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## The potent synergistic effects of the combination of liraglutide and canagliflozin on glycemic control and weight loss

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDEF **David S.H. Bell**

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**Patient:** Male, 57  
**Final Diagnosis:** Diabetes mellitus type 2  
**Symptoms:** Weight loss  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Endocrinology and Metabolic

**Objective:** Unusual or unexpected effect of treatment





**Background:** Studies of the efficacy of the combination of the incretin mimetic liraglutide and the SGLT2 inhibitor canagliflozin or indeed studies of the combination of any incretin mimetic with an SGLT2 inhibitor have neither been performed nor published. Pharmacologically, the combination of an incretin-mimetic and an SGLT2-receptor blocker should result in a more significant weight loss and a greater reduction in postprandial glucose and HbA1c.

**Case Report:** An insulin-dependent type 2 diabetic patient with multiple diabetic complications was placed on the combination of liraglutide and canagliflozin and 4 weeks later was able to discontinue insulin. In addition, in spite of discontinuing insulin, his HbA1c dropped from 7.0% to 6.8%, and he had reductions in body (weight from 247 to 218 lbs), BMI (from 34 to 29.5 Kg/m<sup>2</sup>), waist circumference (from 47 to 44 ½ inches), and neck circumference (from 19 ½ to 18 ¼ inches).

**Conclusions:** The combination of an SGLT2 inhibitor and an incretin mimetic/analog results in improved glycemic control accompanied by significant weight loss. This combination needs to be studied in a prospective randomized trial because the effect of each of the components of this combination is synergistically magnified by the addition of the partner drug.

**MeSH Keywords:** Diabetes Mellitus, Type 2 • Incretins • Sodium-Glucose Transporter 2

**Full-text PDF:** <http://www.amjcaserep.com/download/index/idArt/890626>

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## Background

In choosing drugs to treat type 2 diabetes, those that cause hypoglycemia (insulin, sulfonylureas, and other secretagogues) are not a good initial choice due to the increased risk of coma, cardiac arrhythmias, and cardiac events that can occur with hypoglycemia [1]. In the obese, drugs that cause weight gain (secretagogues, insulin, and thiazolidinediones) should whenever possible be avoided and drugs that are weight neutral (DPP-4 inhibitors, metformin, and  $\alpha$ -glucosidase inhibitors) preferred [2]. Since the vast majority of type 2 diabetic patients are overweight, there is a need not only to avoid weight gain but to lower body weight, which will improve insulin sensitivity. Therefore, the use of drugs that have the potential to lower body weight (incretin mimetics and sodium-glucose transporter-2 [SGLT2] inhibitors) should, with metformin, be the preferred initial therapy in obese and overweight type 2 diabetic patients. To date, studies of the combination of incretin mimetics and SGLT2 inhibitors have not been performed.

To illustrate the need for these studies, I describe the effect of the combination of liraglutide (an incretin analog/mimetic) and canagliflozin (an SGLT2 inhibitor) in an obese patient with long-standing type 2 diabetes complicated by both microvascular and macrovascular complications and who prior to the initiation of these drugs needed to use twice daily mixed insulin to obtain glycemic control. In this patient the combination of liraglutide and canagliflozin not only maintained but also improved glycemic control due to very significant weight loss that improved insulin sensitivity to the point that the patient's remaining endogenous insulin was all that was required for effective insulin action and exogenous insulin injections were discontinued.

## Case Report

A 57-year-old white male had type 2 diabetes complicated by macular edema, cataracts, distal symmetrical polyneuropathy, autonomic neuropathy, hypertension, and ischemic heart disease for at least 17 years. Nine years after diagnosis, because of poor glycemic control (partially due to an inability to tolerate metformin), he was started on twice daily premixed 70/30 insulin aspart in combination with a sulfonylurea, which was later replaced by the DPP4 inhibitor (sitagliptin). Prior to commencing insulin therapy, he weighed 210 lbs (BMI 29 Kg/m<sup>2</sup>) and with insulin his weight increased to 247 lbs (BMI 34 Kg/m<sup>2</sup>).

