Empagliflozin Improves Cognitive Impairment in Frail Older Adults With Type 2 Diabetes and Heart Failure With Preserved Ejection Fraction

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Diabetes Care 2022;45:1247–1251 | https://doi.org/10.2337/dc21-2434

OBJECTIVE

To assess whether the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin improves cognitive impairment in frail older adults with diabetes and heart failure with preserved ejection fraction (HFpEF).

RESEARCH DESIGN AND METHODS

We designed a prospective study to assess cognitive and physical function in consecutive frail older adults with diabetes and HFpEF, comparing the effects of empagliflozin, metformin, and insulin.

RESULTS

A total of 162 frail older adults with HFpEF and diabetes successfully completed the study. Montreal Cognitive Assessment scores at baseline and after 1 month were 19.80 ± 3.77 vs. 22.25 ± 3.27 ($P < 0.001$) in the empagliflozin group, 19.95 ± 3.81 vs. 20.71 ± 3.56 ($P = 0.26$) in the metformin group, and 19.00 ± 3.71 vs. 19.1 ± 3.56 ($P = 0.81$) in the insulin group. A multivariable regression analysis confirmed the beneficial effects of empagliflozin. Additionally, we observed a marked amelioration of physical impairment, assessed by the 5-m gait speed test, in the empagliflozin and metformin groups but not in the insulin group.

CONCLUSIONS

This study is the first to show significant beneficial effects of the SGLT2 inhibitor empagliflozin on cognitive and physical impairment in frail older adults with diabetes and HFpEF.

Heart failure (HF) with preserved ejection fraction (HFpEF) is common in older adults with type 2 diabetes (1–3), and elderly patients with HFpEF and diabetes have a high risk of frailty, with cognitive and physical impairment, depression, adverse outcomes, and overall reduced quality of life (3–6). Moreover, diabetes has been shown to have a negative impact on HFpEF, leading to a high risk of death and rehospitalization, but few data are available on the clinical management of these patients (5–8).

Empagliflozin is a selective sodium–glucose cotransporter 2 (SGLT2) inhibitor that has been shown to have beneficial effects in patients with diabetes and to

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Received 22 November 2021 and accepted 11 February 2022

Clinical trials reg. no. NCT04962841, clinicaltrials.gov

reduce mortality and rehospitalization for HF (9–11). Preclinical assays have also shown that empagliflozin can reduce vascular damage and cognitive impairment in a mixed murine model of diabetes and Alzheimer disease (12). However, empagliflozin's actual effects on cognitive function have never been tested, and we sought to investigate such effects in frail older adults with diabetes and HFpEF.

RESEARCH DESIGN AND METHODS

Study Design and Participants

We designed a prospective observational study to enroll consecutive frail older adults with a previous diagnosis of type 2 diabetes and HFpEF admitted from March 2021 to October 2021 at Sant'Angelo dei Lombardi Hospital, Azienda Sanitaria Locale Avellino. Inclusion criteria were age >65 years and confirmed diagnoses of diabetes, frailty, and HFpEF. Exclusion criteria were previous stroke and/or acute myocardial infarction, Montreal Cognitive Assessment (MoCA) score >26 (13), and antidiabetic therapy different from monotherapy with empagliflozin, metformin, or insulin. Patients were divided into three groups according to their antidiabetic treatment: empagliflozin, metformin, and insulin. Every patient or legally authorized representative signed a written informed consent. The study was performed in accordance with the ethical standards laid out in the 2013 Declaration of Helsinki of the World Medical Association and in accordance with Good Clinical Practice guidelines and was approved by the institutional review board of Campania Nord (Avellino, Italy).

Data Collection and Definitions

Global cognitive function was assessed at baseline and after 1 month using the MoCA test (14). MoCA scores range from 0 to 30; a score of ≥26 is considered normal.

A diagnosis of physical frailty was made with at least three of the following five previously published criteria (generally known as Fried criteria) (14,15): exhaustion (poor endurance and energy), slowness (walking speed less than the lowest quintile adjusted for sex and height), weight loss (defined as unintentional loss ≥4.5 kg in the past 12 months), low physical activity level (lowest quintile of kilocalories of physical activity during the previous 7 days), and weakness (handgrip strength in the lowest quintile at baseline, adjusted for sex and BMI). All patients participated in a 5-m gait speed (5mGS) test, carried out as previously described (16).

