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Treatment of Type 2 Diabetes with Sodium-Glucose Co-Transporter 2 Inhibitors plus Glucagon-Like Peptide-1 Receptor Agonists

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Abstract

Background: The 2 drug classes of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors are approved for type 2 diabetes, but their concomitant use was not sufficiently studied.

Aim: To assess the safety and efficacy of the combination of GLP-1RAs and SGLT2 inhibitors in type 2 diabetes.

Methods: Systematic review of English literature by search of electronic databases: Pub/MEDLINE from 2000 until July 27, 2020. Search terms included GLP-1 receptor agonists, SGLT2 inhibitors, combination therapy, add-on therapy, type 2 diabetes, efficacy, safety. Randomized trials were included with more focus on double-blind, placebo-controlled trials. Post-hoc analysis and consensus guidelines are also reviewed.

Results: One randomized trial evaluated the co-initiation of weekly exenatide plus dapagliflozin in patients with type 2 diabetes uncontrolled on metformin. After 52 weeks, the reduction in glycated hemoglobin (HbA1c) levels with the combination therapy was less than additive being 1.75%, 1.36%, and 1.23% with weekly exenatide + dapagliflozin, weekly exenatide + placebo and dapagliflozin + placebo, respectively. Two randomized trials evaluated the sequential addition of GLP-1 RA to ongoing SGLT2 inhibitor therapy. Both trials reported greater HbA1c reduction averaging 0.8-1.4% compared with SGLT2 inhibitor + placebo. The combination of GLP-1 RA + SGLT2 inhibitor caused significant weight loss of approximately 3.3 kg, which was slightly less than additive, and 4.5 mmHg reduction in systolic blood pressure (SBP), which was more than additive. In general, the adverse effects of combination therapy were expected, with no emergence of unusual adverse effects. The least tolerated combination included semaglutide due to relatively high rates of gastrointestinal adverse events and mild hypoglycemia.

Conclusion: Combination therapy of GLP-1 RA plus SGLT2 inhibitor is overall effective and safe. Further studies are needed to examine the effects of this combination on cardiovascular (CV), renal and mortality outcomes.

Keywords: Glucagon-like peptide-1 receptor agonist; SGLT-2 inhibitor; Combination; Efficacy; Safety

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Introduction

Large randomized clinical trials have shown that many drugs pertaining to the 2 drug classes of GLP-1 RAs and SGLT2 inhibitors decrease cardio-renal events and mortality in patients with type 2 diabetes. It is reasonable therefore to assume that the use of agents from these 2 classes in combination could further decrease such events. The author here reviews the few randomized trials that examined the short-term efficacy and safety of GLP-1 RA/SGLT2 inhibitor combination. The results of such trials are generally encouraging and suggest that this drug combination results in further reductions in HbA1c levels, weight, and SBP.

These data should pave the way for well-designed long-term trials to examine the incidence of CV, renal and mortality outcomes using this drug combination compared with monotherapy.

The rationale of using a combination of a GLP-1RA plus SGLT-2 inhibitor relies on many factors. First, these 2 classes of drugs have different mechanisms of actions. Thus, GLP-1 RAs stimulates insulin secretion, decrease glucagon secretion, slow gastric emptying, and promotes early satiety, whereas SGLT2 inhibitors increase urinary glucose excretion [1,2]. Second, both drug classes are associated with minimal risk of hypoglycemia [1,2]. Third, and most importantly, several drugs in both classes were shown in well-designed clinical trials to reduce CV and renal events and mortality in patients with type 2 diabetes and atherosclerotic vascular and renal diseases [3-6]. Unfortunately, data regarding the GLP-1RA/SGLT-2 inhibitor combination is limited.

Literature Review

The main purpose of this article is to review clinical trials that evaluate the efficacy and safety of the use of GLP-1RA plus SGLT-2 inhibitor in patients with type 2 diabetes.

Results from randomized double-blind, placebo-controlled trials

There are 3 randomized trials specifically designed to examine the efficacy and safety of the combination of GLP-1 RAs and SGLT2 inhibitors [7-9]. In the DURATION-8 trial, the authors evaluated the simultaneous addition of drugs from both classes, whereas in the AWARD-10 and SUSTAIN-9 trials, the investigators used a sequential approach. Overview of these trials are presented below and summarized in **Table 1** [7-9].

Simultaneous addition of GLP-1 RAs and SGLT2 inhibitor

In the DURATION-8 trial, Jabbour and colleagues randomized patients with type 2 diabetes uncontrolled on metformin (mean baseline HbA1c 9.3%) to 3 drug regimens: weekly exenatide 2 mg subcutaneously plus once daily dapagliflozin 10 mg, exenatide + oral placebo, and dapagliflozin plus injected placebo [7]. After 52 weeks, mean reductions in HbA1c levels were -1.75%, -1.38%, and -1.23%, respectively [7]. Although the reduction in HbA1c values was statistically significant in the combination group compared with the other 2 groups, the decrease in HbA1c values was clearly less than additive.