After an initial assessment, sitagliptin was replaced by the more powerful liraglutide, which was given subcutaneously and slowly increased from 0.6 to 1.8 mg per day. He was also started on canagliflozin 100 mg daily for 1 week, after which the canagliflozin was increased to 300 mg daily. His total

insulin dose, which was initially 0.6 units per Kg, was initially decreased to 0.4 units/Kg, and after 2 weeks was changed to 0.2 units/Kg twice daily in divided doses. Four weeks after starting the combination of canagliflozin and liraglutide, he was able to discontinue insulin.

With maximization of liraglutide and canagliflozin therapy over the following 3 months, his HbA1c, in spite of the removal of exogenous insulin, dropped from 7.0% to 6.8%, and he had reductions in body weight (from 247 to 218 lbs), BMI (from 34 to 29.5 Kg/m<sup>2</sup>), waist circumference (from 47 to 44 ½ inches), and neck circumference (from 19 ½ to 18 ¼ inches).

## Discussion

Improved glycemic control utilizing sulfonylureas and/or insulin will almost invariably result in weight gain [1,2]. One reason for this weight gain is a decrease in urinary glucose excretion, which leads to a net gain in calories. In addition, in type 2 diabetes, through an increase in SGLT2 activity, renal reabsorption of glucose increases [3]. SGLT2 receptor blockers, through increasing glucose excretion, not only result in better glycemic control, but also, through renal calorie loss, lead to a reduction in body weight, and through an osmotic diuresis, a decrease in blood pressure [4].

The renal threshold for glucose excretion in type 2 diabetes, through increased SGLT2 activity, is elevated to a serum glucose level of around 250 mg/dl. SGLT2 inhibitors reduce this threshold to no lower than 70 mg/dl, which is why hypoglycemia rarely if ever occurs with these drugs [5]. However, as the renal threshold for glucose excretion is decreasing, there is a compensatory release of glucagon from the alpha cells in the pancreatic islets, which stimulates hepatic glucose production, which in turn elevates serum glucose, partially negating the SGLT-2 blocker effect [6]. Therefore, used in combination with a SGLT-2 inhibitor, a medication that suppresses hepatic glucose production (metformin) or a medication that suppresses glucagon release (DPP4 inhibitors or incretin mimetics) should complement the overall effect of an SGLT2-inhibitor and maximally lower serum glucose levels. Lowering hepatic glucose production is best achieved with an incretin mimetic, which is more effective than DPP4 inhibitors in elevating GLP1 levels and lowering glucagon level and is more effective than metformin in lowering hepatic glucose production [6].

Liraglutide has a greater effect on weight loss than canagliflozin. By stimulating GLP1 receptors in the mid-brain and hypothalamus, liraglutide has an anorectic effect that is complemented by the GLP-1 effects of decreasing gastric emptying, leading to early satiety and decreased food intake [7]. Canagliflozin lowers body weight through renal glucose excretion and calorie

loss. Thus, through the additive effects of liraglutide and canagliflozin, the body weight in this patient decreased by 11.8%, which resulted in increased insulin sensitivity, which in turn lowered the need for exogenous insulin therapy, which was eventually discontinued.

I have therefore described a patient in whom the combination of an SGLT-2 inhibitor and a GLP-1 agonist/analogue resulted in better glycemic control was accompanied very significant weight loss.

To show that this patient is not an “outlier” and matches my overall clinical experience with this combination, I initiated a

chart audit and found 15 patients who were utilizing this combination. In this group there was an average decrease in the HbA1c from 9.1% to 7.3% and an average decrease in body weight from 249 lbs to 237 lbs.

## Conclusions

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This very recently available highly potent combination of an SGLT-2 receptor blocker and an incretin analog urgently needs to be studied in a prospective randomized trial. I hope the publication of this case report will initiate such a trial.

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