CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST DOCTORAL SCHOOL FIELD OF MEDICINE

DOCTORAL THESIS SUMMARY

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CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST DOCTORAL SCHOOL FIELD OF MEDICINE

THE ROLE OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS AND GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION ASSOCIATED WITH TYPE 2 DIABETES

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Abbreviations

HFpEF - heart failure with preserved ejection fraction

HFrEF - heart failure with reduced ejection fraction

HFmEF - heart failure with mildly reduced ejection fraction

T2DM - type 2 diabetes mellitus

GLP1 RA - glucagon-like peptide 1 receptor agonist

SGLT2i - sodium-glucose cotransporter 2 inhibitor

NTproBNP - N-terminal pro b-type natriuretic peptide

LVEF - left ventricular ejection fraction

KCCQ - Kansas City Cardiomyopathy Questionnaire

GIP - glucose-dependent insulinotropic polypeptide

MACE - major adverse cardiovascular events

LA - left atrium

LV - left ventricle

MNA - Mini Nutritional Assessment

CRP - C-reactive protein

ESR - erythrocyte sedimentation rate

HbA1c - glycated hemoglobin

Introduction

Heart failure (HF) is a major global health issue and one of the leading causes of hospitalization among elderly adults, with a high risk of morbidity and mortality. A significant percentage of these patients suffer from type 2 diabetes mellitus, making them more vulnerable to complications and premature death, both during hospitalization and after discharge. The burden on healthcare systems due to HF hospitalizations is more pronounced in economically developed countries because of increased life expectancy through better cardiovascular disease management. In Europe, the incidence of HF is estimated at 5/1000 patients per year, though this is likely underestimated (1-2). Globally, there are 64 million patients with HF undergoing specific treatment. Prevalence varies by age: over 10% in those over 70 years and under 1% in those under 55 years (3-5).

HF is often underestimated and difficult to diagnose in primary care. From a database of 36,748 patients diagnosed with HF between 2010 and 2013, over 41% reported classic HF symptoms in primary care consultations five years before hospitalization, but no further investigations were conducted (6). HF is classified into three phenotypes based on left ventricular ejection fraction (LVEF): HF with preserved ejection fraction (HFpEF) - LVEF > 50%, HF with mildly reduced ejection fraction (HFmrEF) - LVEF 41-49%, and HF with reduced ejection fraction (HFrEF) - LVEF < 40% (7). This classification has facilitated the treatment of HF patients and has been used in randomized clinical trials with significant outcomes for HFrEF prognosis. HFpEF accounts for approximately half of HF cases and has an increasing prevalence. Obesity and HFpEF are often associated, with evidence suggesting that excess adipose tissue plays a role in the development of HFpEF. Obesity, frequently associated with type 2 diabetes mellitus, triggers common mechanisms contributing to HFpEF, including oxidative stress, renin-angiotensin-aldosterone system activation, and chronic inflammation (8-11). As of August 2023, treatment guidelines for HFpEF recommend the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i), which have been proven effective in improving patient prognosis (12). Additionally, glucagon-like peptide-1 receptor agonists, used in treating obesity associated with type 2 diabetes, may be effective in treating HFpEF due to the common mechanisms of these conditions. This study aims to compare treatments with SGLT2i and glucagon-like peptide-1 receptor agonists in patients with HFpEF and type 2 diabetes.

I.GENERAL PART

1. General Concepts of Heart Failure

1.1 Definition and Classification of Heart Failure

Heart failure is a complex clinical syndrome with structural and functional changes in the heart, manifested by dyspnea on exertion or at rest. Signs include crackles, jugular venous distension, and edema. The most commonly used for functional classification of heart failure is the NYHA class, although it has lower sensitivity compared to LVEF, NT-proBNP, KCCQ, and the 6-minute walk test (13).

1.2 The etiology of heart failure

The etiology of heart failure (HF) varies geographically: in developed countries, atherosclerotic coronary artery disease and arterial hypertension predominate, frequently seen in HF with reduced ejection fraction (HFrEF). Other causes include valvular heart diseases, genetic cardiomyopathies, arrhythmias, infections, infiltrative diseases (amyloidosis, neoplasia, sarcoidosis), cardiotoxicity, storage diseases (Fabry disease, hemochromatosis), pericarditis, and neuromuscular diseases.

1.3 Definition and diagnosis of HFpEF

The definition of HFpEF includes three elements: signs and symptoms of heart failure, LVEF above 50% on echocardiography, and structural and/or functional changes indicating left ventricular diastolic dysfunction/high filling pressures, including elevated NT-proBNP. Diagnosis is challenging because symptoms overlap with other pathologies. HFA-PEFF and H2FPEF scores are proposed for diagnosis but are not recommended in clinical practice due to cost and complexity (14).

1.4 Physiopathogical mechanisms encountered in HFpEF

The heterogeneity of physiopathological mechanisms in HFpEF limits the available therapeutic options. Diastolic dysfunction is a common factor, alongside subclinical systolic dysfunction, increased arterial stiffness, endothelial dysfunction, and other predisposing

factors. Diastolic dysfunction raises pressures in the left ventricle, atrium, and pulmonary capillaries, leading to pulmonary congestion. Diagnosis involves imaging with ultrasound and biomarkers such as NT-proBNP (15, 16).

2.Drug therapy in HFpEF: current horizons

2.1 Congestion therapy in HFpEF

As of August 2023, there were no definitive recommendations regarding drug therapy for HFpEF. Clinical studies have yielded neutral results, with loop diuretics being recommended for symptom relief.

