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IMPACT OF SGLT-2 INHIBITORS ON CONGESTION AND QUALITY OF LIFE IN DECOMPENSATED HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION

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Abstract: Introduction: Heart failure has a high global prevalence and incidence. This is reflected in high morbidity and mortality rates and continues to be a significant challenge, with a high rate of hospitalization and readmission. **Objective**: To evaluate the impact of iSGLT-2 on volemia, congestion, functionality and quality of life of patients hospitalized with HF functional classes III and IV (NYHA) with reduced ejection fraction. **Methods**: This was a prospective, interventional study of patients admitted to a tertiary hospital in Curitiba for decompensated heart failure with reduced ejection fraction. The following variables were analyzed: pulmonary, jugular vein and inferior vena cava congestion, quality of life, functionality and laboratory tests assessed on admission, the 15th, 30th, 60th and 90th day after hospital discharge and the start of the drug Dapagliflozin 10 mg, orally, in a single dose for 90 days. **Results**: The results reflect significant overall improvement in the clinical, ultrasound and laboratory assessment of the patients, with a reduction in clinical symptoms of congestion obtained by the diameter of the vena cava ($p<0.03$) and in the presence of pulmonary B-lines ($p<0.001$), as well as increases in the distance covered in the walking test ($p<0.001$), improvement in O2 saturation ($p<0.014$) and in the KCCQ-12 score ($p<0.001$). **Conclusions**: In the main, there was a significant reduction in pulmonary congestion and global volemia, reflected in the ultrasound improvement and in the patients' quality of life, according to the KCCQ-12. In addition, there was an increase in patient functionality and less dependence for daily tasks, as well as a reduction in blood glucose and NT-Pro-BNP levels, indicating less morbidity and a higher quality of life.
Keywords: Heart failure; SGLT-2 inhibitors; Volemia; Congestion.

INTRODUCTION

Heart failure (HF) affects around 23 million people globally, with a high prevalence and incidence. The overall prevalence is approximately 2% in the adult population and 5% to 9% in people aged 65 and over [1, 2] . HF results in high morbidity and mortality rates and continues to be a significant challenge, with frequent hospitalizations and a high readmission rate, particularly in patients with acute heart failure (AHF) . [3,4]

Treatment with guideline-directed medical therapy (GDMT) is crucial for reducing mortality and morbidity in patients with reduced ejection fraction (HFrEF) [7] . GDMT includes inhibitors of the renin-angiotensin-aldosterone system (RAAS), β-blockers, mineralocorticoid receptor antagonists and, more recently, inhibitors of the sodium-glucose cotransporter type 2 (iSGLT-2) [8] . The latter, originally used only for diabetic patients, have also shown benefits in non-diabetic patients with HFpEF, promoting reduced mortality and hospitalizations and offering renal protection .[9]

Although the exact mechanisms of iSGLT-2 are not fully understood, one hypothesis suggests that inhibition of SGLT-2 reduces sodium and glucose reabsorption, promoting osmotic diuresis and relieving congestion [11,13] . Studies, such as EMPEROR-Reduced and EMPULSE, have shown that iSGLT-2, such as Empagliflozin, improve HF outcomes and quality of life, both during hospitalization and after discharge .[15,16]

The lack of consensus on the ideal time to start iSGLT-2, either during hospitalization or after discharge, motivates our study to investigate the introduction of these drugs during hospitalization, according to Brazilian guidelines. The aim is to evaluate quality of life, functionality, and the status of pulmonary and abdominal congestion associated with the use of iSGLT-2.

METHODS

This is a prospective, interventional study with the aim of evaluating the influence of using iSGLT-2 (Dapaglifozin 10 mg) on indicators of blood volume, congestion, readmission, quality of life and functionality in patients with decompensated heart failure with reduced ejection fraction (HFrEF).

The study was approved by the Ethics Committee (CAAE: 56889022.6.0000.0020), and the terms of free and informed consent were duly signed by each patient admitted to the study, with one version remaining with the patient and the other with the author.