Statistical Analysis

Comparisons between subsets of patients were performed by using descriptive analyses. Differences for continuous variables were assessed via *t* test; the χ^2 test was used to measure associations between dichotomous and categorical variables. Multivariable logistic regression was applied using the improvement of MoCA score as the dependent variable, adding to the model potential confounders. Pearson correlation was used to measure the association between MoCA score and 5mGS. A significance level of 0.05 for two-sided comparisons was considered statistically significant. The minimum sample size had been calculated a priori using GPOWER software (α cutoff 5%, β cutoff 20%). All

Table 1—Baseline patient clinical characteristics

	Empagliflozin	Metformin	Insulin
No. of patients	52	56	54
Age (years)	80.6 ± 6.6	80.0 ± 6.3	81.4 ± 5.5
Female sex	29 (55.7)	33 (58.9)	32 (59.2)
BMI (kg/m^2)	27.6 ± 1.5	27.7 ± 1.6	28.1 ± 1.8
Systolic blood pressure (mmHg)	118.4 ± 7.1	119.4 ± 7.9	120.4 ± 8.3
Diastolic blood pressure (mmHg)	79.4 ± 7.1	79.2 ± 6.1	79.6 ± 6.7
Heart rate (beats/min)	87.8 ± 8.9	86.9 ± 9.1	86.9 ± 8.5
Ejection fraction (%)	56.2 ± 5.4	57.1 ± 5.7	55.8 ± 5.3
Comorbidities			
Hypertension	38 (73.0)	41 (74.0)	38 (71.0)
Dyslipidemia	32 (61.0)	35 (63.0)	34 (63.0)
Chronic obstructive pulmonary disease	20 (38.0)	20 (36.0)	21 (40.0)
Chronic kidney disease	17 (33.0)	17 (31.0)	18 (34.0)
Laboratory parameters			
Plasma glucose (mg/dL)	163.1 ± 39.8	167.7 ± 41.2	168.7 ± 40.1
Cholesterol (mg/dL)	207.3 ± 20.5	205.5 ± 19.9	205.7 ± 19.3
LDL cholesterol (mg/dL)	133.4 ± 19.5	132.2 ± 19.1	132.2 ± 16.9
HDL cholesterol (mg/dL)	36.5 ± 3.6	36.6 ± 3.4	36.1 ± 3.0
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
HbA_{1c} (%)	7.2 ± 0.7	7.1 ± 0.9	7.3 ± 0.6
Brain natriuretic peptide (pg/mL)	465.3 ± 23.6	463.4 ± 23.9	467.4 ± 24.5
Cognitive and physical evaluation			
MoCA score	19.8 ± 3.77	19.9 ± 3.81	19.0 ± 3.72
5mGS (m/s)	0.64 ± 0.07*	0.65 ± 0.08*	0.56 ± 0.09

Data are mean ± SD or *n* (%). *$P < 0.05$ vs. insulin group.

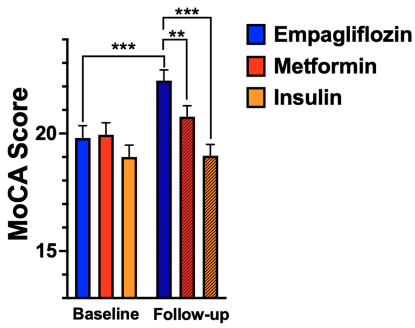

Figure 1—MoCA score in the empagliflozin, metformin, and insulin groups evaluated at baseline and follow-up. Data are means ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$.

analyses were performed using SPSS version 26 statistical software (IBM Corporation, Armonk, NY).

RESULTS

Baseline Patient Characteristics

We evaluated 201 frail elders with HFpEF and diabetes. Since 12 patients were unwilling to provide clinical information and 27 did not meet inclusion criteria, 162 patients were included in the study. Our population was divided into three groups on the basis of antidiabetic treatment: empagliflozin (52 patients), metformin (56 patients), and insulin (54 patients). Baseline characteristics of these patients are reported in Table 1. There were no significant differences among the groups at baseline, except for MoCA score and 5mGs when comparing the empagliflozin or metformin groups with the insulin group.

