Journal of Obesity & Metabolic Syndrome 2018;27:1-3
https://doi.org/10.7570/jomes.2018.27.1.1

Editorial

jomes
pISSN 2508-6235
eISSN 2508-7576

Sodium-Glucose Co-transporter 2 Inhibitor: The Magic Bullet for Obesity in Diabetes?

Ji A Seo*

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

Received February 7, 2018
Reviewed February 14, 2018
Accepted February 19, 2018

*Corresponding author
Ji A Seo

https://orcid.org/0000-0002-1927-2618

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
Tel: +82-31-412-4275
Fax: +82-31-412-5984
E-mail: seo-ji-a@hanmail.net

Obesity has been associated with diabetes incidence and complications. In South Korea, the mean body mass index (BMI) of diabetic subjects has gradually increased, and the proportion of obesity (BMI ≥ 25 kg/m^2) and abdominal obesity are 48.6% and 58.9%, respectively.[1] The first line treatment of obesity is a combination of a low calorie diet, increased physical activity, and behavioral therapy. However, it is very difficult for obese subjects to reduce and maintain their weight by life-style modification alone. Several kinds of newly developed antidiabetic medications showed useful advantages in obese diabetic patients. Such patients show not only reduced hypoglycemia, but also moderate effects of weight reduction and decrease in blood pressure.

Cho et al.[2] retrospectively investigated the effect of dapagliflozin on body weight reduction in Korean subjects with type 2 diabetes mellitus (T2DM). Although the study had no control group, metformin based-combination treatment of dapagliflozin with other classes of oral hypoglycemic agents in Korean patients with T2DM showed comparable efficacy of body weight reduction, blood pressure lowering, and antihyperglycemic effects to a previous report[3] and few adverse events. However, the number of subjects was too small for further subgroup analyses with stratification of baseline anthropometry or laboratory findings. Because many patients with T2DM are overweight/obese and/or have hypertension, weight loss and blood pressure reduction are important components of T2DM management as well as achieving glycemic control. The prescription of sodium-glucose co-transporter 2 inhibitor (SGLT2i) has steadily increased in Korea due to various advantages in T2DM and is eligible for national health insurance coverage. Moreover, much more use is expected since empagliflozin and canagliflozin have shown beneficial cardiovascular effects in high cardiovascular risk patients in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose Study[4] and the Canagliflozin Cardiovascular Assessment Study.[5]

Currently available SGLT2is in South Korea are dapagliflozin, empagliflozin, and ipragliflozin. All of these inhibit SGLT2 and thereby reduce renal tubular glucose reabsorption, resulting in increased glycosuria. SGLT2i induces weight reduction through a negative caloric balance and blood pressure reduction caused by natriuresis. However, SGLT2i-associated weight loss is less than the amount predicted based on urinary glucose excretion.[6] This might be due to the role of SGLT1 upregulation in renal reabsorption of

glucose, which can decrease weight loss, but was not inhibited by SGLT2is[7] or might be more complicated than we currently expect. Meta-analysis showed that all named SGLT2is in clinical trials significantly reduced body weight, and the best reduction was achieved when the SGLT2i was used alone or in combination with metformin.[8] For example, compared with placebo, dosage-dependent body weight reduction by dapagliflozin treatment was ~2.24 kg.[8] Although the amount of weight loss by SGLT2i was not sufficient to consider the material as a primary anti-obesity drug, the finding that some portion of SGLT2i-treated subjects experienced ≥ 3% body weight reduction cannot be ignored.[9] In addition, recent animal studies have reported encouraging results on the protective effects against complications of obesity such as nonalcoholic fatty liver disease. Empagliflozin, ipragliflozin, and dapagliflozin ameliorated liver steatosis and slowed the progression of liver fibrosis in obese diabetic animals.[10-12] Moreover, a growing body of evidence has suggested that SGLT2 inhibition affords renal protection by attenuation of glomerular hyperfiltration and long-term glomerular damage.[13]