Nineteen participants were initially included, aged over 18 and under 85, with a diagnosis of heart failure with reduced ejection fraction (LVEF ≤ 40%), New York Heart Association (NYHA) functional classes II and III, optimized according to the *guidelines* and taking iECA/BRA or Sacubitril-Valsartan, beta-blockers and mineralocorticoid antagonists with fixed doses of medication (for at least 4 weeks) and who had not previously been treated with iSGLT-2. Patients with renal dysfunction were excluded if their glomerular filtration rate (GFR) was less than 30 ml/min/1.73m^2 ; if they were unable to perform the functionality test; if they were pregnant, breastfeeding or over 85 years old.

The patients selected were suffering from decompensated heart failure, profile B (no signs of low output or congestion), New York Heart Association (NYHA) functional classes III and IV. Follow-up of the study sample began on admission to Cajuru University Hospital and continued after discharge. Dapaglifozin 10 mg (Atrazeneca Tdv Ltd) (D0) was introduced in-hospital at the time of HF decompensation. The patients remained in hospital until their condition cleared up and were discharged with optimized treatment and referred to the hospital's HF outpatient clinic.

After the patients were discharged from hospital, Dapagliflozin 10 mg (Atrazeneca Tdv Ltd) was offered and advised to be used orally every day for 90 days, reconciling the medications already in use. The medication was donated by the researchers (at no extra cost to the participants) and dispensed by the support team at the clinical research center (PUC-trials).

After the start of the study, some of these patients were discontinued due to adverse events, such as death (1 patient), readmission and discontinuation of medication (3), worsening renal function (1), and failure to return for consultations (2).

In this study, the patients were reassessed and the variables of pulmonary congestion (by ultrasound analysis of the lungs, jugular vein and inferior vena cava); quality of life score (by the Kansas City Cardiomyopathy Questionnaire); functionality; and laboratory tests on the 15th, 30th, 60th and 90th day after hospital discharge and starting the drug Dapagliflozin 10 mg orally, without introducing or increasing the dose of loop diuretics. The results obtained were attached to a database in a spreadsheet and computed for later analysis.

The pulmonary, jugular and vena cava ultrasound examinations were carried out by the researcher in the hospital environment and at the PUCPR Clinical Simulation Center, at no additional cost to the participants.

The purpose of lung ultrasound was to assess the prevalence of congestion in patients hospitalized with acute decompensated heart failure. This was done by analyzing the B-lines, which represent hyperechogenic artifacts of pleural origin, which comprise the thickened interlobular septa and are present in pulmonary congestion and help in the differential diagnosis of dyspnea. When three or more B lines are identified, the field is considered positive.

The jugular venous ultrasound of each patient was also analyzed to measure the ratio between the diameter of the internal jugular vein before and after a Valsalva maneuver. To take this measurement, the patient was first reclined at an angle of 45°, identifying the angle of Louis below the angle of the mandible, on the left side of the neck, and the ultrasound was positioned. Next, the diameter of the internal jugular vein and its possible alterations were measured at three moments: a) before a Valsalva maneuver (patient at rest); b) during a Valsalva maneuver; c) after a Valsalva maneuver (inspiratory phase).

Finally, the ultrasound analysis of congestion was complemented by checking the variability of the inferior vena cava, with a variation of less than 50% of its diameter being suggestive of congestion.

In order to assess changes in the patients' quality of life, the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) was presented to the participants and answered by them. This material aims to assess the patients' perception of any changes in their daily lives after using the medication.

In addition, a functional test was carried out on the patients involved. This test consisted of measuring vital data such as blood pressure, heart rate and respiratory rate after walking for a standardized time of 6 minutes. This test was carried out in conjunction with the periodic medical assessments to be conducted.

A blood sample was also taken to test blood count, creatinine, urea, sodium, potassium, transaminases, TSH, glycemia, microalbuminuria, serum albumin, glycated hemoglobin and NT-Pro-BNP in each of the patients at each of the times evaluated.

RESULTS

The analysis presented below was based on data from 12 patients with HF who used an SGLT2 inhibitor and were assessed on hospital admission (before starting the medication) and 15, 30, 60 and 90 days after starting the medication. In the following tables, only patients with data from the five stages of assessment were included, so the *n* varies.

Table 1 shows the clinical data at the five assessment points. The values from 0 to 2 in the variable 'Crepitant rales', 0 to 3 in 'Peripheral edema' and 0 to 4 in 'History of orthopnea in the last week' refer to the intensity of the symptoms, the higher the number the more intense the symptoms (0 being the absence of symptoms).

