Left Ventricular hypertrophy (LVH) regression with Dapagliflozin in Diabetic and Hypertensive patients.

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Abstract

Background: Left ventricular hypertrophy (LVH) is a significant predictor of cardiovascular events, including myocardial infarction and heart failure. Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, has shown potential for LVH regression through mechanisms such as afterload reduction and anti-inflammatory effects. This study evaluates the impact of dapagliflozin on LVH regression in diabetic and hypertensive patients.

Methods: This prospective study enrolled 90 patients with diabetes, hypertension, and echocardiographically confirmed LVH. Participants were randomly assigned to the dapagliflozin group (10 mg daily; n=45) or the control group (n=45). Baseline characteristics, including anthropometric measures, blood pressure, and comorbidities, were comparable between groups. Follow-up occurred at 2, 4, and 6 months, assessing LV mass index (LVMI), systolic (SBP) and diastolic blood pressure (DBP), HbA1c, and other cardiac parameters. Statistical analysis was conducted using SPSS v26, with a p-value <0.05 considered significant.

Results: Dapagliflozin significantly reduced LVMI at 4 months (112.15 ± 17.01 vs. 119.79 ± 9.65 g/m²; p=0.016) and 6 months (110.09 ± 16.53 vs. 117.85 ± 9.90 g/m²; p=0.021). SBP was also significantly lower in the dapagliflozin group at 4 and 6 months (p=0.043 and p=0.012, respectively), while DBP showed no significant differences. HbA1c levels declined significantly in the dapagliflozin group at 4 and 6 months (p<0.001). Other cardiac parameters, including ejection fraction and end-diastolic volume, remained comparable.

Conclusion: Dapagliflozin effectively promotes LVH regression and blood pressure control in diabetic and hypertensive patients. These findings highlight its potential as a cardioprotective agent.

Keywords: LVH, Dapagliflozin, Diabetes mellitus, Hypertension, LVMI

Introduction:

Diabetes mellitus and hypertension are both broadly recognized cardiovascular risk factors **[1]**, and visualizing left ventricular hypertrophy (LVH) in such patients heralds significant morbidity and mortality risk, increasing the relative risk for CVD in males by 1.49 with each 50g/m increase in left ventricular mass, while in females it increased by 1.57. This was similarly highlighted when addressing the relative risk for cardiovascular mortality **[2]**. The control of blood pressure as well as the control of the renin-angiotensin system (RAS) are generally considered the standard of care in alleviating LVH; however, the comprehensiveness of this approach is questionable since LVH is still visualized in patients with proper control of HbA1c and

blood pressure **[3]**. Another underlying mechanism for the development of LVH is insulin resistance **[4]**. Nevertheless, it has not been thoroughly ascertained, in the current literature, whether glycemic control alone can reduce cardiovascular risks in diabetic and hypertensive patients **[5, 6]**.

In this prospective study, we followed up a sample of diabetic patients with comorbid hypertension who were treated with dapagliflozin, aiming to assess its potential effects on LVH regression.

Patients and Methods

Study Design

This prospective interventional study was conducted over six months at Beni-Suef University Hospital and Sohag Specialized Cardiac Center. The primary objective was to evaluate the effect of dapagliflozin on left ventricular hypertrophy (LVH) regression and blood pressure control in patients with type 2 diabetes mellitus (T2DM) and hypertension. Clinical outcomes were assessed at the 2nd, 4th, and 6th months to determine the drug's impact on cardiac remodeling.

Hypothesis

The study hypothesized that dapagliflozin would significantly reduce LVH in diabetic and hypertensive patients. The null hypothesis stated that there would be no significant effect, while the alternative hypothesis suggested notable LVM regression with dapagliflozin treatment. The study was conducted over 1 year (from October 2023 till December 2024) with 6 months follow up.

