



## **The Role of SGLT-2 Inhibitors as an Adjuvant to Insulin Therapy in Type-1 Diabetes Mellitus- Literature Review**

**Sultan Ali Alshehri<sup>1\*</sup>, Sultan Abdulwahab M. Asiri<sup>1</sup>, Aalaa Mohammad Algarni<sup>1</sup> and Manal Mohammed Alamari<sup>1</sup>**

<sup>1</sup>Department of pediatrics, Khamis Mushait Maternity and children Hospital, Abha, Saudi Arabia.

### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Background:** Type 1 diabetes mellitus is the main risk factor for cardiovascular complications. Therefore, intensified insulin therapy might be needed to achieve better glycemic control in some patients. However, insulin therapy might lead to increase body weight and induce hypoglycemia. Increase body weight is directly correlated to insulin resistance, the main factor for cardiovascular risk.

**Objective:** To assess the effectiveness of adding SGLT2 inhibitors to insulin therapy in type 1 diabetes mellitus.

**Methods:** We searched in the PubMed database looking for relevant articles on the topic. We used Mesh words search, including SGLT2 inhibitor, sotagliflozin, type 1 diabetes mellitus, insulin treatment.

**Conclusion:** Adding oral antidiabetic agents, such as SGLT2 or dual SGLT inhibitors to insulin regimen might be beneficial in improving insulin resistance. Thus, it achieved better insulin resistance by decrease daily insulin requirements and bodyweight control, leading to better cardiovascular outcomes among Type-1 diabetes patients.

\*Corresponding author: E-mail: shehry07@hotmail.com;

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## 1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease manifested by immune-mediated destruction of pancreatic beta cells, resulting in decreased or absent insulin secretion [1-2]. As a result, hypoglycemia is developed with increase glucagon concentration in the fasting and postprandial state [1-2]. The disease resulted from a combination of genetic susceptibility and environmental factors, and it is the most common chronic metabolic disease in childhood, affecting all parts of the body, significantly, micro and macrovascular components [1, 3].

The goal of T1DM management is to ensure alpha-cell suppression, reduce HbA1c without increasing the risk of hypoglycemia, induce weight loss in obese patients and reduce cardiovascular risk. Moreover, adequate insulin therapy is the mainstay of treatment and prevents late diabetic complications; nevertheless, intensified insulin therapy also increases the risk of hypoglycemia [2]

Further, intense insulin therapy is associated with weight gain, increased blood pressure, and LDL-cholesterol, negatively increasing cardiovascular risk. In addition, obesity is a progressive disorder among T1DM patients, with an estimated incidence of about 50% in developed countries [2]. Notably, the risk of hypoglycemia becomes apparent once the HbA1c approaches optimal levels. Therefore, adding an oral hyperglycemic agent can be a reasonable option to improve glycemic control and reduce the risk of late diabetic complications, especially cardiovascular disease [4].

**Activity of Sodium-glucose co-transporter:** Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are oral antidiabetic agents that reduce renal glucose reabsorption and induce glucosuria [5]. SGLT-2 is the primary transporter in the kidney, responsible for almost 97% of the transport across the luminal membrane, where SGLT1 is responsible for 3% [6]. Recent clinical trials approved the cardiovascular safety of SGLT2i and cardiovascular protection, such as decreased hospitalization for heart failure in diabetic people atherosclerotic complications [5]. However, SGLT1 is found predominantly in the small intestine for glucose absorption, where

missense mutation in SGLT1 resulted in glucose intolerance, obesity, and cardiometabolic risk [7].

Sotagliflozin, a novel, first-in-class dual SGLT1, and SGLT2 inhibitor (SGLTi), glucose reduction through the gut and the kidneys. The additional effect of sotagliflozin provides incremental benefits over selective SGLT2i by preventing post-prandial glycemic excursions and glycemic variability, reducing bolus insulin correction, and, significantly, reducing hypoglycemic events. Additionally, glucose availability in the distal small intestine stimulates glucagon-like peptide-1 (GLP-1), resulting in enhanced weight loss and counteracted glucagon-induced ketogenesis [7].

