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Commentary

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Various clinical efficacy of sodium-glucose co-transporter-2 inhibitor (SGLT2i) to sarcopenia, muscle mass and function

Abstract

Regarding pharmacological therapy for diabetes, sodium-glucose co-transporter-2 inhibitor (SGLT2i) has been in focus for various clinical efficacy. They include cardiovascular disease, chronic heart failure (CHF) and chronic kidney disease (CKD). Various discussion has been observed concerning the relationship among diabetes, frailty, sarcopenia, SGLT2i, aging and senile syndrome. By SGLT2i, weight and visceral fat area (VFA) are decreased, and the results of skeletal muscle index (SMI) and bone mineral content (BMC) vary in some reports. Using abdominal CT, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), muscle mass and BMC have been lately studied. SGLT2i may maintain muscle mass and function.

Keywords: sodium-glucose co-transporter-2 inhibitor (SGLT2i), sarcopenia, visceral fat area (VFA), skeletal muscle index (SMI), bone mineral content (BMC)

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Abbreviations: CKD, chronic kidney disease; SMI, skeletal muscle index, BIA, bioelectrical impedance analysis; VFA, visceral fat area; LCD, low carbohydrate diet; CHF, chronic heart failure, ADL, activities of daily living

Introduction

Diabetes has been on the rise across the world.[1]. Regarding diet therapy, the usefulness of low carbohydrate diet (LCD) has been rather prevalent in medical and health care region, associated with actual efficacy.[2] The authors have been involved in diabetic practice and research. Furthermore, we have developed Japan low carbohydrate diet promotion association (JLCDPA), and continued social and educational activities of LCD.[3] As for pharmacological therapy, various novel agents have been introduced.[4] Among them, sodium-glucose co-transporter-2 inhibitor (SGLT2i) has been in focus associated with beneficial efficacy. This shows the mechanism by which carbohydrates are excreted in the urine. Therefore, both of LCD and SGLT2i have common background for decreasing the involvement of carbohydrate.[5] SGLT2i was initially indicated for type 2 diabetes (T2D). After that, the indication has been expanded to chronic heart failure (CHF) and chronic kidney disease (CKD).

SGLT2i and sarcopenia

On the other hand, the problems of aging and sarcopenia related to diabetes are now attracting attention.[6]. Various debates have been found about the relationship between SGLT2i and sarcopenia.[7] In other words, SGLT2i may influence sarcopenia for protection or exacerbation. Such related information would be described in this article. Some kinds of SGLT2i have been used so far. The indication was recently expanded, in which dapagliflozin was for CHF and CKD, and empagliflozin was for CHF.[8] However, elderly patients may show senile syndrome, and then careful attention should be paid to the presence of sarcopenia, mild cognitive impairment (MCI), dementia, and decreased activities of daily living (ADL).[9]

Regarding pharmacological therapy for diabetes, sodium-glucose co-transporter-2 inhibitor (SGLT2i) has been in focus for clinical efficacy. They include type 2 diabetes (T2D), chronic heart failure (CHF) and chronic kidney disease (CKD). Various discussion has observed concerning the relationship among diabetes, frailty, sarcopenia, SGLT2i, aging and senile syndrome. Some observational reports were observed. As the protocol, 24 diabetic cases with HbA1c 7.7% were given ipragliflozin (50 mg/day) for 16 weeks, and changes in visceral tissue were investigated.[10] The results showed i) visceral fat area (VFA) decrease from 110 to 101cm^2, ii) weight reduction -2.49kg, iii) fat decrease -1.77kg, iv) water decrease -0.55kg, and v) small but significant decrease of skeletal muscle index (SMI). Concerning epicardial fat volume (EFV), 19 diabetic cases were provided luseogliflozin 2.5mg daily for 12 weeks.[11] As a result, significant decrease was found in EFV (from 117 to 111), SMI (from 7.81 to 7.58), BMI, weight, HbA1c, IRI, HOMA-IR, triglycerides, and body fat. However, VFA or liver attenuation index (LAI) did not reveal significant changes.