Population

Inclusion Criteria

Eligible participants included adults aged 18–80 years who were diagnosed with both diabetes and hypertension according to the American Diabetes Association (ADA) and European Society of Cardiology (ESC) guidelines **[7].** Inclusion criteria required echocardiographic evidence of LVH, defined as a left ventricular (LV) mass index greater than 115 g/m² for men or 95 g/m² for women when indexed to body surface area, or greater than 48 g/m² for men and 44 g/m² for women when indexed to height **[8].** Participants also had stable blood pressure (<140/90 mmHg) maintained on antihypertensive medications for at least three months.

Exclusion Criteria

Exclusion criteria included significant non-cardiovascular diseases (e.g., active malignancy), renal impairment with an estimated glomerular filtration rate (eGFR) below 25 ml/min/1.73m², severe valvular heart disease, pregnancy or breastfeeding, acute cardiovascular conditions, and poor-quality echocardiographic images.

Sample Size Calculation:

The sample size was calculated based on previous research by Brown et al. (2020) **[9],** focusing on left ventricular mass (LVM) regression. With a significance level of 0.05 and 80% power, 60 participants were required to detect meaningful differences. To account for a potential 30% dropout rate, 90 participants were enrolled (45 in each group).

Data Collection

At baseline, participants underwent a detailed medical history review, physical examination, and blood pressure measurement using a mercury manometer (average of three readings). Electrocardiograms and echocardiograms confirmed the diagnosis of LVH using the American Society of Echocardiography (ASE) criteria **[10].** Echocardiographic evaluations were performed with a GE Vivid T8 ultrasound machine, measuring left ventricular internal diameters, interventricular septum thickness, posterior wall thickness, and left ventricular mass, calculated using Devereux's formula. Left ventricular ejection fraction (LVEF) was also assessed **[11].**

Intervention

Participants received dapagliflozin at a dose of 10 mg daily for six months. Follow-up assessments at the 2nd, 4th, and 6th months monitored changes in left ventricular mass and other cardiac parameters.

Echocardiographic Protocol (using GE vivid t8 Echo machine) was conducted with GE Vivid T8 ultrasound machine by trained operators. Left ventricular internal diameters (end-diastole and end-systole), interventricular septum thickness (IVS), posterior wall thickness (PWT), left ventricular mass (LVM): Calculated using Devereux's formula **[11],** left ventricular ejection fraction (LVEF) were measured. All measurements taken during end-diastole using ASE protocols. **[10]**

Statistical Analysis

Data were analyzed using SPSS version 26. Qualitative data were presented as numbers and percentages, while quantitative data were

expressed as mean ± standard deviation. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate, and continuous variables were analyzed using the Student's t-test. Statistical significance was set at $p \leq 0.05$.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Beni-Suef University number FMBSUREC/07052024/ Saleep. Written informed consent was secured from all participants, and strict confidentiality was maintained throughout the study.

Results:

