Comparison of the Effects of Sodium-Glucose Cotransporter-2 Inhibitors and Dipeptidyl Peptidase-4 Inhibitors on Body Weight and Body Composition in Elderly Patients with Type 2 Diabetes

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Abstract

Objective: To compare the effects of dapagliflozin and linagliptin on body weight and body composition in elderly patients with type 2 diabetes mellitus and poor glycemic control despite metformin therapy. Methods: A total of 106 elderly patients with type 2 diabetes mellitus who had received metformin therapy with HbA1c levels of 7.0%-8.5% were enrolled and randomly divided into dapagliflozin and linagliptin groups. Bioelectrical impedance analysis was used for body composition assessment before and after the study. Results: The mean change in body weight from baseline to 24 weeks was -3.78 kg in the dapagliflozin group. Dapagliflozin also significantly reduced muscle mass and total body protein. Compared with linagliptin, dapagliflozin induced a greater reduction in fat mass from baseline to week 24, with a statistically significant difference. Conclusion: Dapagliflozin significantly reduces body weight, including both fat mass and lean body mass, and should be used with caution in elderly frail patients.

Full Text

Preamble

Comparative Effects of Sodium-Glucose Cotransporter-2 Inhibitors and Dipeptidyl Peptidase-4 Inhibitors on Body Weight and Body Composition in Elderly Patients with Type 2 Diabetes

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Abstract

Objective: To compare the effects of dapagliflozin and linagliptin on body weight and body composition in elderly type 2 diabetes mellitus (T2DM) patients with inadequate glycemic control on metformin therapy.

Methods: A total of 106 elderly T2DM patients who had received metformin treatment and had HbA1c levels between 7.0% and 8.5% were enrolled and randomly assigned to either the dapagliflozin or linagliptin group. Bioelectrical impedance analysis was used to assess body composition before and after the study period.

Results: The mean weight change from baseline to 24 weeks in the dapagliflozin group was -3.78 kg. Dapagliflozin also significantly reduced muscle mass and total body protein. Compared with linagliptin, dapagliflozin produced a significantly greater reduction in body fat mass from baseline to week 24.

Conclusion: Dapagliflozin significantly reduces body weight, including both fat mass and lean mass, and should be used cautiously in elderly frail patients.

Keywords: dapagliflozin; linagliptin; weight; body composition; T2DM; elderly

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally. Concurrently, with rapid economic development, extended life expectancy, and societal aging, the number of elderly ($ $60 years) patients with T2DM continues to grow. Since cardiovascular and renal risks increase with age and diabetes duration, and sodium-glucose cotransporter-2 (SGLT2) inhibitors have robust evidence for reducing cardiovascular and renal events, elderly T2DM patients are increasingly likely to be prescribed this class of antidiabetic medications. As "negative energy" drugs, SGLT2 inhibitors may affect body composition during glycemic control, potentially reducing muscle mass alongside fat mass. For elderly diabetic patients, particularly those who are frail, muscle loss can decrease

quality of life, increase fall risk, and shorten life expectancy. In contrast, dipeptidyl peptidase-4 (DPP-4) inhibitors are recommended by major guidelines for elderly T2DM patients due to their good glycemic efficacy, low hypoglycemia risk, excellent tolerability, and weight-neutral profile. Currently, comparative studies examining the effects of SGLT2 inhibitors and DPP-4 inhibitors on muscle mass, strength, and body composition in elderly T2DM patients are limited. This study aims to evaluate the effects of these two drug classes on body composition in elderly T2DM patients.

Methods

1.1 Study Subjects and Inclusion/Exclusion Criteria

We conducted a randomized, parallel-controlled study of elderly T2DM patients treated at Sichuan Provincial People's Hospital between September 2020 and April 2023.

Inclusion criteria: T2DM patients aged 60-80 years; BMI \$ $22kg/m\hat{}\{2\}$\$; receiving adequate metformin treatment combined with diet, exercise, or other oral hypoglycemic agents; and HbA1c between 7% and 8.5%.

Exclusion criteria: (1) Type 1 diabetes, gestational diabetes, diabetic ketoacidosis, genitourinary infection within 3 months before enrollment, or hyperglycemia (fasting glucose >11.1 mmol/L or HbA1c >8.5%); (2) SGLT2 inhibitor or glucagon-like peptide-1 receptor agonist treatment within 12 weeks; insulin use within 12 weeks; (3) impaired cognitive function; (4) Acute coronary syndrome, stroke, or transient ischemic attack within 12 weeks; (5) eGFR <45 mL/min/1.73 m^2; (6) Sarcopenia: dominant hand grip strength <28 kg in men or <18 kg in women; or inability to complete the sit-to-stand test according to protocol.

1.2 Research Methods

A total of 106 patients were enrolled and randomly divided into two groups receiving either linagliptin 10 mg once daily (n=53) or dapagliflozin 10 mg once daily (n=53). Among these, 97 patients completed bioelectrical impedance analysis (BIA) before and after treatment (linagliptin group, n=51; dapagliflozin group, n=46) and were included in the efficacy analysis. Body composition was measured using BIA with four-pole technology (X-Scan Plus II, SELVAS Healthcare Co., Ltd.). All BIA measurements were performed by the same investigator.

