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# Effects of sodium-glucose cotransporter-2 inhibitors on nutritional status in heart failure with reduced ejection fraction

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## SUMMARY

**OBJECTIVE:** This study aimed to evaluate the effects of sodium-glucose cotransporter-2 inhibitors on nutritional status in patients with heart failure with reduced ejection fraction.

**METHODS:** The sodium-glucose cotransporter-2 inhibitor treatment was initiated in 153 patients with heart failure with reduced ejection fraction who were symptomatic despite optimal medical treatment and were followed up for 6 months. The Minnesota Living With Heart Failure Questionnaire scores, New York Heart Association functional class, NT-pro-BNP levels, and nutritional index scores of the patients were evaluated before sodium-glucose cotransporter-2 inhibitor treatment and at the 6-month follow-up. The nutritional status of the patients was evaluated with the COntrolling NUTritional Status score, Geriatric Nutritional Risk Index, and Prognostic Nutritional Index.

**RESULTS:** After sodium-glucose cotransporter-2 inhibitor treatment, significant changes were observed in the mean scores of the three different nutritional indexes: COntrolling NUTritional Status (before: 2.76±2.43 vs. after: 1.12±1.23, p<0.001), Geriatric Nutritional Risk Index (before: 98.2±9.63 vs. after: 104.4±5.83, p<0.001), and Prognostic Nutritional Index (before: 37.9±4.63 vs. after: 42.9±3.83, p<0.001) scores. A significant decrease in the number of patients with malnutrition was observed according to the COntrolling NUTritional Status (before: 46.4% vs. after: 9.7%, p<0.001), Geriatric Nutritional Risk Index (before: 41.8% vs. after: 18.9%, p=0.006), and Prognostic Nutritional Index (before: 36.6% vs. after: 13.7%, p=0.007) scores. A significant functional improvement was observed in patients after sodium-glucose cotransporter-2 treatment: Minnesota Living With Heart Failure Questionnaire scores (before: 39.2±7.2 vs. after: 20.4±7.4, p<0.001), NT-pro-BNP levels (before: 2989±681 vs. after: 1236±760, p<0.001), and New York Heart Association class (before: class II-III: 95.5%; class IV: 4.5% vs. after: class II-III: 78%; class IV: 0%, p<0.001).

**CONCLUSION:** In patients with heart failure with reduced ejection fraction who are symptomatic despite optimal medical treatment, the addition of an sodium-glucose cotransporter-2 inhibitor to treatment can significantly improve both the nutritional and functional statuses.

**KEYWORDS:** Heart failure. Malnutrition. Nutrition assessment. Sodium-glucose transporter 2 inhibitors.

## INTRODUCTION

Heart failure (HF) is a chronic inflammatory syndrome with typical symptoms and signs, which reduces the quality of life and increases the risk of mortality and morbidity[1]. HF can lead to malnutrition by causing inadequate nutrient intake and malabsorption due to intestinal edema and anorexia and an increased resting metabolic rate secondary to the high energy needs of the heart[2]. Malnutrition can lead to poor prognosis in patients with HF by leading to fluid retention, inflammation, and increased neurohormonal activity due to hypoproteinemia[3].

The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trials showed that sodium-glucose cotransporter-2 (SGLT-2) inhibitor treatment improves the quality of life and HF symptoms in patients with heart failure with reduced ejection fraction (HFrEF) who describe symptoms in the New York Heart Association (NYHA) class II-IV categories despite optimal medical treatment[4,5]. We can conclude that the symptomatic and functional improvement with SGLT-2 inhibitor treatment in patients with HFrEF does not occur only with diuresis, but SGLT-2 inhibitors can improve the nutritional status of patients.