In relation to the ultrasound exams, Table 2 shows that some other echocardiographic variables are assessed, such as the presence or absence of B-lines by pleuro-pulmonary fields. Under 'Functional class', the values range from 0 to 4, with 4 being the worst symptoms.

Table 3 shows the analysis of the KCCQ12 score in the five evaluation stages, with higher values representing a better quality of life.

Finally, Table 4 shows the oxygen saturation indices before and after the walking test, as well as the total distance covered in meters.

DISCUSSION

An overall improvement was observed, not only in the clinical, ultrasound and laboratory evaluation of the sample, but also in the patients' perception of their quality of life and functionality.

In relation to the clinical evaluation, the variables 'Crackles', 'B3 galloping sound', 'Jugular distension' and 'Peripheral history' were abolished after 90 days of medication. Only 'Peripheral edema' remained in one patient, with less intensity.

Variable	n valid	Moment				
		Admission	After 15 days	After 30 days	After 60 days	After 90 days
Crackling sounds						
0	12	2 (16,7%)	10 (83,3%)	11 (91,7%)	12 (100%)	12 (100%)
1		8 (66,7%)	1 (8,3%)	1 (8,3%)	0 (0%)	0 (0%)
2		2 (16,7%)	1 (8,3%)	0 (0%)	0 (0%)	0 (0%)
B3 - galloping sound						
No	12	11 (91,7%)	12 (100%)	13 (100%)	14 (100%)	15 (100%)
Yes		1 (8,3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Jugular distension						
No	11	8 (72,7%)	10 (90,9%)	11 (100%)	10 (90,9%)	11 (100%)
Yes		3 (27,3%)	1 (9,1%)	0 (0%)	1 (9,1%)	0 (0%)
Peripheral edema						
0	12	8 (66,7%)	10 (83,3%)	9 (75%)	10 (83,3%)	11 (91,7%)
1		1 (8,3%)	1 (8,3%)	1 (8,3%)	2 (16,7%)	1 (8,3%)
2		2 (16,7%)	1 (8,3%)	2 (16,7%)	0 (0%)	0 (0%)
3		1 (8,3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hist, Orthopnea last week						
0	12	2 (16,7%)	9 (75%)	10 (83,3%)	12 (100%)	12 (100%)
1		1 (8,3%)	2 (16,7%)	2 (16,7%)	0 (0%)	0 (0%)
2		1 (8,3%)	1 (8,3%)	0 (0%)	0 (0%)	0 (0%)
3		5 (41,7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4		3 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 1 - Comparison of the clinical assessment parameters between the 5 assessment moments.

Variable	n valid	Moment				
		Admission	After 15 days	After 30 days	After 60 days	After 90 days
Hepato-jugular reflux						
No	12	10 (83,3%)	11 (91,7%)	11 (91,7%)	12 (100%)	12 (100%)
Yes		2 (16,7%)	1 (8,3%)	1 (8,3%)	0 (0%)	0 (0%)
Functional class						
1	12	0 (0%)	3 (25%)	0 (0%)	5 (41,7%)	5 (41,7%)
2		3 (25%)	6 (50%)	5 (41,7%)	7 (58,3%)	6 (50%)
3		7 (58,3%)	3 (25%)	6 (50%)	0 (0%)	1 (8,3%)
4		2 (16,7%)	0 (0%)	1 (8,3%)	0 (0%)	0 (0%)
Pulmonary B-line						
No	12	1 (8,3%)	9 (75%)	11 (91,7%)	10 (83,3%)	11 (91,7%)
Yes		11 (91,7%)	3 (25%)	1 (8,3%)	2 (16,7%)	1 (8,3%)
Vena Cava Variability						
<50%	12	11 (91,7%)	6 (50%)	4 (33,3%)	6 (50%)	7 (58,3%)
>50%		1 (8,3%)	6 (50%)	8 (66,7%)	6 (50%)	5 (41,7%)

Table 2 - Comparison of the proportion of vena cava variation between the 5 time points.

