Suez Canal University Medical Journal Vol. 28 (3), 2025
Pages 1-8

The Role of Dapagliflozin in Reducing Anthracycline-Induced Cardiotoxicity in Type 2 Diabetes Mellitus Patients with Breast Cancer

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Abstract

Background: **Although anthracyclines are a mainstay of treatment for breast cancer, they can cause serious cardiotoxicity, especially in patients who already have other medical problems including type 2 diabetic mellitus (T2DM). A sodium-glucose cotransporter-2 (SGLT2) inhibitor called dapagliflozin has demonstrated possible cardioprotective benefits. This study examines whether dapagliflozin can help T2DM patients with breast cancer postpone the development of anthracycline-induced cardiotoxicity.** ***Methods:*** **A total of 112 newly diagnosed breast cancer patients with T2DM were recruited and divided into two groups: the Dapagliflozin Group (n=61), which received dapagliflozin 10 mg in addition to standard antidiabetic therapy, and the Control Group (n=49), which received only standard antidiabetic therapy. Echocardiographic parameters (ejection fraction [EF], global longitudinal strain [GLS]) and biomarkers of cardiotoxicity (troponin I, BNP) were assessed at baseline and follow up at 3 and 6 months.** ***Results:*** **At 3 and 6 months follow up, the Dapagliflozin group showed significantly lower levels of troponin I and BNP, along with better-preserved EF and GLS compared to the control group. The cardioprotective effects of dapagliflozin became more pronounced over time. Receiver Operating Characteristic (ROC) curve analysis demonstrated that dapagliflozin had a strong predictive ability for preventing cardiotoxicity.** ***Conclusion:*** **Dapagliflozin showed significant cardioprotective effects in T2DM patients receiving anthracycline-based chemotherapy, suggesting its potential role in reducing anthracycline-induced cardiotoxicity. Further randomized controlled trials are necessary to confirm the cardioprotective benefits of SGLT2 inhibitors in this patient population.**

Keywords: Cardiotoxicity, Dapaglflozine, Anthracyline

Introduction

Although anthracyclines are frequently used to treat breast cancer, their usage is restricted because to the possibility of cardiotoxicity, which in as many as 10–15% of

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individuals might result in heart failure (HF) or asymptomatic left ventricular decompensation. The risk of cardiotoxicity is increased in patients with pre-existing diseases such as type 2 diabetes. As of right now, there are no proven treatments to stop or lessen anthracycline-induced cardiotoxicity (AIC). SGLT2 inhibitors which is initially created to treat diabetes, have demonstrated cardioprotective advantages in heart failure patients with both intact and decreased ejection fraction. According to preliminary findings, SGLT2 inhibitors may also lower the risk of heart failure in individuals receiving anthracycline therapy. With an emphasis on early cardiotoxicity detection using speckle tracking echocardiography (STE), this study attempts to assess the cardioprotective effects of dapagliflozin in T2DM patients undergoing anthracycline-based chemotherapy.

Subjects and Methods

Study Design and Population

112 newly diagnosed patients with type 2 diabetes who were scheduled to receive chemotherapy based on anthracyclines were included in this prospective case-control study. Two groups of patients were formed:

- Dapagliflozin Group (n=61): received 10 mg of dapagliflozin per day in addition to their usual course of antidiabetic medication.
- Control Group (n=49): Received only standard antidiabetic therapy without SGLT2 inhibitors.

Patients with T2DM who have recently been diagnosed with breast cancer are slated to receive chemotherapy based on anthracyclines were included. While, patients with a history of ketoacidosis, significant renal impairment (eGFR <30 mL/min/1.73 m2), or pre-existing heart failure (LVEF <50%) were excluded.

Endpoints

Primary Endpoint: incidence of Anthracycline-related cardiac toxicity, which is indicated by a decrease in global longitudinal strain (GLS) of at least 15% from baseline or a decrease in left ventricular ejection fraction (LVEF) of at least 10% to a final value below 50%.

Secondary Endpoint: alterations in echocardiographic parameters (EF, GLS) and cardiotoxicity biomarkers (troponin I, BNP) at three and six months.