## PATIENTS AND METHODS

### Patients

This prospective study included patients with the diagnosis of HFrEF. The study's inclusion criteria were as follows: (1) the presence of left ventricular ejection fraction (LVEF) of less than 40%, (2) having an NYHA functional class II–IV despite optimal

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medical treatment, (3) having an SGLT-2 inhibitor drug added to the treatment and used regularly for at least 6 months, (4) attendance at the 6-month follow-up and attendance at least two of the three follow-up visits. The study's exclusion criteria were as follows: In the past 6 months, before and during the study's follow-up (1) undergone cardiac pacemaker, implantable cardioverter-defibrillator (ICD) implantation or cardiac resynchronization therapy (CRT), (2) undergone coronary artery bypass graft surgery, (3) undergone surgical or percutaneous intervention for heart valve disease, (4) undergone percutaneous coronary intervention for acute coronary syndrome, (5) having an inflammatory and infectious disease under follow-up or treatment, (6) having a malignancy, and (7) having advanced liver and kidney failure (glomerular filtration rate <30 mL/min/1.73 $m^2$).

*Optimal medical treatment*: The fact that the patients were symptomatic despite optimal medical treatment was expressed after applying the maximum doses of the maximum number of optimal medical treatment drug groups that they could tolerate[1].

Patient follow-ups and data records were made prospectively in the cardiology outpatient clinic. Patients who were initiated SGLT-2 inhibitor treatment were invited to follow-ups at the first, third, and sixth months to monitor treatment adherence. Demographic characteristics of the patients, blood test results, systolic and diastolic blood pressures, heart rates, body weight, and height measurements were recorded at the follow-up visits. At each follow-up visit, nutritional index scores and body mass index (BMI) values of patients were calculated, blood samples were taken to test serum albumin and NT-pro-BNP levels, and NYHA functional classification and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) were repeated.

## Nutritional indexes

The nutritional status of all patients was assessed using three scoring systems: (1) Geriatric Nutritional Risk Index (GNRI), (2) COntrolling NUTritional Status (CONUT), and (3) Prognostic Nutritional Index (PNI). The GNRI scores were calculated as follows: 1489xserum albumin (g/L)+41.7x[weight (kg)/ideal body weight][6]. Ideal body weight (IBW) was calculated using the formula: 22x(height in meters)$^2$[2,7]. The GNRI scores were evaluated as follows: <82 points: severe, 82–91 points: moderate, 92–98 points: mild malnutrition, and >98 points: normal. The CONUT score was calculated by the previously described formula based on serum albumin level, total lymphocyte count, and total cholesterol level[8]. The CONUT scores were evaluated as follows: 0–1 points: normal, 2–4 points: mild, 5–8 points: moderate, and 9–12 points: severe malnutrition. The PNI score was calculated by the formula: 10xserum albumin (g/dL)+0.005xtotal lymphocyte count (µl)[9]. The PNI scores were evaluated as follows: >38 points: normal, 35–38 points: mild, and <35 points: severe malnutrition. In our study, patients with normal nutritional status and patients with malnutrition were evaluated mutually in the subgroup analyses. Patients were considered malnourished if GNRI score <98, CONUT score ≥2, and PNI score <38.

## Ethical standards

For this study, written consent was obtained from the patients, and approval was obtained from the local ethics committee with the decision number 2022/046. This study was performed in accordance with the 1964 Declaration of Helsinki.

## Statistical analysis

The IBM Statistical Package for Social Sciences, version 20 for Windows (Chicago, IL, USA) was used for statistical analyses. The compatibility of the parameters with the normal distribution was evaluated using the Kolmogorov-Smirnov test and the normality using the Shapiro-Wilk test. Normally distributed data were presented as the mean±standard deviation (SD) and non-normally distributed data were presented as the median with 25–75%. The categorical variables were expressed as percentages. The Student's t-test and Mann-Whitney U test were used to compare the differences in variables between the groups. The chi-square test was used to analyze categorical variables. The McNemar test and sample t-test were performed according to the normality of malnutrition using three scoring systems before and after the SGLT-2 inhibitor treatment. Pearson's and Spearman's correlation tests were used to evaluate the correlation between the variables. A $p \leq 0.05$ was considered significant for all statistical analyses.

# RESULTS

A total of 153 patients with HFrEF were included in the study. The mean follow-up period of the patients was 245±22 days. Demographic, clinical, and laboratory characteristics of the patients are presented in Table 1. The mean age of the patients was 62.4±10.6 years, and 35 (22.8%) patients were female. In 58.8% of the patients, the cause of HF was ischemic heart disease.