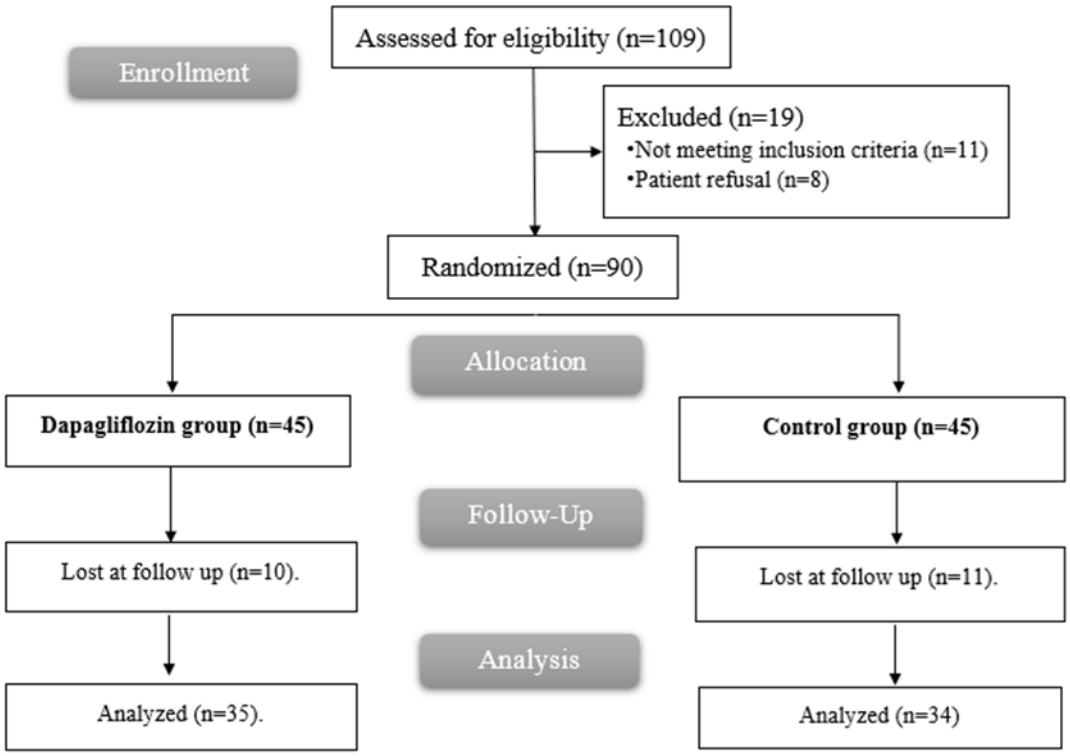

Figure (1) Consort flow chart

The study included 2 groups; 45 patients in each arm with age, sex, weight, height and BMI, smoking and comorbidities were insignificantly different between both groups as shown in **Table 1.**

Table (1): Demographic data of the studied groups.

Demographic data		Dapagliflozin group (n=45)	Control group (n=45)	P value
Age (years)	**Mean ± SD**	52.6 ± 14.84	50.8 ± 17.48	0.600
	Range	27 – 74	21 - 77	
Sex	**Male**	24 (53.33%)	29 (64.44%)	0.284
	Female	21 (46.67%)	16 (35.56%)	
BMI (kg/m^2)	**Mean ± SD**	29.91 ± 3.8	28.58 ± 3.14	0.073
	Range	22.8 - 37.7	23.1 - 36.7	
Diabetes mellitus		45 (100%)	45 (100%)	---
Hypertension		45 (100%)	45 (100%)	---
Hypercholesterolemia		23 (51.11%)	21 (46.67%)	0.673
IHD		4 (8.89%)	6 (13.33%)	0.739
Smoking	**Smokers**	7 (15.56%)	5 (11.11%)	0.652
	Ex-smokers	17 (37.78%)	21 (46.67%)	
	Non-smokers	21 (46.67%)	19 (42.22%)	

BMI: Body mass index.

As shown in Tabe 2, Statin, ACE inhibitor, calcium channel blocker, sulphonlylurea, insulin, angiotensin receptor blocker, beta-blocker and GLP-1 agonist were insignificantly different between both groups. All patients in both groups took metformin.

Table (2): Medications of the studied groups.

Medications	Dapagliflozin group (n=45)	Control group (n=45)	P value
Metformin	45 (100%)	45 (100%)	---
Statin	33 (73.33%)	36 (80%)	0.455
Ace inhibitor	22 (48.89%)	25 (55.56%)	0.527
Calcium channel blocker	11 (24.44%)	14 (31.11%)	0.480
Sulphonlylurea	10 (22.22%)	12 (26.67%)	0.624
Insulin	10 (22.22%)	8 (17.78%)	0.598

Angiotensin receptor blocker	6 (13.33%)	7 (15.56%)	0.764
Beta-blocker	6 (13.33%)	5 (11.11%)	0.748
GLP-1 agonist	5 (11.11%)	3 (6.67%)	0.714

GLP: Glucagon like peptide.

