamorano JL, Domingo M, et al. Impact of dapagliflozin on cardiac remodelling in patients with chronic heart failure: The DAPA-MODA study. Eur J Heart Fail. 2023 Aug; 25(8):1352-1360.

[8] Gianluigi Savarese, Peter Moritz Becher, Lars H Lund, et al. A comprehensive and updated review of epidemiology, Cardiovascular Research, Volume 118, Issue 17, December 2022, Pages 3272–3287.

[9] Shaimaa B. El-Saied, Wafaa S. El-Sherbeny, Sara I. El-sharkawy. Impact of sodium glucose co-transporter-2 inhibitors on left atrial functions in patients with type-2 diabetes and heart failure with mildly reduced ejection fraction. IJC Heart & Vasculature. 2024; Volume 50, 101329.

[10] Jakkula SK, Maddury J, Nakka S, et al. Effect of dapagliflozin on left ventricular diastolic function in diabetics - A prospective interventional study. Indian J Cardiovasc Dis Women 2022; 7:137-42.

[11] Theofilis P, Oikonomou E, Tsioufis K, et al. Diabetes Mellitus and Heart Failure: Epidemiology, Pathophysiologic Mechanisms, and the Role of SGLT2 Inhibitors. Life (Basel). 2023 Feb 10; 13(2):497.

[12] Cortés M, Lorenzo O, Lumpuy-Castillo J, et al. Dapagliflozin Improved Cardiac Function and Structure in Diabetic Patients with Preserved Ejection Fraction: Results of a Single Centre, Observational Prospective Study. Journal of Clinical Medicine. 2023; 12(20):6698.

[13] Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32(6):670–9.

[14] Machino-Ohtsuka T, Seo Y, Ishizu T, et al. Clinical utility of the 2016 ASE/EACVI recommendations for the evaluation of left ventricular diastolic function in the stratification of post-discharge prognosis in patients with acute heart failure. Eur Heart J Cardiovasc Imaging. 2019; 20(10):1129–37.

[15] McDonagh T.A., Metra M., Adamo M., et al. 2023 focused update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023; 44 (37): 3627-3639.

[16] Baker WL, Smyth LR, Riche DM, et al. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014 Apr; 8(4):262-75.e9.

[17] Santos-Gallego, C.G.; Vargas-Delgado, A.P.; Requena-Ibanez, J.A.; et al. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. J. Am. Coll. Cardiol. 2021, 77, 243–255.

[18] Kusaka H, Koibuchi N, Hasegawa Y, et al. Empagliflozin lessened cardiac injury and reduced visceral adipocyte hypertrophy in prediabetic rats with metabolic syndrome. Cardiovasc Diabetol. 2016; 15:157.

[19] Maragkoudakis S, Marketou M, Katsi V, et al. The early effect of dapagliflozin on strain and tissue Doppler parameters of diastolic function in diabetic patients with heart failure with reduced ejection fraction. Arch Med Sci Atheroscler Dis. 2021 Oct 4; 6:e176-e181.

[20] Kosiborod MN, Jhund PS, Docherty KF, et al. Effects ofdapagliflozin on symptoms, function, and quality of lifein patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation 2020; 141: 90-9.

Maria Concetta Pastore, Andrea Stefanini, Giulia Elena Mandoli, et al. Dapagliflozin Effects on Cardiac Deformation in Heart Failure and Secondary Clinical Outcome, JACC: Cardiovascular Imaging. 2024; ISSN 1936-878X.