Serum albumin levels were found to be increased significantly after treatment (before: 4.1±0.5 vs. after: 4.9±0.67, p=0.022). NT-pro-BNP levels were found to be decreased significantly after treatment (before: 2989±681 pg/mL vs. after: 1236±760 pg/mL, p<0.001) (Table 1).

According to the NYHA functional classification, 64 (42%) patients were grouped under class II, 82 (53.5%) patients were

**Table 1.** Demographic characteristics, clinical and laboratory parameters, and nutritional index scores of the study population (baseline and after treatment).

| Parameter | Baseline (n=153) | | |
|---|---|---|---|
| Age (years) | 62.4±10.6 | | |
| Gender: female, n (%) | 35 (22.8) | | |
| Ischemic heart failure, n (%) | 90 (58.8) | | |
| Hypertension, n (%) | 98 (64.1) | | |
| Diabetes mellitus, n (%) | 50 (32.6) | | |
| Coronary artery disease, n (%) | 104 (67.9) | | |
| Dyslipidemia (n/%) | 77 (50.3) | | |
| COPD (n/%) | 35 (22.8) | | |
| Atrial fibrillation | 34 (22.2) | | |
| LVEF, n (%) | 27.5±4.7 | | |
| β-Blocker use, n (%) | 143 (93.4) | | |
| ACE inhibitor use, n (%) | 80 (52.2) | | |
| Sacubitril use, n (%) | 71 (46.4) | | |
| Spironolactone use, n (%) | 98 (64.1) | | |
| Statin use, n (%) | 30 (19.6) | | |
| Ivabradine use, n (%) | 56 (36.6) | | |
| Diuretic use, n (%) | 142 (92.8) | | |
| Digoxin use, n (%) | 26 (16.9) | | |
| | **Baseline** | **After treatment** | **p-value** |
| SBP (mmHg) | 126.3±24 | 124.9±22 | 0.456 |
| DBP (mmHg) | 68.4±13 | 66.3±12 | 0.518 |
| Sodium (mmol/L) | 137.8±4.6 | 138.6±4.4 | 0.356 |
| Potassium (mmol/L) | 4.4 (3.2–5.8) | 4.5 (3.3–5.8) | 0.408 |
| Hematocrit (%) | 38.5±4.6 | 39.2±4.8 | 0.486 |
| Lymphocyte ($10^9$/L) | 1.82±0.39 | 1.88±0.32 | 0.398 |
| eGFR, mL/min/1.73 $m^2$ | 66.8±15.4 | 68.2±14.2 | 0.246 |
| Total cholesterol (mg/dL) | 172.46±12.66 | 174.38±14.06 | 0.286 |
| LDL (mg/dL) | 108.82 (52.4–140.6) | 109.64 (56.8–148.5) | 0.308 |
| CRP | 4.9 (2.4–12.6) | 4.5 (3.1–10.4) | 0.382 |
| Heart rate | 74.1±4.8 | 73.8±4.4 | 0.412 |
| HbA1c (%) | 6.9±1.4 | 6.7±1.2 | 0.422 |
| BMI (kg/$m^2$) | 27.9±5.2 | 27.7±4.7 | 0.620 |
| Weight (kg) | 75.6±13 | 76.1±14 | 0.668 |
| Albumin (g/dL) | 4.1±0.5 | 4.9±0.6 | 0.022 |
| NT-pro-BNP, pg/mL | 2989±681 | 1236±760 | <0.001 |
| NYHA class, n (%) | | | <0.001 |
| I | 0 | 34 (22) | |
| II | 64 (42) | 88 (58) | |
| III | 82 (53.5) | 31 (20) | |
| IV | 7 (4.5) | 0 | |
| MLWHFQ score | 39.2±7.2 | 20.4±7.4 | <0.001 |
| CONUT score | 2.76±2.4 | 1.12±1.2 | <0.001 |
| CONUT ≥2, n (%) | 71 (46.4) | 14 (9.7) | <0.001 |
| GNRI score | 98.2±9.6 | 104.4±5.8 | <0.001 |
| GNRI <98, n (%) | 64 (41.8) | 29 (18.9) | 0.006 |
| PNI score | 37.9±4.6 | 42.9±3.8 | <0.001 |
| PNI <38, n (%) | 56 (36.6) | 21 (13.7) | 0.007 |