Systolic blood pressure was insignificantly different at baseline and 2 months between both groups. Systolic blood pressure was significantly lower at 4 months and 6 months in dapagliflozin group than control group (P value=0.043 and 0.012 respectively). On the other hand, the DBP was insignificantly different between the studied groups during the follow up period as shown in **Table 3.**

N:B: the number of cases was 45 in each group at baseline measurement and dropped to 40 in each group from 2 months of follow up.

Table (3): Systolic and diastolic blood pressure of the studied groups.

Variables	Dapagliflozin group (n=45)	Control group (n=45)	P value
	SBP		
Baseline	133.67±3.73	134.96±2.76	0.066
2 months	127.2±8.89	130.69±7.89	0.072
4 months	**(n=41)** 125.27±8.57	**(n=39)** 129.1±8.05	**0.043***
6 months	**(n=35)** 124.83±8.32	**(n=34)** 129.32±5.82	**0.012***
	DBP		
Baseline	86.18±2.08	85.89±2.04	0.507
2 months	83.51±4.73	84.29±4.44	0.424
4 months	**(n=41)** 82.44±4.86	**(n=39)** 83.38±4.34	0.362
6 months	**(n=35)** 81.43±4.83	**(n=34)** 82.82±3.37	0.170

*: Significant as P value<0.05.

Table 4 showed that the HbA1c was insignificantly different at baseline and 2 months between both groups. HbA1c was significantly lower at 4 months and 6 months in dapagliflozin group than

control group (P value<0.001). The creatinine level didn't differ significantly between both groups during the following up period.

Table (4): Labs (HbA1c and creatinine) of the studied groups.

Labs	Dapagliflozin group (n=45)	Control group (n=45)	P value
	HbA1c		
Baseline	7.68±0.47	7.57±0.47	0.246
2 months	6.82±0.77	7.12±0.71	0.057
4 months	**(n=41)** 4.78±1.23	**(n=39)** 6.02±1.15	**<0.001***
6 months	**(n=35)** 4.17±1.34	**(n=34)** 5.66±1.33	**<0.001***
	Creatinine		
Baseline	1.12±0.16	1.07±0.23	0.201
2 months	1.07±0.22	0.99±0.2	0.070
4 months	**(n=41)** 0.98±0.19	**(n=39)** 0.92±0.18	0.112
6 months	**(n=35)** 0.88±0.15	**(n=34)** 0.86±0.18	0.654

*: Significant as P value<0.05.

Table 5 showed that the LV mass index was insignificantly different at baseline and 2 months between both groups. LV mass index was significantly lower at 4 months and 6 months in dapagliflozin group than control group (P value=0.016 and 0.021 respectively). The ejection fraction didn't differ significantly between both groups during the following up period.

Table (5): LV mass index and Ejection fraction of the studied groups

Variables	Dapagliflozin group (n=45)	Control group (n=45)	P value
	LV mass		
Baseline	125.38±16.55	120.73±10.99	0.120
2 months	117.07±16.26	120.16±11.03	0.295
4 months	**(n=41)** 112.15±17.01	**(n=39)** 119.79±9.65	**0.016***

	(n=35)	**(n=34)**	
6 months	110.09±16.53	117.85±9.9	**0.021***
	Ejection fraction		
Baseline	70.69±6.87	72.87±5.14	0.092
2 months	71.11±6.94	73.44±5.26	0.076
	(n=41)	**(n=39)**	
4 months	72.98±7.21	74.41±5.42	0.319
	(n=35)	**(n=34)**	
6 months	74.23±7.35	75.18±5.4	0.544

*: Significant as P value<0.05.

Both ESV and EDV were insignificantly different at baseline, 2 months, 4 months and 6 months between both groups as shown in **Table 6.**

Table (6): End systolic and diastolic volume of the studied groups.