2.2 Sodium-glucose contransporter 2 inhibitor in HFpEF

2.2.1 Mechanismis of action of the sodium-glucose contransporter 2 inhibitor

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are oral agents used in the treatment of type 2 diabetes mellitus. They block SGLT2 channels in the kidneys, preventing the reabsorption of glucose and thus reducing blood glucose levels without the risk of hypoglycemia. SGLT2 inhibitors reduce the reabsorption of glucose and electrolytes, thereby decreasing glomerular hyperfiltration and renal stress. They induce hormonal adaptations, decrease plasma insulin, increase glucagon, and stimulate hepatic gluconeogenesis. Therapy with SGLT2 inhibitors leads to weight loss, shifts the energy substrate from carbohydrates to lipids, and improves cardiac and renal performance. Additionally, they improve renal oxygenation, stimulate erythropoiesis, and reduce systemic inflammation, providing significant cardiorenal benefits (17-19).

2.2.2 The evidence of sodium-glucose cotransporter 2 inhibitor treatment in HFpEF

Currently, two SGLT2 inhibitors, empagliflozin and dapagliflozin, are available for use. Randomized clinical trials have demonstrated their efficacy in reducing cardiovascular deaths and hospitalizations due to heart failure (HF). In the EMPEROR-Preserved study, empagliflozin reduced hospitalizations and severity of HF episodes. Dapagliflozin, in the DELIVER study, showed similar benefits. Both molecules have improved patients' quality of life and positively influenced clinical outcomes, prompting changes in therapeutic recommendations for patients with HFpEF (20-21).

2.3 Glucagon-like peptide 1 receptor agonist in HFpEF

2.3.1 Mechanisms of action of the glucagon-like peptide 1 receptor agonist

The GLP-1 receptor agonist acts similarly to the incretin hormone GLP-1, stimulating insulin biosynthesis and release, suppressing glucagon, and delaying gastric emptying (22). It improves glycemic metabolism and satiety, with receptors located in the pancreas, gastrointestinal tract, cardiac muscle, liver, central and peripheral nervous systems. In type 2 diabetes, it aids in pancreatic β-cell function, reducing apoptosis and increasing pancreatic microRNA expression, thereby delaying age-related decline (23-25). The GLP-1 receptor agonist has a significant impact on obesity, characterized by excessive accumulation of adipose tissue. Adipose deposits, responsible for rapid energy mobilization and heat production, contribute to oxidative stress and inflammation. Central obesity leads to peripheral insulin resistance and other cardiovascular complications (26). GLP-1 receptor agonists interfere with the sympathetic nervous system, increasing glycemic and fatty acid metabolism (27-28). They reduce inflammation and provide cardiovascular protection, nephroprotection, and benefits on cardiac function and remodeling. Clinical studies confirm a reduction in renal and cardiovascular events in diabetic patients (29-30).

2.3.2 Current evidence of GLP-1 receptor agonist treatment in HFpEF

Patients with heart failure with preserved ejection fraction (HFpEF) often present with obesity and type 2 diabetes mellitus (T2DM), conditions that worsen prognosis and increase mortality risk by up to 50%. Treatment with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) has proven effective in T2DM and obesity, but results regarding efficacy in HFpEF have been conflicting. The STEP HFpEF study, conducted over 52 weeks with 529 patients, showed that semaglutide improved functional status and quality of life in patients, also reducing body weight (31). Similarly, the STEP HFpEF DM study demonstrated similar benefits in patients with T2DM, with significant improvements in the 6-minute walk test and reduced hospitalizations for decompensation (32). In conclusion, GLP-1 RAs represent a promising option for treating HFpEF associated with obesity and T2DM, with encouraging results in symptom improvement and reduction of adverse cardiac events.

II. SPECIAL PART

3. Working hypotheses and general objectives

HFpEF represents approximately 50% of all heart failure cases, often associated with obesity, sharing common pathophysiological mechanisms, with an increasing incidence predominantly in the diabetic population (33). The presence of type 2 diabetes mellitus (T2DM) alone in patients with HFpEF and obesity increases the risk of mortality by 30-50% (34). Until August 2023, there were no definitive recommendations regarding therapy for HFpEF with outcomes on major adverse cardiovascular events (MACE). Subsequently, there has been a focus on the heart failure guideline with the introduction of SGLT2 inhibitor therapy in HFpEF as a Class I indication, Level of Evidence A. It is essential to note that this work was conducted from January 2023 to May 2024, initiated prior to the publication of the heart failure guideline supplement in August 2023.

GLP-1 receptor agonist (GLP-1 RA) medication represents a new drug class currently available in the arsenal of therapies for T2DM and obesity, with increasing and encouraging results in treating both comorbidities. Considering the common pathophysiology between these conditions, this work aims to explore the possibility that GLP-1 RAs may represent another promising treatment for patients with HFpEF and T2DM. Another option explored as therapy for HFpEF with T2DM is SGLT2 inhibitors, for which there is a pursuit to supplement the current level of evidence.

The main objectives pursued in this work are:

- Supplementing evidence supporting the use of SGLT2 inhibitors as therapy in HFpEF with type 2 diabetes;
- Establishing the efficacy of a potential new treatment option (GLP-1 receptor agonist) in HFpEF therapy with type 2 diabetes on improving quality of life, weight loss, and ameliorating structural/functional changes in the left ventricle accompanying heart failure in HFpEF with type 2 diabetes;
- Monitoring the treatment outcomes of SGLT2 inhibitors vs GLP-1 receptor agonists in HFpEF patients with type 2 diabetes.