Numerical variables with normally distributed data were presented as the mean±standard deviation (SD), numerical variables without normally distributed data were presented as the median (25th and 75th percentages), and categorical variables were presented as percentages. COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; LDL: low-density lipoprotein; CRP: C-reactive protein; BMI: body mass index; NT-pro-BNP: N-terminal-pro B-type natriuretic peptide, NYHA: New York Heart Association; MLWHFQ: Minnesota Living with Heart Failure Questionnaire; CONUT: COntrolling NUTritional status; GNRI: Geriatric Nutritional Risk Index; PNI: Prognostic Nutritional Index.

grouped under class III, and 7 (4.5%) patients were grouped under class IV before SGLT-2 treatment. Significant symptomatic and functional improvement was observed in patients after SGLT-2 inhibitor treatment. After treatment, the rate of patients in NYHA class III decreased to 20%, the rate of patients in NYHA class II-III decreased to 78%, and there were no patients in the NYHA class IV category (p<0001). The mean MLWHFQ score was found to be decreased significantly after treatment (before: 39.2±7.2 vs. after: 20.4±7.4, p<0.001) (Table 1). We found that MLWHFQ score, NT-pro-BNP level, and NYHA classification were significantly correlated with each other (Table 2).

We found that there was a significant improvement in the mean index scores we used for nutritional status assessment after SGLT-2 inhibitor treatment compared to before treatment (CONUT—before: 2.76±2.43 vs. after: 1.12±1.23, p<0.001; GNRI—before: 98.2±9.63 vs. after: 104.4±5.83, p<0.001; PNI—before: 37.9±4.63 vs. after: 42.9±3.83, p<0.001). The distribution of patients with malnutrition was determined according to the nutritional indexes as follows: CONUT ≥2 [before, n (%): 71 (46.4%) vs. after, n (%): 14 (9.7%)]; GNRI <98 [before, n (%): 64 (41.8%) vs. after, n (%): 29 (18.9%)], and PNI <38 [before, n (%): 56 (36.6%) vs. after, n (%): 21 (13.7%)]. The rate of patients with malnutrition was found to be decreased significantly after SGLT-2 inhibitor treatment (p: <0.001, 0.006, 0.007, respectively) (Figure 1). We found that the nutritional index scores were significantly correlated with

**Table 2.** Correlation analyses of Minnesota Living with Heart Failure Questionnaire score, NT-pro-BNP level, and New York Heart Association class with nutritional index scores of patients.

| Variables | MLWHFQ score | NT-pro-BNP level | NYHA class | CONUT score | GNRI score | PNI score |
|---|---|---|---|---|---|---|
| MLWHFQ score | | r: 0.230 | r: 0.454 | r: 0.302 | r: -0.364 | r: -0.392 |
| | | p: 0.028 | p<0.001 | p: 0.004 | p<0.001 | p<0.001 |
| NT-pro-BNP level | r: 0.230 | | r: 0.278 | r: 0.320 | r: -0.339 | r: -0.388 |
| | p: 0.028 | | p: 0.006 | p: 0.001 | p<0.001 | p<0.001 |
| NYHA class | r: 0.454 | r: 0.278 | | r: 0.288 | r: -0.310 | r: -0.354 |
| | p<0.001 | p: 0.006 | | p: 0.007 | p: 0.001 | p<0.001 |
| CONUT score | r: 0.302 | r: 0.320 | r: 0.288 | | r: -0.402 | r: - 0.388 |
| | p: 0.004 | p: 0.001 | p: 0.007 | | p<0.001 | p<0.001 |
| GNRI score | r: -0.364 | r: -0.339 | r: -0.310 | r: -0.402 | | r: 0.672 |
| | p<0.001 | p<0.001 | p: 0.001 | p<0.001 | | p<0.001 |
| PNI score | r: -0.392 | r: -0.388 | r: -0.354 | r: - 0.388 | r: 0.672 | |
| | p<0.001 | p<0.001 | p<0.001 | p<0.001 | p<0.001 | |

