HHS Public Access

Author manuscript

Pharmacol Res. Author manuscript; available in PMC 2024 September 06.

Published in final edited form as:

Pharmacol Res. 2024 February ; 200: 107055. doi:10.1016/j.phrs.2023.107055.

Effects of SGLT2 inhibition via empagliflozin on cognitive and physical impairment in frail diabetic elders with chronic kidney disease

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Declaration of Competing Interest

None.

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Keywords

Aging; Empagliflozin; Immunology; Lipid pharmacology; SGLT2 inhibitors

Chronic kidney disease (CKD) is a relatively common condition in patients with type 2 diabetes (T2D), and its prevalence augments with age [1]. It is well established that older adults have a higher risk of frailty with functional impairment and adverse events [2]. Moreover, frail older adults have many comorbidities that further contribute to both cognitive and functional impairment [2]. Empagliflozin is an inhibitor of sodium glucose cotransporter 2 (SGLT2), which has shown nephroprotective and cardioprotective actions and other salutary effects [3–7].

The actual effects of empagliflozin on cognitive impairment in elderly patients remain to be fully determined [8]; specifically, there are no studies exploring this aspect in frail older adults with T2D and CKD. In order to fill this knowledge gap, we enrolled consecutive frail older adults with confirmed diagnoses of T2D and CKD presenting at the Local Health Company of the Italian Ministry of Health of Avellino (ASL AV) from May 2021 to July 2022. Every patient (or legally authorized representative) signed a written informed consent. All subjects fulfilled the following criteria: Diagnosis of diabetes, frailty, and CKD with glomerular filtration rate (GFR) > 30 and < 60; age > 65; no previous myocardial infarction or revascularization procedures, EF > 50%; Montreal Cognitive Assessment (MoCA) Score < 26.

Patients were divided into two groups according to their antidiabetic treatment: empagliflozin 10 mg in addition to standard therapy *vs.* no empagliflozin. We performed this investigation following the ethical standards of the 1964 Declaration of Helsinki and its later

amendments. We obtained formal IRB approval from Campania-Nord and we registered the trial in clinicaltrials.gov (Identifier-NCT04962841).

We evaluated global cognitive function at baseline and after 6-months using the MoCA test: scores range from zero-to-30; a score > 25 is considered normal [9]. We diagnosed physical frailty when at least three of the following Fried criteria [9] were present: exhaustion (poor endurance and energy); weakness (handgrip strength in the lowest 20% quintile, adjusted for sex and BMI); slowness (walking speed under the lowest quintile adjusted for sex and height); weight loss (unintentional loss ≥4.5 kg in the past 12-months); low physical activity (lowest quintile of kilocalories of physical activity during the previous 7-days). A 5-meter gait speed test (GST) was performed in all patients, as described [9]. We assessed differences for continuous variables using the Wilcoxon signed-rank test, a non-parametric alternative to paired t-test. We used chi-square to evaluate associations between dichotomous and categorical variables. Multivariable regression analysis was applied to adjust for potential confounders. We considered significant a $P < 0.05$ for two-sided comparisons.

We screened 166 frail elders with diabetes and CKD. Since 47 subjects did not fully meet the inclusion/exclusion criteria mentioned above and/or were unwilling to provide information, 119 patients entered the study. We divided our cohort in 2 groups based on the antidiabetic treatment: empagliflozin plus standard therapy (59 patients) and no-empagliflozin (60 patients).

Importantly, there were no significant differences between groups at baseline. We tested the MoCA scores in the 2 groups at baseline and at 6-month follow-up: 19.7 ± 3.68 *vs.* 21.4 ± 3.66 (p: 0.009) in the empagliflozin-group; 19.4 ± 3.76 *vs.* 19.5 ± 3.67 (p: 0.119) in the no-empagliflozin-group (Fig. 1A). We then performed a multivariable regression analysis using the improvement of MoCA score as dependent variable, adding to the model potential confounders, confirming the significant effect of empagliflozin treatment on the amelioration of cognitive impairment (Fig. 1B).