4. General methodology of the research

In a single-center prospective and observational study, we included patients with type 2 diabetes mellitus and heart failure with preserved ejection fraction (HFpEF) at a clinical hospital from January 2023 to May 2024. Approved by the Ethics Committee of "Nicolae Malaxa" Clinical Hospital, the study aimed to evaluate the therapies of SGLT2 inhibitors versus GLP-1 receptor agonists on quality of life, metabolic profile, and other parameters. Two study visits were conducted at six-month intervals, clinically, echocardiographically, and biologically evaluating patients according to predefined criteria.

4.1 Anthropometric assessment

During both study visits, anthropometric measurements were performed for weight, height, BMI, BSA, arm circumference, and calf circumference according to WHO standards for assessing obesity and overweight in the investigated patients. Measurements were conducted following specific protocols, including before and after decongestive diuretic therapy.

4.2 Clinical objective assessmen

During the clinical assessment, signs of heart failure were recorded, including classification into NYHA functional class, current medication, medical history, and cardiovascular risk factors. The medical history included monitoring of atherosclerotic diseases and associated chronic conditions, including chronic kidney disease. Blood pressure was measured at the end of the examination using a calibrated manual sphygmomanometer.

4.3 Biological sampling

At "Nicolae Malaxa" Clinical Hospital, analyses were conducted on patients after a 12-hour fasting period, including complete blood count, blood glucose, glycated hemoglobin, lipid profile, renal function, liver enzymes, and NT-proBNP for differential diagnosis of dyspnea. NT-proBNP was rapidly interpreted using the Pathfast analyzer, known for its high specificity in diagnosing cardiac-origin dyspnea. Analyses were collected at both study visits, and normal values and units of measurement can be found in appendix 3.

4.4 Cardiac ultrasound evaluation

In the study, to meet eligibility criteria, transthoracic echocardiography was performed to exclude severe valvular diseases and difficulties in obtaining images. The images were recorded and analyzed online, obtained at the end of expiration for optimal clarity. Evaluation was conducted using a specific machine, and classic structural parameters were recorded, including chamber dimensions and ventricular wall thickness. The Simpson method was used to calculate the left ventricular ejection fraction. Additionally, valve function was assessed along with parameters of diastolic and systolic cardiac function, including the RV-RA gradient and systolic pulmonary artery pressure.

4.5 Quality of life assessment

In the study, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess the quality of life and symptomatic status of congestive heart failure (CHF) patients. Originally consisting of 23 questions, this instrument was adapted to 12 questions to simplify its use in research (36). It has been found that the KCCQ score closely correlates with symptom severity and prognosis, playing an important role in patient monitoring. Additionally, the Mini Nutritional Assessment (MNA) test was administered to evaluate the nutritional status of patients, which is essential for their proper management (37).

4.6 Additional tests: electrocardiogram

In the study, an electrocardiogram was performed at each visit, including patients with consistent sinus rhythm. The included patients had early stages of heart failure with preserved ejection fraction (HFpEF), which had been minimally investigated previously. The development of atrial fibrillation could indicate a more advanced progression of the disease.

4.7 Patient eligibility and establishing the diagnosis of HFpEF

The diagnosis of HFpEF involved patients with symptoms of heart failure in the last three months, requiring intravenous diuretic therapy, and classified as NYHA Class I-IV. Criteria included an ejection fraction above 40%, left ventricular hypertrophy, and/or left atrial dilation.

5. The role of sodium-glucose cotransporter 2 inhibitors in patients with HFpEF and type 2 diabetes

5.1 Working hypothesis and specific objectives

ICFEP is a common form of heart failure, characterized by various pathophysiological mechanisms and often associated with obesity and type 2 diabetes. Therapy with SGLT2 inhibitors, initially intended for type 2 diabetes, has shown significant benefits in preventing cardiovascular complications and rehospitalizations for decompensated heart failure in patients with ICFEP. This study proposes investigating this therapy to improve the quality of life and metabolic profile of patients in two study visits over a period of six months.

5.2 Materials and methods

In the study, 37 patients with HFpEF were included, hospitalized in the Diabetes and Nutrition Department of Nicolae Malaxa Clinical Hospital due to metabolic imbalance upon admission. Evaluation included clinical, biological measures (including NTproBNP), ECG, and cardiac ultrasound at two visits: at baseline and after six months of iSGLT2 therapy. Analyses and tests were performed under standardized conditions, and patients with atrial fibrillation were excluded from the analysis.

5.2.1 Statistics

The initial data in Excel format was transferred to the statistical analysis software SPSS (version 29, SPSS Inc, IBM). Continuous variables were analyzed for mean ± standard deviation, and categorical variables for percentages or frequencies. The analysis included ultrasound measurements, biological values, questionnaire results, and grip strength test results, using tests such as Student's t-test, paired t-test, chi-square test, or ANOVA, with a p-value < 0.05 considered statistically significant.

5.3 Results

5.3.1 Demographic characteristics

In the study, 37 patients were treated with sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), with a balanced distribution between sexes (54% females, 46% males). The majority had obesity (73%), with an average initial BMI of 33.57 kg/m² and body surface area of 1.97 m². The mean age at inclusion was 64.3 years, and the average duration of diabetes was 12 years. Smoking was a risk factor in 24.3% of cases, and 97.3% suffered from dyslipidemia. SGLT2 therapy significantly reduced systolic blood pressure and weight, with a mean reduction in BMI and arm circumference. The study confirmed the benefits of this treatment in managing cardiovascular risk and indicated the need for further research on a larger sample.