1.3 Statistical Analysis

Continuous data were expressed as mean ± standard deviation and tested for normal distribution. Comparisons between groups were performed using t-tests.

For non-normally distributed data, non-parametric tests were used. Statistical analysis was performed using SPSS 22.0 software, with P<0.05 considered statistically significant.

Results

2.1 Baseline Characteristics of the Two Groups

Table 1 shows the baseline characteristics of study participants, with no statistically significant differences between groups (P>0.05).

2.2 Comparison of Weight and Body Composition Changes

After 24 weeks of treatment, both groups showed reductions in blood glucose. In the dapagliflozin group, both fasting plasma glucose and HbA1c decreased significantly with statistical significance. In the linagliptin group, although fasting plasma glucose and HbA1c showed downward trends, only the reduction in fasting plasma glucose reached statistical significance.

Comparing weight and body composition changes between groups, linagliptin did not significantly alter body weight from baseline to 24 weeks ($0.1\$\pm0.61kg, P = 0.27$), $whereasdapagliflozinproducedsignificantweightloss(-3.78\pm2.45kg, P < 0.001).After24weeks, changesinbodyfatmasswere0.29\pm2.61kg(P = 0.43)inthelinagliptingroupand-$ $1.01\pm\$0.74$ kg (P<0.001) in the dapagliflozin group. Linagliptin did not change body fat, while dapagliflozin reduced total body fat mass.

Muscle mass changes differed between groups from baseline to 24 weeks. The dapagliflozin group showed a statistically significant reduction in muscle mass (−0.34 kg, P<0.001), while the linagliptin group showed no change. Additionally, the dapagliflozin group exhibited a statistically significant reduction in body protein content.

Total body water components (including total body water, intracellular water, and extracellular water) did not change significantly in either group before and after treatment, although a decreasing trend was observed in the dapagliflozin group compared with the linagliptin group.

Table 2 presents the changes in metabolic parameters and body composition before and after treatment in both groups.

Discussion

T2DM is often accompanied by insulin resistance and visceral fat accumulation, which is associated with pancreatic β-cell dysfunction, diabetes progression, and increased risk of diabetic complications including cardiovascular and renal disease. Therefore, glycemic control combined with modest weight loss may help

delay diabetes progression and prevent complications. However, weight loss involves not only fat reduction but also skeletal muscle mass loss. Given that elderly patients have lower baseline muscle mass and face age-related risks of further skeletal muscle mass and strength decline, most guidelines recommend cautious use of "negative energy" drugs such as SGLT2 inhibitors or glucagon-like peptide-1 receptor agonists in elderly patients to avoid potential frailty [1]. Asian populations face higher sarcopenia risk compared with Western populations, yet few studies have examined the effects of SGLT2 inhibitors on muscle in elderly diabetic patients.

This study found that in elderly T2DM patients, dapagliflozin provided superior glycemic efficacy compared with linagliptin after 24 weeks and significantly reduced body weight and fat mass without significantly decreasing total body water, partially consistent with previous research [2,3]. A systematic review reported that SGLT2 inhibitors induce weight loss of approximately 0.5 to 3.9 kg after 8-104 weeks [4]. SGLT2 inhibitors promote weight loss not only through glucosuria-induced caloric loss and increased energy expenditure but also by activating AMPK pathways via increased fatty acid β-oxidation and affecting adiponectin and leptin expression [5]. Dapagliflozin improves visceral adipocyte dysfunction, reducing leptin, endotrophin, and plasminogen activator inhibitor-1 expression while promoting adiponectin expression, thereby effectively promoting lipolysis and reducing visceral fat [6].

Rizzo et al. reported that DPP-4 inhibitors significantly reduce intrahepatic fat and fat mass while preventing muscle mass loss in T2DM patients compared with sulfonylureas, demonstrating better anti-atrophic effects [7] and preserving muscle mass and function [8]. However, this study did not find differences in fat mass or muscle mass before and after linagliptin treatment, possibly due to the relatively short 24-week study duration. In contrast, we observed that dapagliflozin significantly reduced muscle mass and body protein content. SGLT2 inhibitors may decrease insulin levels, reducing glucose and amino acid uptake by muscle and enhancing proteolysis through elevated glucagon, thereby accelerating muscle atrophy [9]. SGLT2 inhibition can lead to negative energy balance and reduced blood insulin levels, potentially inducing various catabolic responses outside skeletal muscle, such as adipose tissue lipolysis, which may increase free fatty acid and ketone body production [10]. Evidence suggests that SGLT2 inhibitor-mediated chronic hyperketonemia can oxidize peripheral tissues, including skeletal muscle, as an energy fuel [11]. Although SGLT2 is not expressed in animal skeletal muscle, its family protein SGLT3 is expressed near the neuromuscular junction [12]. The physiological function of SGLT3 remains unclear, but it may act as a glucose sensor [13]. Unlike our findings, animal studies have shown that canagliflozin reduces inflammatory cytokine concentrations in obese mice, enhances skeletal muscle function, and improves muscle contractility [14]; however, this conclusion lacks support from large-scale human studies.