Statistical Analysis

Continuous elements were provided as means ± standard deviation and compared using Welch's t-test. Categorical elements were in comparison using the chi-square test or Fisher's exact test. Statistical significance was set at $p < 0.05$. A post-hoc power analysis was used to ensure enough statistical power. Receiver Operating Characteristic (ROC) curve analysis was done to demonstrate the predictive ability of dapagliflozin in avoiding cardiotoxicity.

Results

Baseline Characteristics

Prior to starting therapy, the Dapagliflozin and Control Groups showed similar features, with no significant differences between them at baseline (Table 1).

Primary Outcome

In comparison to the Control Group, the Dapagliflozin Group had significantly decrease levels of troponin I and BNP at 3 and 6 months, as well as better-preserved EF and GLS ($p<0.0001$). (Tables 2 and 3).

In comparison to the control group, patients on dapagliflozin had significantly reduced troponin I and BNP levels at three months, as well as better-preserved EF%

and GLS%, indicating early cardioprotective effects. The Dapagliflozin Group also had a significantly lower incidence of true clinical cardiotoxicity at both 3 and 6 months, including reduced EF and clinical heart failure. This suggests that dapagliflozin may not only prevent early cardiotoxicity but also lower the risk of advanced cardiac dysfunction. The Dapagliflozin Group demonstrated a significantly lower incidence of subclinical cardiotoxicity at both 3 and 6 months, as evidenced by fewer patients with reduced GLS, elevated troponin I, and elevated BNP.

Table 1: Baseline Characteristics of the Study Groups

Parameter	**Dapagliflozin group (61 patients)**	**Control group (49 patients)**	***p*-value**
Age (years)	49.87	50.76	0.676
Height (cm)	162.05	160.61	0.229
Weight (kg)	88.00	88.50	0.792
BSA (m^2)	1.95	1.96	0.770
Systolic BP (mmHg)	128.44	122.96	0.073
Diastolic BP (mmHg)	75.79	73.31	0.294
Heart Rate (bpm)	83.00	83.50	0.695
MAPSE (mm)	12.79	13.20	0.201
LA Volume (ml)	39.44	39.33	0.810
Ejection Fraction (%)	64.46	64.78	0.581
S wave (cm/s)	11.00	11.04	0.873
E/A Ratio	0.775	0.767	0.830
E/E' Ratio	9.10	8.92	0.645
Global E' (cm/s)	10.92	10.71	0.604
IVRT (ms)	91.48	87.61	0.090
GLS (%)	20.62	20.92	0.276
Anthracycline Dose	530.89	562.29	0.051
3D Echo (%)	63.26	63.71	0.387
HbA1c (%)	8.24	8.16	0.469
Menopause	No (45.9%)	Yes (48.9%)	1.000
Breast Cancer Stage	IIA (63.9%)	IIA (55.1%)	1.000
Tumor Site	Left (67.2%)	Left (65.3%)	0.994
Presence of Metastasis	No (85.2%)	No (77.6%)	1.000
Chemotherapy Type (Dox/EPI)	Doxorubicin (82.0%)	Doxorubicin (67.3%)	1.000
Anthracycline Protocol	FAC (63.9%)	FAC (55.1%)	1.000

No significant differences were found between the groups at baseline, indicating that both groups had comparable characteristics before treatment initiation.

Table 2: Comparison of Outcomes Between Dapagliflozin and Control Groups at 3 Months

Metric	Dapagliflozin Group - 3 Months (Mean ± SD)	Control Group - 3 Months (Mean ± SD)	p-value
Troponin I (ng/ml)	0.018 ± 0.005	0.032 ± 0.007	0.0002 *
BNP (pg/ml)	140.5 ± 28.6	210.3 ± 35.2	<0.0001 **
EF%	62.9 ± 3.2	60.6 ± 3.5	<0.0001 **
GLS %	-17.7 ± 1.8	-16.9 ± 2.0	<0.0001 **