5.3.2 Comorbidities associated in the study population

The study highlights the close link between diabetes mellitus and atherosclerotic cardiovascular diseases, including diabetic nephropathy (38-39). The average duration of diabetes in the study group was 12 years, and therapies with SGLT2 inhibitors have shown benefits in preserving renal function and glomerular filtration. Patients were assessed for stages of chronic kidney disease using the CKD-EPI 2021 formula. The presence of advanced chronic kidney disease may exacerbate diastolic dysfunction and contribute to decompensation of heart failure with preserved ejection fraction.

5.3.3 Cardiovascular therapy in the study population at the initial visi

Patients in the study received personalized therapies, including beta-blockers in 83.8% of cases, with bisoprolol, metoprolol, and carvedilol at varying doses. ACE inhibitors and sartans were present in 59.5% and 40.5% of cases, respectively. Platelet antiaggregants such as aspirin and clopidogrel were administered in 73% and 13.5% of the study cohort, respectively. Statins were used by all participants, with other lipid-lowering treatments including ezetimibe and PCSK9 inhibitors. The majority of patients received amlodipine and antianginal therapies, while diuretics were prescribed to all.

5.3.4 The anti-diabetic therapy associated with the study population

In the study, SGLT2 inhibitors were added to the existing antidiabetic therapy. The majority of patients (64.9%) were using basal insulin combined with OADs (oral antidiabetic drugs), while 24.9% were using rapid insulin. Oral antidiabetic therapy included metformin (70.3%) and gliclazide (2.7%), while the rest (27%) were not on oral antidiabetic medication.

5.3.5 Initiation of iSGLT2 therapy

The therapy with iSGLT2 (empagliflozin or dapagliflozin) was initiated within the first 7 days of hospitalization for metabolic decompensation. The standard dose was 10 mg for both medications. Non-compliance led to exclusion from the study. In total, 65% of patients received empagliflozin and 35% dapagliflozin in the studied cohort.

5.3.6 The biological characteristics of the study population

In the current study, participants had biological samples collected at both visits, including hemoglobin and hematocrit. Anemia was an exclusion criterion. There were no significant differences in hemoglobin and hematocrit between visits, possibly due to the small sample size. Uric acid significantly decreased between visits, with no changes in antiuricemic treatment between study visits. Inflammatory parameters (CRP, ESR, fibrinogen) showed significant improvements, reducing cardiovascular risk. Blood glucose and HbA1c decreased significantly, indicating the effectiveness of the new therapy. NTproBNP significantly decreased, reflecting improvement in cardiovascular status.

5.3.7 The ultrasound characteristics of the study population

In the current study, multiple aspects of cardiac function were evaluated in patients treated with iSGLT2 inhibitors. Significant improvement in systolic function was observed, with a mean increase in EF and a reduction in E/A and E/E' ratios, indicating improved diastolic function. iSGLT2 therapy demonstrated efficacy in optimizing hemodynamics and reducing the risk of cardiovascular complications. These findings suggest that iSGLT2 inhibitors may play a crucial role in managing patients with heart failure and type 2 diabetes mellitus.

5.3.8 Quality of life and functional status in the study population

The NYHA class is the most frequently used tool to assess mortality in HF patients: in the study cohort, participants with early stages of HFpEF were 43% in NYHA class II and only 19% in class III. At follow-up, 16% remained in class II NYHA, and no patients were in class III (notably, NYHA class improvement was not a primary objective in this study). Discrepancies between NYHA class and the KCCQ questionnaire have been noted in multiple studies, with the latter significantly associated with subsequent mortality over 4 years (40). The study utilized the 12-item KCCQ questionnaire, validated and translated into over 100 languages including Romanian (41,42). At baseline, the mean KCCQ score was 48.5 ± 26.7 points SD, indicating significantly impaired quality of life due to HF. To assess muscular blood flow and endothelium-dependent vasodilation during dynamic handgrip exercise in peripheral vessels, patients with HF underwent a handgrip test, yielding a mean score of 20.7 ± 10.3 points SD at the initial visit.

5.4 Discussions

Improvement in LVEF was observed by 2.59 ± 2.42 SD (95% confidence interval [CI], 1.7-3.4, $p < 0.001$) between study visits, with no significant difference in stroke volume. Improvement in diastolic profile included an E/A ratio change of 0.06 ± 0.11 SD (95% CI, 0.02-0.09, $p < 0.003$), an E/E' ratio change of 2.9 ± 2.1 SD (95% CI, 2.2-3.6, $p < 0.001$), and no statistically significant impact on E wave deceleration time. Improvement in diastolic dysfunction was also documented in a randomized, double-blind study of 74 type 2 diabetes patients followed for 2 years, with a statistically significant E/E' ratio difference of $p < 0.011$ (43). Functional and symptomatic status improved with an average KCCQ score improvement of 13.6 ± 7.8 SD (95% CI, 11-16.2, $p < 0.01$). Furthermore, handgrip strength improved by 5.1 ± 3.1 SD (95% CI, 4-6.2, $p < 0.01$).

The current study monitored weight loss outcomes: significant reductions were achieved in weight (mean reduction of 1.3 ± 2.4 SD kg, 95% CI 0.5-2.2, $p = 0.002$), BMI (mean reduction of 0.37 ± 1 SD kg/m², 95% CI 0.04-0.07, $p = 0.029$), and arm circumference (mean reduction of 0.28 ± 0.67 SD cm, 95% CI 0.05-0.5, $p = 0.015$). No statistically significant results were

found for calf circumference. Significant weight reduction outcomes were similarly noted in other studies, correlating with the time interval between visits (44). There was no significant difference in MNA results between visits.