Moreover, SGLT1 is expressed in the salivary glands, liver, lung, skeletal muscle, heart, pancreatic alpha cells, and brain, but their effect in these tissues is unknown [8]. Their combined inhibition leads to blunting and delaying glucose absorption from the gastrointestinal system and reducing the glucose reabsorption, respectively [8-9]. Additionally, sotagliflozin is 20-time more selective for SGLT2 compared to SGLT1 [8].

**The additional effect of SGLTi with insulin in people with T1DM:** Gaining weight could be the adverse outcome of long-term insulin monotherapy in T1DM, which may progress to microvascular and macrovascular diabetic complications. Consequently, the addition of pharmacological therapy to insulin regimen in T1DM patients started to gain some interest in the clinical research field. Further, SGLT2i alone was found to be effective in addition to insulin regimens in T1DM. In addition, osmotic diuresis and natriuresis lead to weight loss, which indirectly affects and improves blood pressure [9].

In regards to the SGLTi, sotagliflozin was tested in three large phases 3 randomized clinical trials in the inTandem clinical program that evaluated the efficacy and safety of sotagliflozin in addition to insulin therapy for T1DM treatment. As a result, sotagliflozin initiation leads to a 30% reduction in mealtime insulin at the first meal. Moreover, a reduction in the total daily dose of insulin and bolus insulin dose was noticed after sotagliflozin initiation. Adverse outcomes, like

hypoglycemia, were similar in the sotagliflozin group and placebo group. Nevertheless, the use of sotagliflozin was associated with an increased risk of DKA and genital mycotic infections. In addition, it was associated with diarrheal illnesses and volume depletion [10].

Further clinical trials confirm the clinical efficacy of adding sotagliflozin to insulin therapy, including reducing HbA1c, insulin dose, hypoglycemic attacks, and potential decrease in blood pressure and body weight. Therefore, the cardioprotective effect of SGLT2i in people with T2DM might hopefully be similar in people with T1DM. Importantly, the long-term effect of T1DM on the cardiovascular system should be considered more than T2DM. Likewise, DKA was marginally higher with sotagliflozin than dapagliflozin [11]. In the inTandem1 and inTandem2 trials, the addition of sotagliflozin 200 or 400mg once daily to insulin therapy showed a significant reduction in HbA1c compared to placebo [12].

In the inTandem3 trial, a 400mg/day sotagliflozin daily reduces HbA1c by 0.46%, weight loss around 3kg, and systolic blood pressure was 3.5mmHg in the sotagliflozin group compared to placebo [12-13]. The trial achieved HbA1c <7% without reported severe hypoglycemia or DKA at week 24 weeks in randomized patients to a 400mg of sotagliflozin compared to placebo, which is the primary endpoint [13-14]. Similarly, the addition of sotagliflozin to insulin therapy reduced total bolus and basal insulin doses [12]. The primary endpoint was successfully achieved mainly in the sotagliflozin group (28.6%) compared to the placebo group (15.2%) [15]. However, more frequent volume depletion, diarrhea, or genital infection were reported in the sotagliflozin group [13-14].

In a meta-analysis comparing SGLT2i to placebo, the conclusion favored adding SGLT2i to insulin therapy due to the beneficial effects, such as better glycemic control, weight loss, lower insulin dosage, without the risk of hypoglycemia. Nonetheless, this combination should be used with caution and proper education and counseling due to the increased risk of DKA and genital infection [16]. Moreover, in Thomas Danne et al. analysis, adding sotagliflozin to insulin therapy resulted in lower hypoglycemia events than the placebo group. Both 200 and 400mg of sotagliflozin were related to a substantially lower incidence of hypoglycemic attacks than placebo [17].