Meanwhile, SGLT2is imparts increased risk of urogenital infections and possible risk of "euglycemic" diabetic ketoacidosis. Care should be taken to warn patients about genital fungal infections and to avoid use in people with risk factors for SGLT2i-associated ketoacidosis. Due to the risk for ketoacidosis, SGLT2i has not been indicated in type 1 diabetes yet. In a phase 2 clinical trial with type 1 diabetes, investigators reported ketoacidosis in 5.1%–9.4% of patients randomly assigned to canagliflozin, but none in those randomly assigned to placebo.[14] However, a recent phase 3 clinical trial with dapagliflozin showed promising results that dapagliflozin treatment for 24 weeks in patients with inadequately controlled type 1 diabetes had significant and clinically relevant benefits including weight loss (−2.96 to 3.72 kg vs. placebo) and improvement of HbA1c without increasing hypoglycemia as add-on to adjustable insulin, with no significant increase of ketoacidosis events.[15] This result might be due to the careful monitoring of blood glucose and ketone to prevent ketoacidosis in that study. Further long-term trials with larger numbers of type 1 diabetic subjects assessing broader safety and efficacy are necessary.

Although the Action for Health in Diabetes (Look AHEAD) trial focusing on weight loss did not show that an intensive lifestyle intervention reduced cardiovascular events in overweight or obese adults with T2DM[16], secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document other benefits of weight loss in patients with T2DM, including improvements in mobility, physical and sexual functioning, and health-related quality of life.[17] Also, a post hoc analysis of the Look AHEAD study suggests that the heterogeneous treatment effects which included significantly reduced cardiovascular events with intensive lifestyle intervention in some groups.[18] Current guidelines for the treatment of overweight and obese subjects with T2DM support that modest and sustained weight loss improves glycemic control and reduces the need for glucose-lowering medications.[19,20] For overweight or obese patients with T2DM, personalized selection of glucose-lowering medications to focus on weight reduction and a combined lifestyle modification are unequivocally necessary.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. Korean Diabetes Association. Korean diabetes fact sheet 2016 [Internet]. Seoul: Korean Diabetes Association; 2016 [cited 2018 Feb 4]. Available from: http://www.diabetes.or.kr
2. Cho HA, Jung YL, Lee YH, Lee YC, Lee JE, Lee SJ, et al. Efficacy of body weight reduction on the SGLT2 inhibitor in people with type 2 diabetes mellitus. J Obes Metab Syndr 2017; 26:107-13.
3. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010;375:2223-33.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
6. Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferran-

nini E. Energy balance after sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38:1730-5.
7. Wilding JP. The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors. Metabolism 2014;63:1228-37.
8. Cai X, Yang W, Gao X, Chen Y, Zhou L, Zhang S, et al. The association between the dosage of SGLT2 inhibitor and weight reduction in type 2 diabetes patients: a meta-analysis. Obesity (Silver Spring) 2018;26:70-80.
9. Merton K, Davies MJ, Vijapurkar U, Inman D, Meininger G. Achieving the composite endpoint of HbA1c, body weight, and systolic blood pressure reduction with canagliflozin in patients with type 2 diabetes. Curr Med Res Opin 2018;34:313-8.
10. Tang L, Wu Y, Tian M, Sjöström CD, Johansson U, Peng XR, et al. Dapagliflozin slows the progression of the renal and liver fibrosis associated with type 2 diabetes. Am J Physiol Endocrinol Metab 2017;313:E563-76.
11. Honda Y, Imajo K, Kato T, Kessoku T, Ogawa Y, Tomeno W, et al. The selective SGLT2 inhibitor ipragliflozin has a therapeutic effect on nonalcoholic steatohepatitis in mice. PLoS One 2016;11:e0146337.
12. Jojima T, Tomotsune T, Iijima T, Akimoto K, Suzuki K, Aso Y. Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. Diabetol Metab Syndr 2016;8:45.
13. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol 2017;13:11-26.
14. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care 2015;38:2258-65.
15. Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschöpe D, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:864-76.
16. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-54.
17. Wilding JP. The importance of weight management in type 2 diabetes mellitus. Int J Clin Pract 2014;68:682-91.
18. Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial. Lancet Diabetes Endocrinol 2017;5:808-15.
19. American Diabetes Association. 7. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2018. Diabetes Care 2018;41(Suppl 1):S65-72.
20. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2017 executive summary. Endocr Pract 2017;23:207-38.