A decrease in systolic blood pressure was noted by 8.7 ± 12.8 SD mmHg (95% CI 4.6-12.8, p = 0.001), with no significant differences in diastolic blood pressure or ventricular width.

5.5 Conclusion

The current study revealed improvement in symptoms, quality of life, diastolic dysfunction, LVEF, inflammatory markers, and weight loss in patients with type 2 diabetes and heart failure with preserved ejection fraction treated with sodium-glucose co-transporter 2 inhibitors, demonstrating efficacy across the cardio-reno-metabolic continuum.Study limitations include a small participant sample size, but the results recommend expansion to a larger cohort for statistical significance. A second limitation is related to the interval between study visits, which could be extended in future research.

6. Role of treatment with glucagon-like peptide-1 receptor agonist in patients with HFpEF and type 2 diabetes

6.1 Working hypothesis and specific objectives

In 2023, approximately 64 million people were diagnosed with heart failure (HF) and required specific treatment, with a significant percentage also having type 2 diabetes mellitus. Heart failure with preserved ejection fraction (HFpEF) is becoming increasingly common, primarily associated with elderly and obese patients, often with multiple comorbidities . In the treatment of HFpEF, the GLP-1 receptor agonist has demonstrated efficacy in glycemic control and weight reduction, but significant improvements in patient prognosis have not been observed (45). This study investigates the potential of GLP-1 receptor agonists in improving quality of life and structural and functional heart parameters in HFpEF, based on clinical, biological, and echocardiographic evaluations in two distinct visits.

6.2 Materials and methods

Twenty-eight patients diagnosed with HFpEF were enrolled, selected from those hospitalized in the Diabetes and Nutrition Department of Nicolae Malaxa Clinical Hospital due to metabolic imbalance upon admission. Inclusion and exclusion criteria were detailed in Chapter 4. Patients underwent clinical evaluation, including anthropometric measurements, biological assessments including NTproBNP, ECG, and standard and tissue Doppler echocardiography at two visits: at the initiation of iSGLT2 therapy and after six months of treatment, following a design similar to the previous study.

6.2.1 Statistics

The same software and methods as in the previous study were used.

6.3 Results

6.3.1 Demographic characteristics

In the study, 28 patients treated with GLP-1 receptor agonist were included, with a balanced distribution between female and male genders. Participants had a mean age of 61.4 years and the majority were obese (93%). Detailed anthropometric evaluations were conducted, including measurements of BMI, weight, height, and arm and leg circumferences. GLP-1 receptor agonist therapy demonstrated significant reductions in blood pressure, body weight, BMI, and arm and leg circumferences, as well as improvement in MNA score. Most patients also had comorbidities such as dyslipidemia and a history of cardiovascular diseases in varying percentages.

6.3.2 Associated comorbidities in the study population

Cardiovascular diseases, heart failure, and renal insufficiency are the most commonly associated comorbidities in diabetic patients. GLP-1 receptor agonists are the treatment of choice in patients with uncontrolled metabolic risk and chronic kidney disease (46). The presence of obesity is strongly correlated with the risk, progression, and evolution towards end-stage atherosclerotic kidney disease, findings that persist even after adjusting for age, sex, race, and comorbidities (47). One of the mechanisms considered essential for these renal outcomes is believed to be linked to the effect of GLP-1 receptor agonists on weight control and obesity, thereby reducing the progression of chronic kidney disease.

6.3.3 Cardiovascular-focused therapy in the study population at the initial visit

In the mentioned study, patients were treated individually according to comorbidities, including beta-blockers in 71% of cases and angiotensin-converting enzyme inhibitors in 68%. Hypolipidemic therapy mostly consisted of statins (60% atorvastatin, 40% rosuvastatin). Antiplatelet therapy was administered in 42% of cases with acetylsalicylic acid. In the STEP HFpEF DM study, 83% of participants received beta-blockers, and in STEP HFpEF, beta-blockers were given in 76% of cases. Renin-angiotensin-aldosterone system blockers were used in 80% and 79% of cases, respectively, in these two mentioned studies.

6.3.4 Antidiabetic therapy associated in the study population

The addition of GLP1 RA treatment was implemented on top of the existing baseline antidiabetic therapy. In the current study, 96% of patients were also on prandial insulin therapy, and only 60% were on basal insulin therapy. Regarding oral antidiabetic treatment, it was present in 89% of the studied group (with 40% having a combined ADO-insulin therapy).

6.3.5 Initiation of GLP-1 receptor agonist therapy

In the study, GLP-1 receptor agonist therapy (semaglutide, dulaglutide, or liraglutide) was initiated within the first 7 days of hospitalization for metabolic decompensation in patients with type 2 diabetes. Dosages varied depending on the formulation (oral or subcutaneous). Non-compliance led to exclusion from the study.

6.3.6 Biological characteristics of the study population

The biological sample collection in the study included hemoglobin and hematocrit, excluding patients with moderate to severe anemia. The mean initial values for hemoglobin and hematocrit were 13 ± 1.3 g/dL and 42.8 ± 6%, respectively. Creatinine and uric acid were analyzed for renal profile, revealing a significant decrease in uric acid between visits (0.73 ± 0.68 SD, $p<0.001$). No significant changes were recorded in hemoglobin, hematocrit, or creatinine values between study visits. The lipid profile showed significant improvement in total cholesterol, LDL, and triglycerides, with no significant changes in HDL. Inflammation was reduced with GLP-1 receptor agonist therapy, demonstrating potential benefits in cardiovascular diseases and glycemic control. Reduction in NT-proBNP indicated improved prognosis for heart failure.