We also analyzed GST scores in the 2 groups at baseline and at 6-month follow-up: 0.603±0.11 *vs.* 0.688±0.13 (p<0.001) in the empagliflozin-group; 0.618±0.12 *vs.* 0.627±0.15 (p: 0.687) in the no-empagliflozin-group (Fig. 1C). We confirmed these results *via* a multivariable regression analysis using the improvement in GST as dependent variable (Fig. 1D).

The management of diabetic complications is a rapidly rising health problem. Kidney disease is a typical complication in T2D patients, which increases the risk of adverse events, including cognitive and physical impairment, particularly in frailty. In this scenario, we evaluated the effects of empagliflozin treatment. We observed a favorable action on both cognitive and physical function. Salutary vascular properties have been proposed for SGLT2-inhibitors, and we have previously observed beneficial effects on physical and cognitive function in hypertensive patients, by improving endothelial dysfunction and reducing mitochondrial oxidative stress [10]. To the best of our knowledge, we are the first group exploring the effects of empagliflozin on cognitive and physical impairment in frail older adults with diabetes and CKD, further supporting our view that SGLT2-inhibitors may

be considered anti-frailty drugs. Nevertheless, additional studies with larger follow-up and larger sample size are warranted to confirm our data.

Funding

The Santulli's Lab is currently supported in part by the National Institutes of Health (NIH): National Heart, Lung, and Blood Institute (NHLBI: R01-HL164772, R01-HL159062, R01-HL146691, T32-HL144456), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK: R01-DK123259, R01-DK033823), National Center for Advancing Translational Sciences (NCATS: UL1-TR002556-06, UM1-TR004400) to G.S., by the Diabetes Action Research and Education Foundation (to G.S.), and by the Monique Weill-Caulier and Irma T. Hirschl Trusts (to G.S.). This publication was also produced with the co-funding European Union – Next Generation EU, in the context of The National Recovery and Resilience Plan, Investment Partenariato Esteso PE8 "Conseguenze e sfide dell'invecchiamento", Project Age-It (Ageing Well in an Ageing Society).

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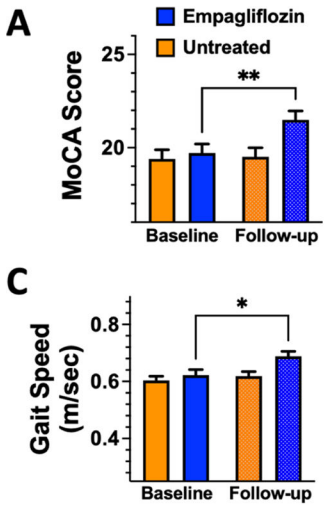

B

	B	95% CI		P
		Lower Bound	Upper Bound	
Age	-,375	-,431	-,320	,000
Dyslipidemia	-,042	-,775	,690	,909
COPD	-,825	-1,599	-,052	,037
Cerebrovascular disease	-1,447	-2,206	-,689	,000
BMI	-,086	-,195	,023	,121
Hypertension	-,802	-1,535	-,069	,032
Empagliflozin treatment	,794	,073	1,516	,031

D

	B	95% CI		P
		Lower Bound	Upper Bound	
Age	-,011	-,014	-,008	,000
Dyslipidemia	,035	-,008	,077	,109
COPD	-,017	-,062	,028	,450
Cerebrovascular disease	-,039	-,083	,005	,079
BMI	-,001	-,007	,005	,781
Hypertension	-,047	-,089	-,004	,032
Empagliflozin treatment	,042	,001	,084	,047

Fig. 1.

Effects of empagliflozin on cognitive and physical impairment. A) Montreal Cognitive Assessment (MoCA) Score at baseline and follow-up in patients treated or not with empagliflozin; B) multivariable regression analysis using the improvement in MoCA score as dependent variable; C) Gait Speed at baseline and follow-up in patients treated or not with empagliflozin; D) multivariable regression analysis using the improvement in GST score as dependent variable. *: 0.05, **: $p<0.01$; paired samples Wilcoxon test.