SGLT2i and muscle

Concerning SGLT2i, sarcopenia and bone mineral content (BMC), luseogliflozin was given to 37 diabetic patients for 24 weeks.[12] Total fat reduction was -1.97kg, and VFA at 24 weeks showed average downward trend with no significance. SMI revealed small and significant decrease after 36 weeks. BMC showed transient significant reduction at 12 weeks, but without significant changes of BMC in other time-points. Consequently, luseogliflozin caused beneficial effects in diabetic metabolism and body composition, associated with minimal decrease of muscle and BMC. Previous reports showed that SGLT2i did not provide negative influence to muscle volume. Comparative study was conducted for dapagliflozin and other anti-diabetic agents for muscle mass and muscle fat content.[13] The protocol included 50 T2D cases with HbA1c 7.9% and BMI 28.1kg/m^2 in average, and biomarkers of weight, HbA1c, fat mass, muscle mass was measured for 6months in two groups. Using abdominal CT and bioelectrical impedance analysis (BIA) method, psoas muscle area (PMA) and psoas muscle index (PMI) was calculated. As a result, dapagliflozin significantly decreased body weight and total fat mass without affecting skeletal muscle mass.

Using BIA and dual-energy X-ray absorptiometry (DXA), 49 T2D patients were compared by add-on ipragliflozin therapy vs no additional treatment.[14] As a result, changes in weight were larger in ipragliflozin group as -2.78kg vs -0.22kg, p<0.0001. In the former group, total muscle mass and BMC were maintained. In detail, no difference in muscle mass between the lower limbs and the trunk was observed, but small and significant decrease in the upper limbs was found. Further investigation will be required for long-term efficacy. Recent reports are found concerning changes of HbA1c, weight and muscle mass for administration of SGLT2i.[15] For retrospective observation study for 2 years, 46 out-clinic T2D patients were included who were on SGLT2i. Several anthropometric and metabolic data were obtained from medical records. The results showed i) remarkable reduction of weight and fat amount, ii) improvement of lipid profile and liver function, iii) decrease of eGFR with all significant difference, and iv) no change in skeletal muscle mass. From these situations, SGLT2i may be safely provided for long term with no risk for sarcopenia.

As an impressive study, grip strength was increased by SGLT2i. It is observational study for clinical efficacy of SGLT2i on muscle strength.[16] The applicants were 112 T2D patients with 62.8years, BMI 25.6, HbA1c 7.0%. Administration of SGLT2i included ipragliflozin 50mg/day, luceogliflozin 2.5mg/day, and dapagliflozin 5-10 mg/day. They were followed and compared for 10.3weeks in average. As a result, the grip strength of both hands was significantly improved as 30.3kg to 31.8kg in male and 18.0 to 20.2kg in female with significant difference (p<0.01). In latest research of SGLT2i, experiments of mice were found. Diabetic model mice (db/db, db/m) were divided into four groups with or without luseogliflozin for 8weeks.[17] SGLT2i brought decreased visceral fat (p=0.004), increased soleus muscle mass (p=0.010) and elevated grip strength (p=0.0001). Thus, SGLT2i can reduce hyperglycemia and also improve lipid metabolism of muscle, leading to preventing muscle atrophy.

Another experiment showed that canagliflozin was given to non-diabetic wild-type mice, and then dietary intake was increased 1.5-fold when food could be freely ingested. This would be from compensating urinary energy glucose loss, leading to no changes in body weight and muscle mass, and increase of grip strength. When the food was restricted, the body weight and muscle weight decreased due to insufficient energy intake, and the muscle strength was also decreased.[18] Further, the influence of canagliflozin on metabolites and gene expression for fast and slow muscles. During SGLT2i administration, fast muscle function is elevated associated with increased food intake, whereas slow muscle function is not changed, where fast and slow muscle mass was maintained.

Conclusion

In summary, the association between SGLT2i and sarcopenia was discussed.[19]. Some reports indicated pathological muscle loss, and others suggested elevated muscle strength.[20]. Further verification would be required for various situations in the future.

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Conflicts of interest

Author declares there are no conflicts of interest.

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