Variables	**Dapagliflozin group (n=45)**	**Control group (n=45)**	**P value**
	End systolic volume		
Baseline	46.02±11.38	45.6±9.64	0.850
2 months	45.16±11.25	45.04±9.65	0.960
	(n=41)	**(n=39)**	
4 months	43.8±11.38	43.38±9.94	0.861
	(n=35)	**(n=34)**	
6 months	43.17±11.01	42.5±9.94	0.791
	End diastolic volume		
Baseline	126.78±9.5	123.91±15.02	0.282
2 months	125.64±9.52	123.49±15.07	0.420
	(n=41)	**(n=39)**	
4 months	125.02±9.28	123.21±14.61	0.506
	(n=35)	**(n=34)**	0.721
6 months	124.43±8.46	123.38±15.01	

ESV: End systolic volume.

As shown in Table 7, the left atrial area was insignificantly different at baseline, 2 months, 4 months and 6 months between both groups.

Table (7): Left atrial area of the studied groups.

Left atrial area	Dapagliflozin group (n=45)	Control group (n=45)	P value
Baseline	23.47±6.98	22.93±6.98	0.718
2 months	22.84±7.32	22.33±7.08	0.737
4 months	**(n=41)** 22.37±7.54	**(n=39)** 21.97±7.68	0.819
6 months	**(n=35)** 22.09±7.05	**(n=34)** 21.68±7.54	0.816

***No adverse side effects noted in the treatment group.**

Discussion

In our study, participants were distributed equally between two groups. The treatment group, consisting of 45 adults with diabetes mellitus and hypertension, received dapagliflozin, and the control group, consisted of 45 adults who also had diabetes mellitus and hypertension but did not receive the drug. The age, sex, and anthropometric measurements of our patients including, BMI, smoking status, comorbidities, hypercholesterolemia, and medications were comparable between both groups, highlighting strict unbiased sample selection.

Aiming to assess the impact of dapagliflozin, a SGLT2 inhibitor, on left ventricular hypertrophy, we ensured that both arms of the study had the same comorbidities (DM and hypertension), with the main variable being the intake of dapagliflozin.

We followed up the systolic blood pressure (SBP) of our studied subjects for a duration of 6 months at 2-month intervals. While the SBP did not differ significantly between the two groups at baseline nor at the 2-month timepoint (p=0.066, p=0.052, respectively), we noted a substantial drop in SBP in the treatment group when compared with the control group (125.27 vs. 129.1 mmHg; p=0.043), and this drop was even more prominent at the 6-month follow-up point (124.83 vs. 129.32 mmHg; p=0.012). These findings were suggestive of the hypothetical benefit of dapagliflozin on comorbid hypertension in diabetic patients. Despite the evident improvement in SBP noted in the treatment arm, we observed no significant changes in diastolic blood pressure (DBP)

among our subjects throughout the follow-up period (p>0.05).

In both the intention-to-treat analysis and the pre-protocol analysis, Brown et al. emphasized the improvement in SBP in patients taking dapagliflozin. Both the 24h SBP and the nocturnal SBP exhibited appreciable differences between the two groups, with a reduction of -2.78 in 24h SBP, and a reduction of -3.47 in nocturnal SBP, compared to 0.85, and 0.91, respectively, in the placebo group (p=0.012, p=0.017, respectively). No statistically prominent differences regarding the 24h, daytime, nor nocturnal DBP were noted, which also aligned with our findings **[9]**.

Kosugi et al. contrasted our findings concerning the improvement in SBP, showing that in both patients who were taking a SGLT2i and those who were not, comparable SBP were observed on baseline and on second examination; however, they did not specify the duration or the circumstances of the second examination, and they omitted data regarding cardiovascular events during the period between the two echocardiographic assessments (p=0.950). When addressing the DBP in both groups, however, their results were consistent with ours as they found no statistically meaningful differences (p=0.603) **[12]**.

Selvaraj et al. reported in discordance with our observations, indicating that the benefits of dapagliflozin in cardiac patients were independent of its effect on blood pressure. However, their sample was significantly larger than ours, encompassing 6,263 patients, and their protocol was divergent from ours as patients were not necessarily diabetic and their baseline characteristics were analyzed under a different approach **[13]**.