6.3.7 Ultrasound characteristics of the study population

In the study, systolic and diastolic function were evaluated in patients with heart failure (HF), using LVEF and other echocardiographic parameters. A significant improvement in LVEF between visits was observed, but without significant changes in stroke volume. For diastolic function, significant improvements were recorded in the E/A ratio, E wave deceleration time,

and E/E' ratio. Initially measured cardiac structures included LVIDd and IVSd, with no significant changes during the study, although an improvement in left atrial volume was observed.

6.3.8 Quality of life and functional status in the study population

In the study, the majority of participants had early stages of HFpEF, with 64% in NYHA class II initially and only 7% in class III. Significant improvements were observed in quality of life (KCCQ) and handgrip strength test between the two study visits.

6.4 Discussions

The presented study evaluated the effects of GLP-1 receptor agonists on key parameters in patients with heart failure with preserved ejection fraction (HFpEF) and obesity. The study included patients with a mean age of 61.4 years, predominantly female, with a mean body mass index (BMI) of 37.6 kg/m². Results showed significant improvements across various domains: cardiac ultrasound parameters, quality of life, inflammatory profile, NT-proBNP, glycemic metabolism, and weight status between study visits.

Regarding cardiac systolic and diastolic function, an improvement in left ventricular ejection fraction (LVEF) was observed, while stroke volume did not show significant changes. Additionally, improvements in diastolic function were noted, reflected in improvements in the E/A ratio, E wave deceleration time, and E/E' ratio. These results are consistent with previous studies that have highlighted the benefits of GLP-1 receptor agonists on diastolic dysfunction and ventricular stiffness. Moreover, GLP-1 receptor agonist administration led to a significant decrease in NT-proBNP, indicating reduced myocardial wall stress and improved clinical status of patients. Concurrently, significant reductions were observed in inflammatory markers such as C-reactive protein, fibrinogen, and erythrocyte sedimentation rate, suggesting a positive effect on systemic inflammation.

In addition to the benefits on cardiac function and inflammation, GLP-1 receptor agonists demonstrated efficacy in glycemic control and reduction of lipid parameters, including total cholesterol, LDL, and triglycerides. Furthermore, patients showed significant reductions

in body weight, BMI, and arm and leg circumference, associated with a corresponding improvement in nutritional status as per the MNA score.

In conclusion, GLP-1 receptor agonists represent a promising therapy for patients with HFpEF and obesity, offering significant benefits across multiple clinical and biological domains in a population often burdened with complex comorbidities.

6.5 Conclusions

In the presented study, the use of GLP-1 receptor agonists led to significant improvements in echocardiographic parameters, functional and symptomatic status in heart failure (HF), as well as in glycemic, lipid, and inflammatory profiles. However, the results are partially consistent with existing literature. Key studies that have raised questions regarding the efficacy and safety of GLP-1 receptor agonists in HF predominantly included populations with HF with reduced ejection fraction (HFrEF), different from HF with preserved ejection fraction (HFpEF) often associated with obesity. The main limitation is the small sample size, but promising results suggest further research on larger patient groups.

7. Role of treatment with glucagon-like peptide-1 receptor agonist versus sodium-glucose cotransporter 2 inhibitor in patients with HFpEF and type 2 diabetes

7.1 Working hypothesis and specific objectives

HFpEF is common in obese patients because they share underlying mechanisms including: altered cardiac filling (modified in obese individuals), increased plasma volume, elevated filling pressures, sympathetic nervous system activation, cardio-renal interactions, lipid and adipose cell accumulation. Crucial is the inflammatory cascade which leads to microvascular dysfunction, endothelial dysfunction, atrial fibrosis, hypertension, diabetes mellitus, chronic kidney disease and, most importantly, HFpEF (48).

Starting in 2023, according to the focus on the heart failure guideline, treatment with iSGLT2 in HFpEF is recommended (49). Obesity is often associated with type 2 diabetes, both conditions being involved in the development of HFpEF. Another class of medication, GLP1-RAs, initially developed as a therapy for type 2 diabetes, has proven benefits in weight reduction and glycemic control.

In this study, the objective is to monitor the treatment outcomes of iSGLT2 versus GLP1-RAs in HFpEF in patients with type 2 diabetes, aiming to explore the use of other new therapeutic classes in this condition - HFpEF (50).

7.2 Material and method

Were enrolled 37 patients in the iSGLT2 treatment group and 28 in the GLP1 receptor agonist (AR GLP1) treatment group, selected from patients hospitalized in the Diabetes and Nutrition Diseases Department of Nicolae Malaxa Clinical Hospital for therapeutic regimen adjustment, all presenting metabolic imbalance upon admission. Patients were clinically evaluated with anthropometric measurements, biological assessments including NT-proBNP, ECG, and standard transthoracic echocardiography and tissue Doppler at two

visits: at initiation of iSGLT2 therapy and after six months of treatment, following a study design similar to previous ones.

7.2.1 Statistics

The same software and methods were used as in the studies presented previously.