Beneficial Effects of Empagliflozin on Cognitive Impairment

The mean ± SD MoCA scores in the three groups at baseline and 1-month follow-up were 19.80 ± 3.77 vs. 22.25 ± 3.27 ($P < 0.001$) in the empagliflozin group, 19.95 ± 3.81 vs. 20.71 ± 3.56 ($P = 0.26$) in the metformin group, and 19.00 ± 3.71 vs. 19.1 ± 3.56 ($P = 0.81$) in the insulin group (Fig. 1). We then performed a multivariable logistic regression analysis using the improvement of MoCA score as the dependent variable, adding to the model potential confounders (Table 2), and confirmed the significant effect of empagliflozin treatment on the amelioration of cognitive impairment (odds ratio 3.609, 95% CI 1.566–8.321, $P = 0.03$).

Favorable Effects of Empagliflozin on Physical Impairment

We also observed a significant improvement in the 5mGS test in the empagliflozin and metformin groups but not in the insulin group (Fig. 2). Of note, while we had observed a significant difference between empagliflozin and metformin at follow-up in terms of MoCA score (Fig. 1), we did not find such a difference in terms of 5mGS ($P = 0.34$) (Fig. 2).

Correlation of Cognitive and Physical Impairment in Frail Patients With HFpEF

To investigate the relationships between brain and body in frail patients with diabetes and HFpEF, we evaluated MoCA scores and 5mGS test results. We found

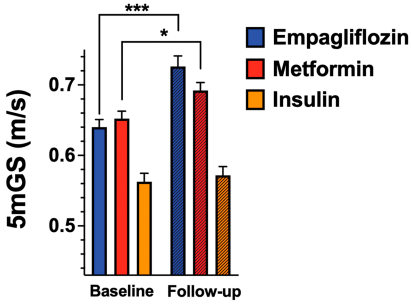

Figure 2—The 5mGS in the empagliflozin, metformin, and insulin groups measured at baseline and follow-up. Data are means ± SD. $^{*}P < 0.05$, $^{***}P < 0.001$.

a significant correlation between MoCA score and 5mGS at baseline in all patients at baseline ($r = 0.508$, $P < 0.001$) (Fig. 3*A*) and at follow-up in the empagliflozin group ($r = 0.711$, $P < 0.001$) (Fig. 3*B*).

CONCLUSIONS

Frailty is a systemic condition that involves many organs and systems, driving functional decline and adverse outcomes, and its management remains a subject of debate (17). Our results suggest a beneficial effect of empagliflozin on cognitive impairment. Empagliflozin drives positive effects on cardiovascular outcomes, particularly on the rehospitalization rate for HF (18); furthermore, SGLT2 inhibitors have been shown to improve cardiovascular energetics, reduce vascular tone and blood pressure, and decrease systemic inflammation (19–22).

Table 2—Logistic regression analysis in the entire patient sample using the improvement in the MoCA score as the dependent variable

	Regression coefficient	SE	Odds ratio	95% CI		*P*
				Lower	Upper	
Age	0.020	0.032	1.021	0.958	1.087	0.526
BMI	0.084	0.122	1.088	0.857	1.381	0.490
Heart rate	0.002	0.023	1.002	0.958	1.047	0.933
Glycemia	−0.004	0.005	0.996	0.986	1.006	0.411
Hypertension	−0.308	0.391	0.735	0.341	1.581	0.430
Hyperlipidemia	0.619	0.393	1.857	0.859	4.012	0.115
Chronic obstructive pulmonary disease	0.297	0.392	1.345	0.624	2.900	0.449
Chronic kidney disease	−0.214	0.380	0.807	0.383	1.699	0.573
Empagliflozin	1.284	0.426	3.609	1.566	8.321	**0.003**

Boldface indicates significance at $P < 0.05$.