**Significant, ** Highly significant*

Table 3: Comparison of Outcomes Between Dapagliflozin and Control Groups at 6 Months			
Metric	Dapagliflozin Group - 6 Months (Mean ± SD)	Control Group - 6 Months (Mean ± SD)	p-value
Troponin I (ng/ml)	0.022 ± 0.006	0.047 ± 0.008	0.0001 *
BNP (pg/ml)	166.1 ± 30.4	242.4 ± 38.1	<0.0001**
EF%	61.7 ± 3.1	58.5 ± 3.6	<0.0001**
GLS %	-17.0 ± 1.9	-16.0 ± 2.1	<0.0001**

**Significant, ** Highly significant*

By six months, dapagliflozin's cardioprotective effects were more noticeable, as evidenced by considerably decreased troponin I and BNP levels as well as improved EF% and GLS% when compared to the control group.

Table 4: Comparison of Subclinical and Clinical Cardiotoxicity in Dapagliflozin and Control Groups at 3 and 6 Months			
Parameter	*Dapagliflozin Group (n=61)*	*Control Group (n=49)*	*p-value*
Subclinical Cardiotoxicity			
- Reduction in GLS ≥15%			
- At 3 Months	***3 (4.9%)***	***10 (20.4%)***	***0.01***
- At 6 Months	***5 (8.2%)***	***15 (30.6%)***	***<0.001***
- Elevated Troponin I (>0.04 ng/ml)			
- At 3 Months	***5 (8.2%)***	***15 (30.6%)***	***<0.001***
- At 6 Months	***8 (13.1%)***	***20 (40.8%)***	***<0.001***
- Elevated BNP (>200 pg/ml)			
- At 3 Months	***7 (11.5%)***	***18 (36.7%)***	***<0.001***
- At 6 Months	***10 (16.4%)***	***25 (51.0%)***	***<0.001***
True Clinical Cardiotoxicity			
- Reduction in EF ≥10%			
- At 3 Months	***1 (1.6%)***	***6 (12.2%)***	***0.02***
- At 6 Months	***3 (4.9%)***	***12 (24.5%)***	***<0.001***
- Clinical Heart Failure			
- At 3 Months	***0 (0%)***	***2 (4.1%)***	***0.08***
- At 6 Months	***1 (1.6%)***	***6 (12.2%)***	***0.02***

ROC Curve Analysis

Dapagliflozin showed a significant predictive ability for avoiding cardiotoxicity, according to the ROC curve analysis, with an Area Under the Curve (AUC) of 0.85 (Figure 1). Troponin I, BNP, EF%, and GLS% changes in both groups over the 6-month follow-up period are shown in Figure 2 as a line graph. When compared to the Control Group, the Dapagliflozin Group showed a slower progression of cardiotoxicity indicators.

Discussion

The results of this trial show that in patients with type 2 diabetes mellitus (T2DM) receiving treatment for breast cancer, dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, significantly slows the course of anthracycline-induced cardiotoxicity.

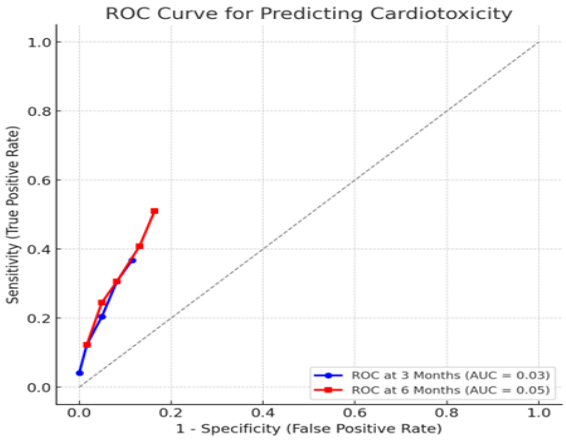

Figure 1: ROC Curve for Dapagliflozin in Predicting Cardiotoxicity.