Compared with linagliptin, dapagliflozin provides better glycemic efficacy and

increasingly recognized cardiovascular and renal benefits, gaining more attention among antidiabetic agents. However, dapagliflozin has a theoretical basis for causing dry weight loss. This study provides a direct comparison of these two new oral antidiabetic drug classes on body composition in elderly T2DM patients. We observed that dapagliflozin reduces body weight and fat mass but also decreases muscle mass and protein content, demonstrating its negative energy effects on the body, which may be detrimental in elderly patients.

This study has several limitations. Due to practicality and relatively low cost, we used BIA to measure body composition, though BIA may differ from computed tomography (CT), which better reflects visceral fat area. Second, we did not obtain information on dietary habits and physical activity, which could significantly affect body composition changes. Additionally, other oral antidiabetic medications may have influenced results. The study duration was relatively short, and generalizability may be limited by racial differences. Therefore, further studies with larger samples are needed to investigate the effects of SGLT2 and DPP-4 inhibitors on muscle strength and physical function, particularly in elderly patients requiring long-term use of these medications.

References

[1] Kalyani, R. R., Corriere, M. & Ferrucci, L. Age-related and disease-related muscle loss: The effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol. 2, 819–829. https://doi.org/10.1016/s2213-8587(14)70034-8 (2014).

[2] Inoue, H. et al. Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, reduces body weight and fat mass, but not muscle mass, in Japanese type 2 diabetes patients treated with insulin: A randomized clinical trial. J. Diabetes Investig. 10, 1012–1021. https://doi.org/10.1111/jdi.12985 (2019).

[3] Schork, A. et al. Effect of SGLT2 inhibitors on body composition, fluid status and renin-angiotensin-aldosterone system in type 2 diabetes: A prospective study using bioimpedance spectroscopy. Cardiovasc. Diabetol. 18, 46. https://doi.org/10.1186/s12933-019-0852-y (2019).

[4] Sheu WHH, Chan SP, Matawaran BJ, Deerochanawong C, Mithal A, Chan J, et al. Use of SGLT-2 inhibitors in patients with type 2 diabetes mellitus and abdominal obesity: An asian perspective and expert recommendations. Diabetes Metab J 2020; 44(1):11-32. doi.org/10.4093/dmj.2019.0208.

[5] Xu, L. & Ota, T. Emerging roles of SGLT2 inhibitors in obesity and insulin resistance: Focus on fat browning and macrophage polarization. Adipocyte 7, 121–128. https://doi.org/10.1080/21623945.2017.1413516 (2018).

[6] Shaheer, A., Kumar, A., Menon, P., Jallo, M. & Basha, S. Effect of add-on therapy of dapagliflozin and empagliflozin on adipokines in Type 2 diabetes

mellitus. J. Endocrinol. Metab. 11, 83–90 (2021).

[7] Sakurai, S. et al. Empagliflozin decreases the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) in patients with type 2 diabetes: Association with improvement of fibrinolysis. J. Diabetes Complicat. 34, 107703. (2020).

[8] Rizzo, M. R. et al. Sarcopenia in elderly diabetic patients: Role of dipeptidyl peptidase 4 inhibitors. J. Am. Med. Dir. Assoc. 17, 896–901. https://doi.org/10.1016/j.jamda.2016.04.016 (2016).

[9] Bouchi, R. et al. Dipeptidyl peptidase 4 inhibitors attenuate the decline of skeletal muscle mass in patients with type 2 diabetes. Diabetes Metab. Res. Rev. https://doi.org/10.1002/dmrr.2957 (2018).

[10] Ferrannini, E., Mark, M. and Mayoux, E. (2016) CV protection in the EMPA-REG OUTCOME Trial: a "Thrifty Substrate" hypothesis. Diabetes Care 39, 1108–1114 https://doi.org/10.2337/dc16-0330

[11] Qiu, H., Novikov, A. and Vallon, V. (2017) Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: basic mechanisms and therapeutic perspectives. Diabetes Metab. Res. Rev. 33, e2886 https://doi.org/10.1002/dmrr.2886

[12] Castaneda F, Layne JE, Castaneda C. Skeletal muscle sodium-glucose cotransporters in older adults with type 2 diabetes undergoing resistance training. Int J Med Sci. 2006;3:84–91.

[13] Sano R, Shinozaki Y, Ohta T. Sodium–glucose cotransporters: functional properties and pharmaceutical potential. J Diabetes Investig. 2020;11:770–82.

[14] Naznin F, Sakoda H, Okada T, Tsubouchi H, Waise TM, Arakawa K, et al. Canagliflozin, a sodium glucose cotransporter 2 inhibitor, attenuates obesity-induced inflammation in the nodose ganglion, hypothalamus, and skeletal muscle of mice. Eur J Pharmacol. 2017;794:37–44.

Note: Figure translations are in progress. See original paper for figures.