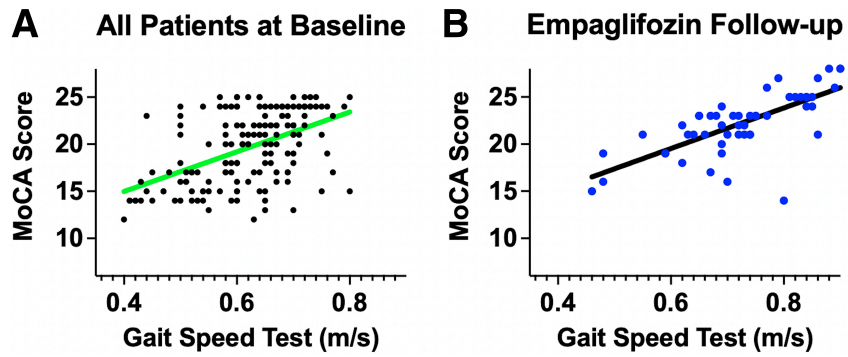

Figure 3—*A*: Dispersion model at baseline between MoCA score and 5mGS ($r = 0.508$, $P < 0.001$). *B*: Dispersion model at follow-up between MoCA score and 5mGS test results in the empagliflozin group ($r = 0.711$, $P < 0.001$).

Potential mechanisms underlying the favorable action of empagliflozin on cognitive function include its antioxidative and atheroprotective effects and the reduction of vascular damage, all proven in animal models (12,19,23). In addition, SGLT2 inhibitors may improve cognitive impairment through more direct neuroprotective mechanisms, including acetylcholinesterase inhibition and increase in cerebral levels of brain-derived neurotrophic factor (24).

In this scenario, empagliflozin plays a pleiotropic role that may be instrumental to improving global cognitive function in HFpEF. We speculate that empagliflozin may be considered a pleiotropic antidiabetic drug in frail older adults. On the basis of these considerations, empagliflozin may also have favorable effects on physical function in HFpEF.

Our study is not exempt from limitations. The main limitations are the brief follow-up and the relatively small population, although within the sample size required according to our a priori power analysis. Further investigations with a longer follow-up in large populations are warranted. Of note, all patients in this study were on monotherapy; therefore, our results cannot be generalized to patients in whom SGLT2 inhibitors are prescribed as sequential add-on therapy (25,26). Nevertheless, the significance of our findings is noteworthy for patients with HF (including HFpEF [27]) especially for patients who need to switch from metformin because of poor efficacy or side effects, including diarrhea, kidney disease, episodes of lactic acidosis, muscle pain, and abdominal discomfort (28–30).

In summary, to our knowledge, this study is the first to show a significant effect of empagliflozin treatment on cognitive impairment (assessed by MoCA score), and physical impairment (assessed by 5mGS test), in frail older adults with diabetes and HFpEF.

Acknowledgments. The authors thank Dr. X. Wang and Dr. F. Varzideh (Albert Einstein College of Medicine, New York, NY) for technical support and helpful discussion.

Funding. This study is supported, in part, by the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases (grants R01-DK123259 and R01-DK033823); National Heart, Lung, and Blood Institute (grants R01-HL146691, R01-HL159062, and T32-HL144456); and National Institute on Aging (grants R56-AG066431) to G.S. The study is also supported by the Irma T. Hirschl and Monique Weill-Caulier Trusts (to G.S.), the Diabetes Action Research and Education Foundation (to G.S.), and by the American Heart Association (AHA-20POST35211151 to J.G.).

The sponsors or funding organizations had no role in the design or conduct of this research.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. P.M. and A.L. contributed to the statistical analysis. P.M., A.L., J.G., A.P., G.M., S.F., and G.S. contributed to the acquisition, analysis, and interpretation of data. P.M., A.L., and G.S. drafted the manuscript. P.M. and G.S. contributed to the study concept and design and supervised the study. J.G., A.P., M.M., S.F., and G.S. contributed administrative, technical, or material support. G.M., M.M., S.F., and G.S. contributed to the critical revision of the manuscript for important intellectual content. All authors contributed to the interpretation of the results and review of the manuscript. P.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and accuracy of the data analysis.

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