MLWHFQ: Minnesota Living with Heart Failure Questionnaire; BNP: B-type natriuretic peptide; NYHA: New York Heart Association; CONUT: COntrolling NUTritional status; GNRI: Geriatric Nutritional Risk Index; PNI: Prognostic Nutritional Index.

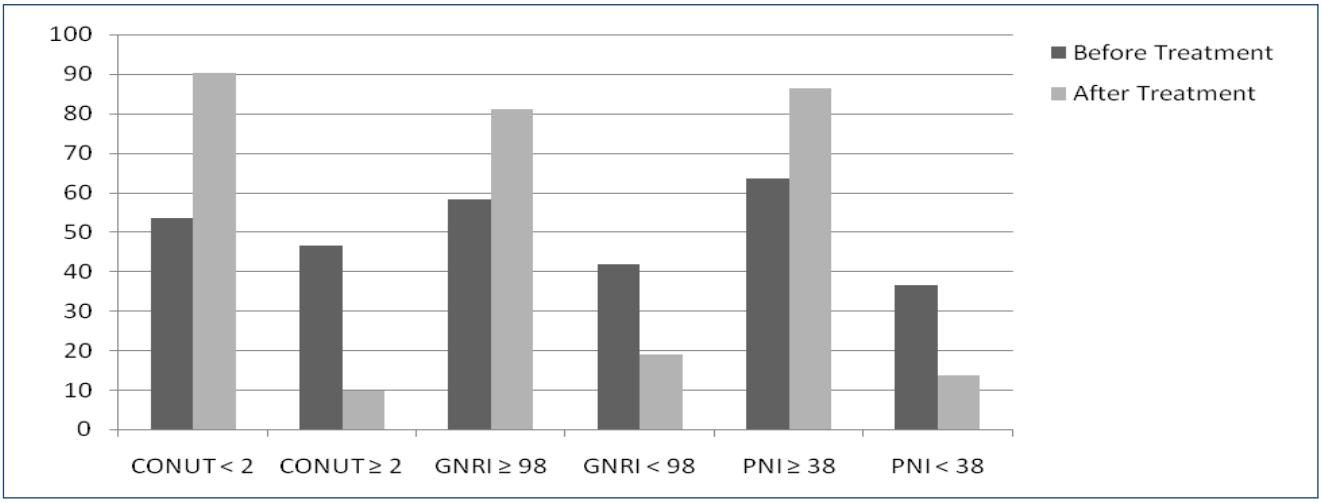


**Figure 1.** Changes in nutritional index scores of patients before and after sodium-glucose cotransporter-2 inhibitor treatment. CONUT: COntrolling NUTritional Status; GNRI: Geriatric Nutritional Risk Index; PNI: Prognostic Nutritional Index.

each other (CONUT vs. GNRI: r=-0.402, p<0.001; CONUT vs. PNI: r=-0.388, p<0.001; GNRI vs. PNI: r=0.672, p<0.001). It was determined that the same 31 (20.2%) patients were in the malnutrition group in three different nutritional index scoring systems (Table 2).

The functional assessment scores and parameters were found to be significantly correlated with the nutritional index scores: (1) MLWHFQ scores were positively correlated with CONUT score (r=0.302) and negatively correlated with GNRI (r=-0.364) and PNI (r=-0.392) scores (p: 0.004, <0.001, <0.001, respectively); (2) NT-pro-BNP levels were positively correlated with CONUT scores (r=0.320) and negatively correlated with GNRI (r=-0.339) and PNI (r=-0.388) scores (p: 0.001, <0.001, <0.001, respectively); (3) NYHA classification was positively correlated with the CONUT score (r=0.288) and negatively correlated with the GNRI (r=-0.310) and PNI (r=-0.354) scores (p: 0.007, 0.001, <0.001, respectively) (Table 2).