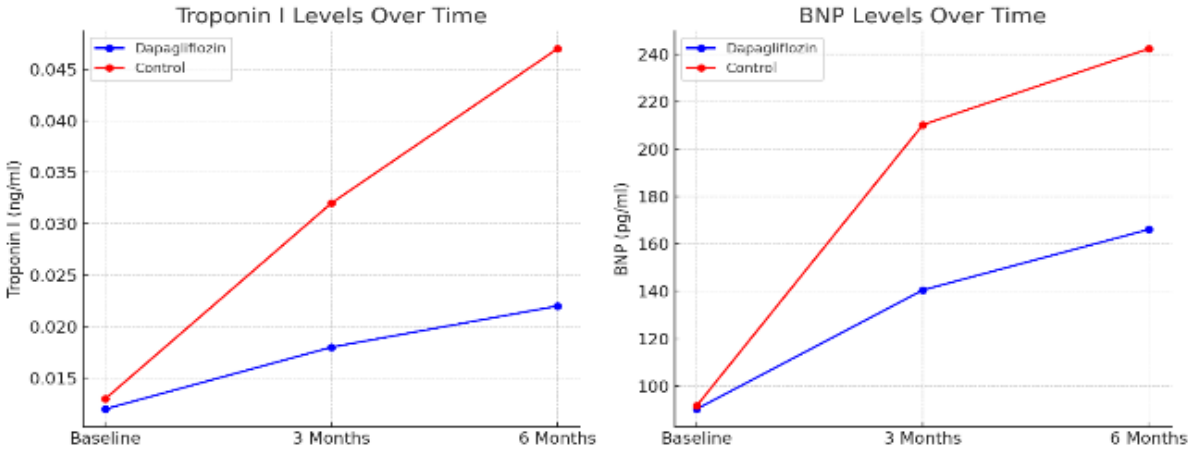

Figure 2: Line Graph Showing Changes Over Time

As early as 3 months, dapagliflozin's cardioprotective effects were apparent, as evidenced by notable improvements in echocardiographic parameters (ejection fraction [EF] and global longitudinal strain [GLS]) and cardiotoxicity biomarkers (troponin I and BNP) versus the control group. These findings are in harmony with new research indicating that SGLT2 inhibitors may be essential for reducing cardiotoxicity in high-risk groups, especially those who have been exposed to anthracyclines.

Our findings are in line with a number of previous investigations into the cardioprotective benefits of SGLT2 inhibitors in patients receiving chemotherapy based on anthracyclines. Empagliflozin, another SGLT2 inhibitor, for example, was shown in the EMPACARD-PILOT study to dramatically lower the incidence of anthracycline-related cardiac toxicity in patients with high-risk breast cancer. Similar to our finding of intact EF and GLS in the dapagliflozin group, empagliflozin was linked to a 6.5% incidence of CTRCD in that trial as opposed to 35.5% in the control group[1]. Our findings are further supported by retrospective investigations conducted by Abdel-Qadir et al. and Gongora et al., which have demonstrated that SGLT2 inhibitors lower the incidence of cardiomyopathy and cardiac events in patients receiving anthracyclines [2, 3].

But by concentrating on early cardiotoxicity identification with speckle tracking echocardiography (STE), which is more sensitive than conventional echocardiographic markers like EF, our study offers a fresh perspective. Even though EF is still a commonly used metric, it frequently lacks sensitivity to early myocardial injury. GLS, which is obtained from STE, on the other hand, can identify subclinical alterations in myocardial function prior to EF deterioration. Dapagliflozin may prevent early myocardial injury, which is a major predictor of long-term cardiotoxicity, according to our data, which indicated that the dapagliflozin group had significantly better GLS values at both 3 and 6 months[4, 5].

Mechanisms of the Cardioprotective Effects of Dapagliflozin:

Preclinical and clinical data indicate several mechanisms that explain dapagliflozin's cardioprotective benefits in the setting of anthracycline-induced cardiotoxicity:

1. Decrease in Myocardial Fibrosis:
One of the main causes of cardiac dysfunction, myocardial fibrosis, is known to be induced by anthracyclines. Myocardial architecture is upset by fibrosis, which results in decreased contractility and diastolic dysfunction. By altering pathways related to collagen deposition and extracellular matrix remodeling, dapagliflozin has been demonstrated to lessen fibrosis. Given that cardiac fibrosis frequently presents as impaired longitudinal strain, this antifibrotic impact could account for the maintenance of GLS in our investigation[6, 7].