When evaluating the HbA1c of both groups, it was revealed that there were no considerable variations in the HbA1c between both groups at baseline and at the 2-month follow-up point (p=0.246, p=0.057, respectively). However, we reported an appreciable reduction in HbA1c in the treatment group at the 4-month (4.78 vs. 6.02%; p<0.001) and the 6-month timepoint (4.17 vs. 5.66%; p<0.001). Brown et al. aligned with our findings, noting that after 12 months of dapagliflozin, cases were found to have significantly lower HbA1c percentages than those taking placebo (-6.28 vs. -0.79; p=0.025) **[9]**.

Dissimilarly, Kosugi et al. reported no notable differences regarding the HbA1c of patients on dapagliflozin and those on other antidiabetic medications when comparing their baseline HbA1c to that on the second examination. These results were not in line with ours, but they could be explained by the fact that their sample was relatively larger than ours (338 patients). We also highlighted a significant limitation in their protocol regarding the use of antidiabetic medications. They modified the drug regimens of their sample to obtain better glycemic control in patients who were undertreated prior to the study, which may have made it difficult to estimate the isolated effect of dapagliflozin on the HbA1c of cases in comparison to the controls, since the similar HbA1c measurements on follow-up could be due to any of the other antidiabetic agents used **[12]**.

According to our data, we found no significant alterations in terms of the serum creatinine between the two groups at baseline and all through the follow-up period ($p>0.05$). Brown et al. relayed similar baseline data, with no significant differences regarding serum creatinine noted among their subjects ($p=0.199$). Moreover, after 12 months on either dapagliflozin or placebo, they found no statistically notable differences in serum creatinine between the two arms ($p=0.123$) **[9]**.

As our primary aim, we assessed the LV mass index of our subjects, which revealed no notable differences at baseline or after 2 months ($p=0.120$, $p=0.295$, respectively). Intriguingly, starting from the 4th month of follow-up, we observed a significantly lower LV mass index (LVMI) in the treatment group when compared with the controls (112.15 vs. 119.79; $p=0.016$) and another drop in the treatment group at the 6-month timepoint (110.09 vs. 117.85; $p=0.021$). Brown et al. inferred that the patients receiving dapagliflozin for 12 months had significantly lower LVM as seen on cardiac MRI, with the change in LVM being substantially higher in the dapagliflozin group compared to the placebo group (-3.95 vs. -1.13g; $p=0.018$) accounting for an absolute reduction in LVM of -2.28g in the treatment group **[9]**.

Paneni et al. intended to elucidate the mechanism underlying the cardioprotective effect of dapagliflozin, citing the work of Brown et al., they suggested that dapagliflozin mitigated LVH by blood pressure lowering means, leading to a decrease in the afterload and thus a significant decrease in LV mass. They

supported this hypothesis by underlining the findings of Brown et al. regarding the correlation between LVH regression and ambulatory (r=0.415, p=0.001) and nocturnal SBP (r=0.321, p=0.012), emphasizing that nocturnal SBP specifically is robust predictor of target organ damage **[9, 14, 15]**.

Kosugi et al. reported that patients with type 2 diabetes mellitus and LVH who were treated with SGLT2i (dapagliflozin) had a considerably lower LVMI on the second examination as opposed to the baseline (46.7 vs. 51.3g/m; p<0.001), and these values were compared to those who were taking medications other than SGLT2i who had a significantly lower change in LVMI from baseline (52 vs. 51.7g/m; p=0.007) **[12]**. In their prospective, double-blinded, randomized, place-controlled trial, Brown et al. concluded that dapagliflozin can effectively lead to the regression of LVH and explained this benefit by the fact that SGLT2i lower the preload as well as the afterload, and with their weight-reducing effects, they can improve tissue resistance to insulin and thus have cardioprotective outcomes **[16]**.