7.3 Results

7.3.1 Demographic characteristics

In the study, 65 patients were included, comprising 54% women and 46% men. The iSGLT2 treatment group consisted of 37 patients (20 women, 17 men), and the AR GLP1 treatment group consisted of 28 patients (15 women, 13 men), with no significant differences between the groups.The average age was 64.3 ± 7.2 years in the iSGLT2 group and 61.4 ± 9.9 years in the AR GLP1 group ($p = 0.14$). Obesity was present in 93% of the AR GLP1 group and 73% of the iSGLT2 group, with a mean BMI of 33.5 ± 5.9 kg/m² in the iSGLT2 group and 37.6 ± 5.7 kg/m² in the AR GLP1 group. The average height was 165 ± 10 cm in the iSGLT2 group and 164 ± 9.8 cm in the AR GLP1 group, while the average weight was 92 ± 19 kg in the iSGLT2 group and 102 ± 15 kg in the AR GLP1 group. The mean duration of diabetes was 8.3 ± 3.8 years in the AR GLP1 group and 12 ± 11.6 years in the iSGLT2 group. The average systolic blood pressure was 140 ± 18 mmHg in the iSGLT2 group and 138 ± 16 mmHg in the AR GLP1 group, and the diastolic blood pressure was 79.3 ± 10 mmHg in the iSGLT2 group and 82.6 ± 10 mmHg in the AR GLP1 group. The average heart rate was 72 ± 9.9 beats/min in the iSGLT2 group and 75 ± 9.5 beats/min in the AR GLP1 group, with no statistically significant differences.Medical history showed that in the AR GLP1 group, 14% had a history of myocardial infarction, 4% of revascularized peripheral arterial disease, and 7.1% of ischemic stroke, while in the iSGLT2 group, 19% had a history of myocardial infarction, 5.4% of revascularized peripheral arterial disease, and 13.5% of ischemic stroke. The most common comorbidities were hypertension and chronic kidney disease. Patients in the AR GLP1 group had higher weight indices and circumference, with AR GLP1 known for its effectiveness in weight reduction compared to other antidiabetic therapies.

7.3.2 Associated antidiabetic therapy

Treatment with iSGLT2 or AR GLP1 was added to the previous antidiabetic therapy, following the detection of glycemic imbalance that led to the hospitalization of patients. A total of 80% (52 participants) of the study cohort were on associated therapy with oral antidiabetic drugs, exclusively represented by metformin. Fifty-four percent were receiving basal insulin therapy, and 15% were on prandial insulin therapy.

7.3.3 Cardiovascular-targeted therapy associated

In the study, patients were on therapy with: beta-blockers (80%), angiotensin-converting enzyme inhibitors (63%, perindopril), angiotensin II receptor blockers (24.6%), and sacubitril/valsartan (1.5%). Hypolipidemic therapy included statins (98.5%), ezetimibe (28%), and PCSK9 inhibitors (1.5%). Calcium channel blockers were used by 72%, while antiplatelet therapy with aspirin was administered to 60% and P2Y12 inhibitors to 8%.

7.3.4 GLP-1 receptor agonist and iSGLT2 inhibitor therapy in the study cohorts

The treatment with GLP-1 receptor agonists or SGLT2 inhibitors was added to achieve glycemic control based on the patients' characteristics by the attending diabetologist. In the group treated with SGLT2 inhibitors, 65% were on empagliflozin and 35% on dapagliflozin.

7.3.5 Biological characteristics of the study population

The patients in the study had analyses conducted at both visits. The average hemoglobin was 13.3 ± 1.3 g/dl in the iSGLT2 group and 13 ± 1.3 g/dl in the AR GLP1 group. The average hematocrit was identical at 42.8 ± 3.7% and 42.8 ± 3.6%. The average creatinine was 0.9 ± 0.3 mg/dl and 0.9 ± 1.6 mg/dl, without significant differences. The average uric acid was 5.8 ± 1.4 mg/dl and 5.4 ± 1.6 mg/dl. HDL cholesterol and triglycerides were lower in the AR GLP1 group. CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), and fibrinogen showed no significant differences. NT-proBNP had mean values of 189 ± 272 pg/ml in the iSGLT2 group and 69 ± 43 pg/ml in the AR GLP1 group, without significant differences. There were no significant differences in carbohydrate metabolism between the groups.

7.3.6 Ultrasound characteristics of the study population

The average LVEF (Left Ventricular Ejection Fraction) was 60.5 ± 7.5% in the iSGLT2 group and 60 ± 6.5% in the AR GLP1 group. The average stroke volume was 43.8 ± 8.9 ml in the AR GLP1 group and 44.6 ± 12.4 ml in the iSGLT2 group. The E/A ratio was 0.7 ± 0.1 in the AR GLP1 group and 0.6 ± 0.1 in the iSGLT2 group. The E/E' ratio was significantly higher in the AR GLP1 group ($p = 0.003$), indicating higher ventricular filling velocities.

7.3.7 Quality of life and functional status in the studt population

In the study cohort, 53% of participants were in NYHA class II and 14% in NYHA class III initially. At follow-up, only 12.3% were in class II and none in class III. The initial mean KCCQ score was 61.6 in the AR GLP1 group and 48.7 in the iSGLT2 group, indicating a lower quality of life in the iSGLT2 group.

7.4 Discussion

In the present study, the effects of iSGLT2 and AR GLP1 on echocardiographic, biological parameters, and weight loss were evaluated. Regarding systolic function, an improvement in left ventricular ejection fraction (LVEF) was observed in both groups: 2.2 ±2.1 SD (AR GLP1) and 2.5 ±2.4 SD (iSGLT2), both statistically significant ($p<0.001$). There was no significant difference in stroke volume between groups. Previous studies indicate similar improvements in LVEF with AR GLP1 but not with iSGLT2 (51, 52). Diastolic profile showed significant improvements in E/A ratio in both groups: 0.05 ±0.08 SD (AR GLP1) and 0.06 ±0.1 SD (iSGLT2). Deceleration time of the E wave showed improvements only in the AR GLP1 group. E/E' ratio showed improvements in both groups, a finding supported by previous studies (54). There were no significant differences in left ventricular hypertrophy, but a reduction in left atrial dilation was noted in the AR GLP1 group. Biologically, there were no significant differences in hemoglobin or hematocrit levels. Likewise, no statistically significant differences were observed in creatinine levels in both patient groups. There is no evidence of reduction in albuminuria in the AR GLP1 class, which is a strong predictor of renal events such as glomerular filtration rate reduction (55). Conversely, data on renal protection conferred by iSGLT2 are abundant (56, 57, 58). The lack of improvement in renal function, specifically creatinine under