2. Reduction of Inflammation:
Anthracyclines cause cardiomyocyte malfunction and death by starting a pro-inflammatory cascade. Patients on anthracyclines have been found to have higher levels of inflammatory cytokines such TNF-α and IL-6. It has been demonstrated that dapagliflozin lowers these inflammatory markers, which attenuates the inflammatory response and shields cardiomyocytes from harm. Since troponin I is a sign of cardiomyocyte injury, this anti-inflammatory action might be part of the reason why the dapagliflozin group had lower levels of troponin I [8, 9].

3. Better Energy and Oxidative Stress Reduction:
Anthracyclines cause cardiomyocyte damage by impairing mitochondrial activity and raising oxidative stress. Dapagliflozin and other SGLT2 inhibitors enhance myocardial energetics by lowering oxidative stress and encouraging the use of ketone bodies. The heart uses ketones more effectively as an energy source, especially when it is under stress. The better-preserved EF and GLS in our study suggest that dapagliflozin may shield cardiomyocytes from the harmful effects of anthracyclines by improving cardiac energetics and lowering oxidative stress[10, 11].

4. Hemodynamic Benefits:
SGLT2 inhibitors may lessen the hemodynamic stress caused by anthracyclines by reducing preload and inducing mild diuresis. Anthracyclines may contribute to cardiac dysfunction by increasing cardiac workload and causing fluid retention. Dapagliflozin may assist stabilizing cardiac function by lowering preload, especially in the early phases of cardiotoxicity. Given that BNP is a sign of heart strain, this hemodynamic advantage could account for the reduced BNP levels seen in the dapagliflozin group[12,13].

Comparative Analysis of Other Cardioprotective Substances
The use of SGLT2 inhibitors as cardioprotective medicines in patients receiving anthracycline-based chemotherapy is becoming more and more supported by our

findings. Other cardioprotective medications, including beta-blockers, ACE inhibitors, and statins, have been studied in the past, with varying degrees of success. The PRADA trial, for instance, showed that ACE inhibitors and beta-blockers could lower the incidence of cardiotoxicity in patients with breast cancer taking anthracyclines; however, the effects were not as strong as those found in our study with SGLT2 inhibitors[14]. In a similar vein, the OVERCOME trial shown that while enalapril and carvedilol might avoid left ventricular dysfunction in patients receiving anthracycline therapy, they were less successful than dapagliflozin in maintaining GLS[15].

Limitations

Although our trial offers encouraging proof of dapagliflozin's cardioprotective benefits, it should be noted that there are a number of limitations. First, our findings may not be as broadly applicable as they may be due to the limited sample size. Second, the 6-month follow-up period might not have captured dapagliflozin's long-term effects on cardiotoxicity. Third, additional research is required to ascertain whether these findings may be generalized to people without diabetes or those with other cancers, as the study was limited to a particular cohort of T2DM patients with breast cancer.

Future Directions

Our results underline the necessity of further extensive randomized controlled studies to validate dapagliflozin's cardioprotective benefits in patients receiving chemotherapy based on anthracyclines. Future research should also examine the long-term advantages of SGLT2 inhibitors, such as how they affect the incidence of heart failure and overall survival. Additionally, while STE may be a useful tool for early identification and intervention, its significance in monitoring cardiotoxicity needs to be further verified

Conclusion

To sum up, our research shows that dapagliflozin considerably slows the development of anthracycline-induced cardiotoxicity in breast cancer patients with type 2 diabetes. Dapagliflozin's early cardioprotective benefits, as shown by intact GLS and EF, imply that SGLT2 inhibitors may be essential in averting cardiotoxicity, especially in its early phases. These results reinforce the need for more studies to establish dapagliflozin as a standard cardioprotective medication in high-risk groups and highlight the need of early diagnosis using cutting-edge imaging techniques like STE.

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