Elaborating on the possible mechanisms through which dapagliflozin ameliorated LVH in a sample of 60 participants with T2DM and LVH, Dihoum et al. assessed the inflammatory markers in their subjects who were taking dapagliflozin for 12 months and found them to be significantly reduced when compared with controls who were taking placebo. They inferred that dapagliflozin led to substantially lower CRP levels compared to placebo (1.07 vs. 3.04mg/L, mean Δ = -1.96; p=0.026); however, other inflammatory markers such as TNF-alpha, IL-1beta, amongst others, did not reveal significant differences between the two groups. Aiming to validate the relevance of this data, they showed that dapagliflozin led to a considerable reduction in LV mass as opposed to placebo over 12 months (-4.61 vs. -0.87g, mean Δ=-3.74g; p=0.004), as well as notable improvements in the global longitudinal strain (GLS). Furthermore, they studied the correlation between inflammatory markers and ventricular mass, which revealed a significant positive correlation, although modest, between changes in GLS and changes in TNF-alpha (r=0.230), neutrophil-lymphocyte ratio (NLR; r=0.311), and IL-1beta (r=0.246). These findings culminated into a potential anti-inflammatory effect of dapagliflozin, which—although perhaps not primarily—may lead to

improvements in the cardiovascular function of diabetic and hypertensive patients **[17]**.

Arow et al. aimed to explain the mechanism through which dapagliflozin exerts its cardioprotective effects by using experimental diabetic rat models in whom cardiomyopathy was induced by angiotensin II infusions, resulting in cardiac hypertrophy, inflammation, and myocardial fibrosis. After exposure to dapagliflozin, blood glucose levels dropped significantly from 874 to 556mg/dL ($p<0.05$). Furthermore, a notable attenuation of cardiac inflammatory and fibrotic changes was observed with a subsequent increase in the left ventricular fractional shortening in diabetic mice. Additionally, isolated cardiomyocytes from rats treated with dapagliflozin were studied for intracellular levels of ROS and inflammatory markers and a considerable drop in those were exhibited along with lower expression of voltage-dependent L-type calcium channels, sodium-hydrogen exchanger 1, and the sodium-calcium exchanger. These findings reflected that ionic modulation in cardiomyocytes, as well as the reduction of oxygen radicals and other inflammatory mediators, may reduce the systolic function of diabetic patients with cardiomyopathy **[18]**.

Lastly, we analyzed the EF, ESV, EDV, and the left atrial area of our subjects and none of those parameters showed any statistically significant differences between the two groups at baseline or at any point during the 6-month follow-up period ($p>0.05$). Brown et al. reported in accordance with these findings, showing that the EF ($p=0.415$), EDV ($p=0.562$), ESV ($p=0.348$), and the left atrial area ($p=0.143$), showed no statistically significant deviation from baseline when comparing both groups, those on dapagliflozin and those on placebo **[9]**. In commentary on those findings, Paneni et al. attempted to explain the lack of improvement in cardiac volumes by highlighting that the NT-proBNP did not change either, which possibly means that the positive effects of dapagliflozin on the heart are not attributable to the preload, and may be solely afterload-dependent **[14]**.

Conclusion:

In conclusion, our study revealed that dapagliflozin is a promising promoter of LVH regression in diabetic patients with comorbid hypertension. Over the 6-month follow-up period, significant reductions in SBP, HbA1c levels, and LVMI were observed in the treatment group, highlighting potential cardioprotective effects of dapagliflozin. No adverse side effects noted in the treatment group.

Limitations:

The study has some limitations, including a small sample size of 90 patients, which may reduce the generalizability of the findings, and a short 6-month follow-up period that might not capture long-term effects of dapagliflozin on LVH regression and cardiovascular outcomes.

Recommendations:

To optimize the use of dapagliflozin, this study recommend to integrate it into treatment regimens for diabetic and hypertensive patients with LVH, especially those unresponsive to traditional therapies, and prioritize its use in high cardiovascular-risk populations. Conduct regular follow-ups to monitor LV mass index, blood pressure, HbA1c levels, and detect adverse effects.

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