iSGLT2 in this study, should be viewed in the context of the short window between visits, with the mechanism of action of this therapy involving a temporary reduction in filtration rate, followed by recovery and long-term maintenance of effect. In terms of the inflammatory syndrome, an improvement in C-reactive protein was observed with a mean of 0.5 ±0.6 SD mg/dl (95% confidence interval [CI], 0.2-0.7, p=0.001) in the iSGLT2 group and 0.6 ±0.6 SD mg/dl (95% confidence interval [CI], 0.3-0.8, p=0.001) in the AR GLP1 group. Evidence of the anti-inflammatory effect of both therapeutic classes is well-documented in the literature (59, 60).

Another analysis where a significant reduction was obtained was NTproBNP with a mean of 76.2 ±124 SD pg/ml (95% confidence interval [CI], 33-119, p=0.001) in the iSGLT2 group and 26±18 SD pg/ml (95% confidence interval [CI], 18-33, p=0.001) in the AR GLP1 group. Regarding glycemic control, a statistically significant decrease was recorded with a mean of 71 ±52 SD mg/dl (95% confidence interval [CI], 50-91, p=0.001) in blood glucose and with 0.7±0.15 SD % (95% confidence interval [CI], 0.5-0.9, p=0.001) in glycosylated hemoglobin in the AR GLP1 group; with a mean of 43±47 SD mg/dl (95% confidence interval [CI], 28-59, p=0.001) in blood glucose and with 0.9±1 76.2 ±124 SD % (95% confidence interval [CI], 0.6-1.3, p=0.001) in glycosylated hemoglobin in the iSGLT2 group. Weight loss was significantly greater in the AR GLP1 group (5.5 ±2.8 kg) compared to the iSGLT2 group (1.3 ±2.4 kg). AR GLP1 demonstrated a significant reduction in arm and leg circumference, as well as an improvement in MNA score, reflecting dietary changes. In terms of symptomatic and functional status, the KCCQ score showed a significant improvement in both groups, with greater improvement in the AR GLP1 group. Functionally, both groups showed significant improvements in handgrip strength test.

8. Conclusions and personal contributions

In the present study, the impact of two classes of hypoglycemic medications on patients with type 2 diabetes and heart failure with preserved ejection fraction (HFpEF) associated with obesity was evaluated. The research focused on multiple clinical and biological aspects, including echocardiographic parameters, metabolic control, weight loss, achievement of lipid targets, inflammatory syndrome, and functional status. Regarding echocardiographic parameters, a significant improvement in left ventricular ejection fraction (LVEF) was observed in all three studies, without an increase in stroke volume, indicating improvement in filling pressures and diastolic relaxation. Diastolic profile, assessed by E/A and E/E' ratios, showed statistically significant improvement, reflecting the benefits of therapy on diastolic function and filling pressures. Glycemic control was effective in both treatment groups, with significant improvements in blood glucose and glycated hemoglobin (HbA1c), confirming the effectiveness of both therapeutic classes in managing type 2 diabetes. Weight loss was significant in the group treated with both medications, with more pronounced effects in the group treated with AR GLP1, which showed greater reductions in body weight, body mass index (BMI), and arm and leg circumference. Biologically, an improvement in lipid profile was observed in both groups, noting that additional therapeutic interventions were required in the iSGLT2-treated group to achieve recommended LDL targets, while AR GLP1 treatment did not require additional modifications in this regard. Regarding the inflammatory syndrome, inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and fibrinogen showed significantly lower values between the two study visits in all three groups. Functional and symptomatic status, evaluated by the KCCQ questionnaire and hand grip strength testing, showed significant improvements in both treatment groups, with better results observed in the AR GLP1 group in terms of KCCQ scores.

In conclusion, the use of both classes of hypoglycemic medications proved effective in improving multiple health aspects of patients with type 2 diabetes and obesity-associated HFpEF. These results support the initial hypothesis, providing new therapeutic options in the complex management of this pathology. In the future, expanding research to a larger number of patients and over a longer period is recommended to evaluate the long-term impact on cardiovascular prognosis.

List of published scientific papers::

1. **Lungeanu-Juravle, Laura** & Nica, Andra-Elena & Rusu, Emilia & Radulian, Gabriela. (2024). The Role of GLP 1 Receptor Agonists in Treating Heart Failure: Useful or Not?. Internal Medicine. 21. 39-47. 10.2478/inmed-2024-0276. https://sciendo.com/article/10.2478/inmed-2024-0276 Internal Medicine 20 4 vol. X I No. 1 - www.srmi.ro2 X/inmed-20 4-0 76.
2. **Lungeanu-Juravle, Laura** & Tache, Mirela & Radu, Ana & Dobjanschi, Carmen & Adamescu, Petrișor & Nica, Andra-Elena & Rusu, Emilia & Radulian, Gabriela. (2024). The role of sodium glucose cotransporter or glucagon-like peptide-1 receptor agonists in treating heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus. Romanian Journal of Medical Practice. 19. 13-20. 10.37897/RJMP.2024.1.2. RJMP_2024_1_Art-02.pdf Romanian JouRnal of medical PRactice – Volume 19, no. 1 (98), 2024.

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