## 2. SAFETY CONSIDERATION

Overall, SGLT2 alone is considered to be a safe agent regarding hypoglycemia due to the counteracting effect of reduced HbA1c and body weight due to improved chronic balance [18]. Further, SGLT2i use might increase the risk of amputations, fractures, and diabetic ketoacidosis, despite being rare [19]. Multiple case reports have correlated SGLT2i to increased risk of DKA, which led to the Food Drug Administration (FDA) warning in May 2015 [20]. The relative risk of DKA induced by SGLT2i was 2.81, with 95% CI, reported in Giovanni Musso et al. meta-analysis [21]. The adverse outcomes of sotagliflozin were generally similar to the reported outcomes with SGLT2i in type 2 diabetes mellitus, including genital mycotic infection and DKA [22].

## 3. CONCLUSION

Controlling blood glucose in type 1 diabetes mellitus is the main factor in controlling micro and macrovascular complications, particularly cardiovascular disease. Therefore, the additional effect of SGLT2 or a combination of SGLT1 and SGLT2 inhibitors to insulin therapy gains a lot of interest in medical research. Adding SGLT2 inhibitors resulted in decreased insulin requirement, which leads to bodyweight control and subsequently reduces insulin resistance, which is the main factor for cardiovascular disease. Further, the SGLT2 inhibitor beneficial effect was noticed to be with no increased risk of hypoglycemia. However, certain adverse outcomes should be dealt with cautiously, including increased risk of diabetic ketoacidosis and genital infection.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Naciu AM, Pozzilli P. Novel blood glucose lowering therapies for managing type 1

- diabetes in paediatric patients. *Expert Opin Pharmacother.* 2018;19(4):355-364. DOI:10.1080/14656566.2018.1441288. Epub 2018 Feb 20. PMID: 29460641.
2. Frandsen CS, Dejgaard TF, Madsbad S, Holst JJ. Non-insulin pharmacological therapies for treating type 1 diabetes. *Expert Opin Pharmacother.* 2018;19(9):947-960. DOI: 10.1080/14656566.2018.1483339. PMID: 29991320.
  3. Lunder M, Janić M, Japelj M, Juretič A, Janež A, Šabovič M. Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. *Cardiovasc Diabetol.* 2018;17(1):153. DOI: 10.1186/s12933-018-0797-6. PMID: 30509271; PMCID: PMC6276165.
  4. Livingstone R, Boyle JG, Petrie JR; Removal Study Team. A new perspective on metformin therapy in type 1 diabetes. *Diabetologia.* 2017;60(9):1594-1600. DOI: 10.1007/s00125-017-4364-6. Epub 2017 Aug 2. PMID: 28770327; PMCID: PMC5552844.
  5. Kumar K, Kheiri B, Simpson TF, Osman M, Rahmouni H. Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Clinical Trials. *Am J Med.* 2020;133(11):e625-e630. DOI: 10.1016/j.amjmed.2020.04.006. Epub 2020 May 7. PMID: 32389659.
  6. Libianto R, Ekinci EI. New Agents for the Treatment of Type 2 Diabetes. *Crit Care Clin.* 2019;35(2):315-328. DOI: 10.1016/j.ccc.2018.11.007. Epub 2019 Jan 23. PMID: 30784612.
  7. Musso G, Gambino R, Cassader M, Paschetta E. Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ.* 2019;365:l1328. DOI: 10.1136/bmj.l1328. PMID: 30967375; PMCID: PMC6454301.
  8. Chatzopoulos G, Tziomalos K. An up-to-date evaluation of sotagliflozin for the treatment of type 1 diabetes. *Expert Opin Pharmacother.* 2020;21(15):1799-1803. DOI: 10.1080/14656566.2020.1793961. Epub 2020 Oct 27. PMID: 33108240.
  9. Rao L, Ren C, Luo S, Huang C, Li X. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: Meta-analysis of randomized controlled trials. *Acta Diabetol.* 2021;58(7):869-880. DOI: 10.1007/s00592-021-01686-x. Epub 2021 Mar 2. PMID: 33651228; PMCID: PMC8187227.
  10. Boeder S, Edelman SV. Sodium-glucose co-transporter inhibitors as adjunctive treatment to insulin in type 1 diabetes: A review of randomized controlled trials. *Diabetes Obes Metab.* 2019;21 Suppl 2(Suppl 2):62-77. DOI: 10.1111/dom.13749. PMID: 31081593; PMCID: PMC6899736.
  11. Ferrannini E, Solini A. Therapy: SGLT inhibition in T1DM - definite benefit with manageable risk. *Nat Rev Endocrinol.* 2017;13(12):698-699. DOI: 10.1038/nrendo.2017.139. Epub 2017 Oct 27. PMID: 29076505.
  12. Akturk HK, Rewers A, Garg SK. SGLT inhibition: a possible adjunctive treatment for type 1 diabetes. *Curr Opin Endocrinol Diabetes Obes.* 2018;25(4):246-250. DOI: 10.1097/MED.0000000000000423. PMID: 29794497.
  13. Patel K, Carbone A. Sodium-Glucose Cotransporters as Potential Therapeutic Targets in Patients With Type 1 Diabetes Mellitus: An Update on Phase 3 Clinical Trial Data. *Ann Pharmacother.* 2019;53(12):1227-1237. DOI: 10.1177/1060028019859323. Epub 2019 Jun 21. PMID: 31226886.
  14. Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, Pozzilli P, Gesty-Palmer D, Lapuerta P, Simó R, Danne T, McGuire DK, Kushner JA, Peters A, Strumph P. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. *N Engl J Med.* 2017;377(24):2337-2348. DOI: 10.1056/NEJMoa1708337. Epub 2017 Sep 13. PMID: 28899222.
  15. Rendell MS. Efficacy and safety of sotagliflozin in treating diabetes type 1. *Expert Opin Pharmacother.* 2018;19(3):307-315. DOI:10.1080/14656566.2017.1414801. Epub 2017 Dec 29. PMID: 29212386.
  16. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: Systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2018;20(7):1755-1761. DOI: 10.1111/dom.13260. Epub 2018 Mar 25. PMID: 29451721.