## DISCUSSION

To the best of our knowledge, this study is the first to show that SGLT-2 inhibitor treatment may be associated with the improvement of nutritional status in patients with HFrEF. SGLT-2 inhibitors are recommended in current guidelines as drugs that improve symptoms and quality of life in patients with HF who are symptomatic despite optimal medical treatment[1]. SGLT-2 inhibitors are a relatively new drug class, and new clinical studies are required to show additional benefits in patients with HF. We conducted this study based on the hypothesis that while SGLT-2 inhibitors provide symptomatic and functional improvement in patients with HFrEF, they also improve the nutritional status of the patients. There are not enough data in the literature to support our hypothesis. For this purpose, we examined the nutritional and functional statuses of patients with HFrEF receiving SGLT-2 inhibitor treatment and investigated the effects of SGLT-2 inhibitors on nutritional status.

In our study, it was observed that the index scores (CONUT, GNRI, and PNI) that we used for nutritional status assessment showed a significant change after SGLT-2 treatment and that the number of patients with malnutrition decreased significantly. In addition, the functional assessment scores and parameters were found to be significantly correlated with nutritional index scores. However, the mechanisms by which SGLT-2 inhibitors may improve nutritional status are not clear. SGLT-2 inhibitors can be thought to regress the congestion in the hepatic and splanchnic areas with their diuretic effects and thus reduce intestinal edema and malabsorption, which is one of the important causes of malnutrition in patients with HF[10-12]. In addition, some studies have shown that SGLT-2 inhibitors reduce the release of pro-inflammatory cytokines[13]. By this mechanism, SGLT-2 inhibitors can reduce anorexia and malnutrition caused by cytokines. Also, in this study, there was a significant increase in serum albumin levels, one of the parameters used in the calculation of nutritional index scores, after SGLT-2 treatment. It is already known as a result of extensive studies that SGLT-2 inhibitors reduce albuminuria and proteinuria[11,14]. In addition, a relative increase in serum albumin levels due to decreased venous volume as a result of the diuretic effect of SGLT-2 inhibitor treatment may also be considered.

After SGLT-2 inhibitor treatment, we observed improvement in the parameters that we used to evaluate the functional status and treatment response of patients with HFrEF. The MLWHFQ scores and NYHA class categories of patients changed significantly, and the NT-pro-BNP levels decreased significantly. Also, these parameters were significantly correlated with each other. Similarly, lower NT-pro-BNP levels were found after SGLT-2 inhibitor treatment in other studies involving patients with HF[15,16]. In some studies, improvement in exercise capacity, quality of life, and NYHA class were observed in patients with symptomatic HF after SGLT-2 inhibitor treatment[16,17]. SGLT-2 inhibitors increase urinary glucose excretion together with sodium excretion. Fluid excretion increases with osmotic diuresis and natriuresis. Thus, SGLT-2 inhibitors, like a diuretic drug, cause a decrease in extravascular and intravascular volume, resulting in a decrease in blood pressure and body weight. As a result of these mechanisms, they may contribute to functional and symptomatic improvements in patients with HFrEF.

## CONCLUSION

In patients with HFrEF who are symptomatic despite optimal medical treatment, the addition of an SGLT-2 inhibitor to treatment can significantly improve both nutritional status and functional capacity. SGLT-2 inhibitors were shown to provide significant improvement in malnutrition when patients with HFrEF are screened for malnutrition using three scoring systems (CONUT, GNRI, and PNI) and followed up after treatment. SGLT-2 inhibitors can assist symptomatic treatment of patients with HFrEF, improve malnutrition, prolong patient survival, and improve quality of life.

## AUTHORS' CONTRIBUTIONS

**KA**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **EY**: Conceptualization, Visualization, Data curation, Investigation, Methodology, Supervision, Validation. **EA**: Visualization, Data curation, Investigation, Writing – review & editing. All authors read and approved the final version of the manuscript.

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