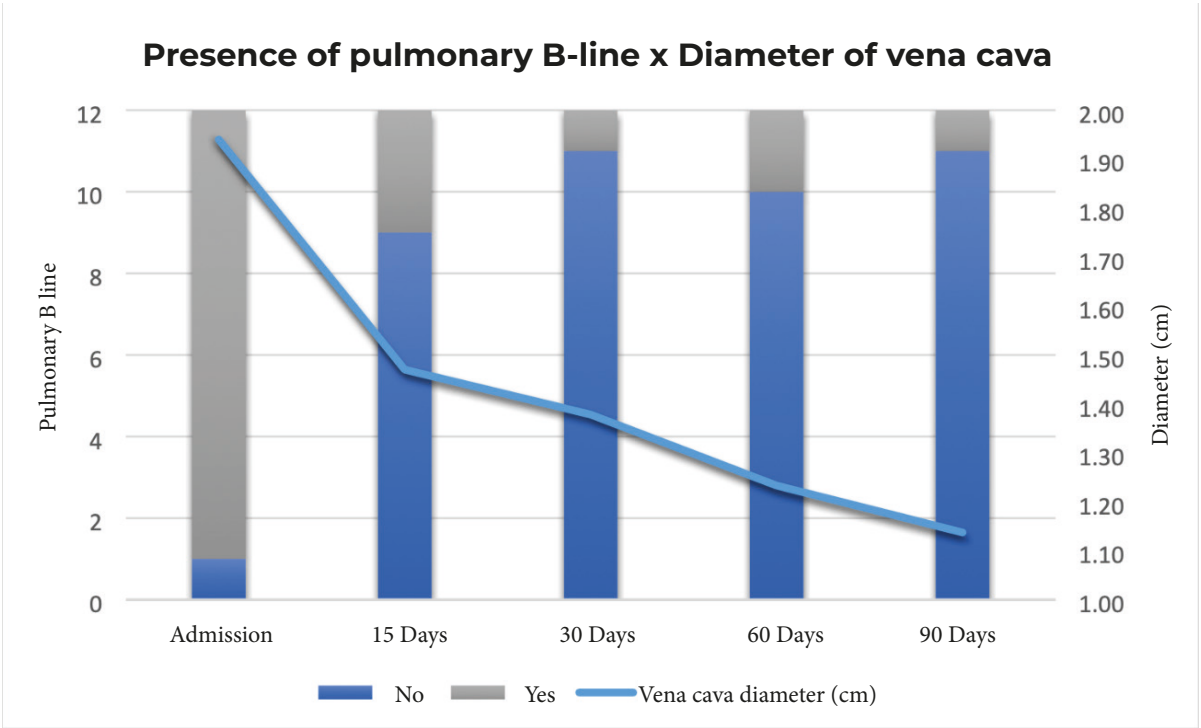

Figure 1. Graph of the presence of a B-line and the diameter of the inferior vena cava on lung ultrasound at admission, 15, 30, 60 and 90 days after evaluation.

	Admission	**After 15 days**	**After 30 days**	**After 60 days**	**After 90 days**
Patient 1	12	31	51	51	61
Patient 2	32	64	61	63	64
Patient 3	19	23	59	58	59
Patient 4	12	23	25	40	46
Patient 5	18	52	60	63	63
Patient 6	20	37	38	40	33
Patient 7	26	63	64	63	61
Patient 8	34	47	57	59	59
Patient 9	14	23	26	33	
Patient 10	13	27	57	49	
Patient 11	15	63	59	57	
Patient 12	52	51	56	63	
Patient 13	13	43	30	64	
Patient 14	16	32			
Patient 15	13	23			
Total Scores	**20.60**	**40.13**	**49.46**	**54.08**	**55.75**

Table 3 - Comparison of the KCCQ12 score for the five moments.

SpO2 Before	Admission	12	95; 94 (93 - 98)
	After 15 days	12	96,7; 96,5 (93 - 99)
	After 30 days	12	96,9; 97 (95 - 99)
	After 60 days	12	96,6; 97 (94 - 99)
	After 90 days	12	97,3; 97,5 (95 - 99)
SpO2 after	Admission	9	93,9; 93 (92 - 98)
	After 15 days	9	95,4; 95 (93 - 99)
	After 30 days	9	95,8; 96 (93 - 98)
	After 60 days	9	96,1; 96 (94 - 99)
	After 90 days	9	96,9; 98 (94 - 99)
Distance in meters	Admission	10	276,9; 270 (200 - 450)
	After 15 days	10	294,5; 300 (230 - 375)
	After 30 days	10	288; 317,5 (0 - 450)
	After 60 days	10	381,5; 375 (275 - 525)
	After 90 days	10	396,5; 387,5 (300 - 550)

Table 4 - Comparison of the parameters of the walk test between the 5 assessment moments.