17. Danne T, Pettus J, Giaccari A, Cariou B, Rodbard H, Weinzimer SA, Bonnemaire M, Sawhney S, Stewart J, Wang S, Castro RC, Garg SK. Sotagliflozin Added to Optimized Insulin Therapy Leads to Lower Rates of Clinically Relevant Hypoglycemic Events at Any HbA1c at 52 Weeks in Adults with Type 1 Diabetes. *Diabetes Technol Ther.* 2019;21(9):471-477. DOI: 10.1089/dia.2019.0157. PMID: 31335194; PMCID: PMC6708262.
18. Secrest MH, Udell JA, Filion KB. The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. *Trends in Cardiovascular Medicine. Trends in Cardiovascular Medicine.* 2017;27(3):194–202.
19. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2019;393(10166): 31-39. DOI: 10.1016/S0140-6736(18)32590-X. Epub 2018 Nov 10. Erratum in: *Lancet.* 2019;393(10166):30. PMID: 30424892.
20. Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. *N Engl J Med.* 2017; 376(23):2300-2302. DOI: 10.1056/NEJMc1701990. PMID: 28591538.
21. Musso G, Sircana A, Saba F, Cassader M, Gambino R. Assessing the risk of ketoacidosis due to sodium-glucose cotransporter (SGLT)-2 inhibitors in patients with type 1 diabetes: A meta-analysis and meta-regression. *PLoS Med.* 2020;17(12):e1003461. DOI:10.1371/journal.pmed.1003461. PMID: 33373368; PMCID: PMC7771708.
22. Peters AL, McGuire DK, Danne T, Kushner JA, Rodbard HW, Dhatariya K, Sawhney S, Banks P, Jiang W, Davies MJ, Lapuerta P. Diabetic Ketoacidosis and Related Events With Sotagliflozin Added to Insulin in Adults With Type 1 Diabetes: A Pooled Analysis of the inTandem 1 and 2 Studies. *Diabetes Care.* 2020;43(11):2713-2720. DOI: 10.2337/dc20-0924. Epub 2020 Sep 14. PMID: 32928957; PMCID: PMC7576419.

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