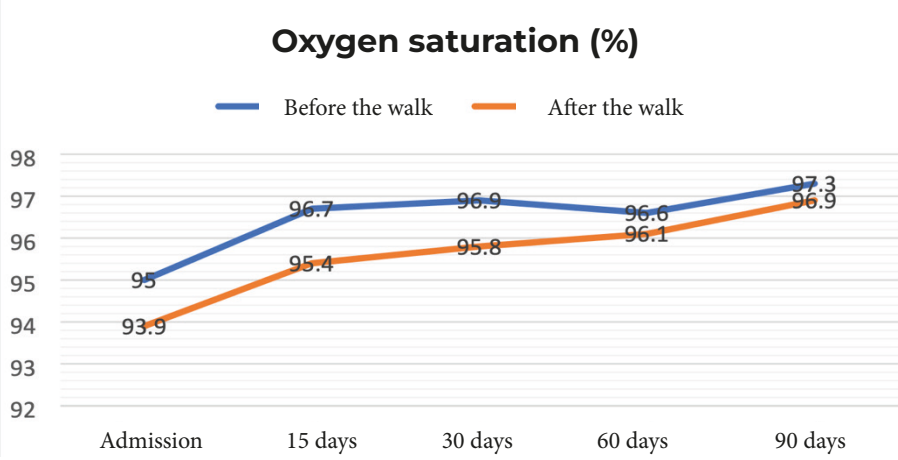

Figure 2 - Graph of patients' oxygen saturation during the progression of the study, before and after the walking test.

In the opinion on the ultrasound data, there was a significant reduction in the diameter of the vena cava at 60 and 90 days after the introduction of the medication evaluated. Meanwhile, the proportion of patients with the presence of a pulmonary B-line on admission is significantly higher than at the four subsequent time points, a sign that at the end of treatment the patient is less congested and helping to elucidate our hypothesis that iSGLT-2 has a positive impact on improving blood volume and congestion.

With regard to functionality, there was a significant difference between the 5 evaluation moments using the walking test in terms of distance covered in meters, so that in 60 and 90 days after the introduction of the medication, this distance was significantly greater than at admission and with fewer negative systemic repercussions, such as dyspnea. This fact is proven when there is a significant overall improvement in diastolic BP afterwards and SpO2 afterwards, because after the walking test, the SpO2 value was significantly higher at 60 and 90 days afterwards when compared to admission.

The results presented in Table 3 show a significant difference in the KCCQ12 scores between the five assessment times. In the comparison, it can be seen that on admission the total score and for each of the domains was significantly higher than at 30, 60 and 90 days. This shows that the patients themselves perceive an improvement in their quality of life according to their answers to the KCCQ-12. Patients reported a reduction in the frequency and severity of symptoms such as shortness of breath and tiredness. In addition, the answers to the questionnaire reflect a reduced impact of heart failure on the patient's general life, associated with an improvement in the patient's perception of their own health. Thus, it can be seen that the KCCQ-12 score has improved compared to previous evaluations, which is a strong indicator of a positive response to treatment.

The results of the laboratory parameters show a significant difference in blood glucose and glycated hemoglobin between the five time points - which was to be expected. In addition, sodium and NT-Pro-BNP were significantly lower, being higher on admission.

CONCLUSION

Ultrasound improvement was observed with a reduction in the diameter of the vena cava and the absence of a pulmonary B-line, indicating a reduction in pulmonary congestion and global blood volume. This result was in line with what the study had previously postulated. This improvement could be measured through the data obtained and can be used as a basis for future analysis

In addition to the improvement in the indicators assessed by ultrasound, there was a perception of improvement in the quality of life reported by the patients themselves, as demonstrated by the answers to the questionnaires completed at each consultation. Added to this is the improvement in life functionality and less dependence on patients to carry out everyday tasks.

Finally, with regard to laboratory data, the improvement in the percentage reduction of glycemia and NT-Pro-BNP is notable. This implies lower morbidity and a better quality of life for patients.

These results not only support the efficacy of the drug, but also indicate a promising advance in the therapeutic approach to heart failure.

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