Sequential addition of GLP-1 RAS to ongoing SGLT2 inhibitors

In the AWARD-10 trial, Ludvik et al. evaluated the GLP-1 RA, dulaglutide, in 2 doses 1.5 mg sc once weekly and 0.75 mg sc once weekly versus placebo as add-on therapy to ongoing SGLT2 inhibitors [8]. After 24 weeks, the reductions in mean HbA1c levels were 1.34%, 1.21%, and 0.54% in patients randomized to dulaglutide 1.5 mg, 0.75 mg, and placebo, respectively; (P < 0.0001 for both dulaglutide groups vs placebo) [8].

In the SUSTAIN 9 trial, Zinman et al. evaluated another GLP-1 receptor agonist, semaglutide 1.0 mg sc once weekly, vs placebo [9]. After 30 weeks, the decreases in mean HbA1c values were 1.5% and 0.1% in the semaglutide and placebo group, respectively; P < 0.0001 vs placebo [9].

Sequential addition of SGLT2 inhibitors to ongoing therapy with GLP-1 RAs

Limited data from Japanese non-placebo, controlled studies examined the addition of the SGLT2 inhibitors: empagliflozin, canagliflozin and luseogliflozin to ongoing therapy with GLP-1 RA liraglutide 0.9 mg sc qday, the maximum approved dose in Japan [10-12]. These 3 studies showed further reduction in mean HbA1c levels (approximately 0.7%), weight (2.7-3.3 kg), and SBP (7.9-8.4 mmHg) 52 weeks after the addition of SGLT2 inhibitors [10-12]. The previous combination therapy was well tolerated with no safety concerns [10-12].

Effect on weight

The GLP-1 RA/SGLT2 inhibitor combination, whether given simultaneously or sequentially, is associated with weight loss. The magnitude of weight loss is slightly less than additive [8]. The latter finding is expected since mechanisms of weight loss are different between the 2 drug classes. Thus, GLP-1 agonists delay gastric emptying and promote early satiety, whereas weight reduction with use of SGLT2 inhibitors is mainly attributed to caloric loss secondary to glycosuria [1,2]. Using bioelectrical impedance analysis, Seino at al. investigated patterns of weight loss in 21 Japanese patients with type 2 diabetes 52 weeks after addition of the SGLT2 inhibitor luseogliflozin to ongoing liraglutide treatment [12]. They found that weight loss was mostly due to loss of fat mass (2.49 kg), whereas reduction in lean mass was minimal (0.44 kg) [12]. Likewise, in a small group of Swedish 25 obese subjects (mean weight 106.4 kg) without diabetes, Lundkvist at al. reported a mean weight loss of 5.7 kg after 52 weeks of administration of dapagliflozin 10 mg/d + weekly exenatide 2 mg sc. By using magnetic resonant imaging, they found that most of this weight loss was due to loss of adipose tissue (5.31 L), and to a lesser extent lean tissue (1.36 L) [13].

Effect on blood pressure

The addition of GLP-1 RA to SGLT2 inhibitors in simultaneous or sequential manner consistently exerts further reduction in SBP [7-12]. Unlike reduction in HbA1c levels, this reduction in SBP was more than additive [7]. On the other hand, no significant difference in diastolic blood pressure was reported in most trials between monotherapy and combination therapy [7-9].

Effects on other intermediate outcomes

Changes in lipid panel are minor with combination therapy compared with monotherapy. Combination therapy is associated with mild reduction in plasma triglycerides levels (10-12% lower than monotherapy) [6,9]. In SUSTAIN-9 trial, levels of low-density lipoprotein cholesterol (LDL-C) are 10% lower in the combination group formed of semaglutide + SGLT2 inhibitor than in the group receiving SGLT2 inhibitor monotherapy, but no inter-group

Table 1 Overview of randomized trials of DLP-1 receptor agonist plus SGLT2 inhibitor.

Trial	Duration-8 [7]	Award-10 [8]	Sustain 9 [9]
Design	Double-blind, placebo- 2 wks	Double-blind, placebo-controlled, 3 groups, 24 wks	Double-blind, placebo-controlled 2 groups, 30 wks
Patient number, age, % of women	N = 695, 54 years, 52%	N = 423, 57 years, 50%	N = 302, 57 years, 42%
HbA1c at baseline	9.3%	8.04%	8.0%
Background diabetes therapy	Metformin (100%)	Metformin (95%) + *SGLT2 inhibitor (100%)	Metformin (71%), sulfonylurea (13%) + SGLT2 inhibitor (100%)
Intervention	Exenatide 2 mg sc /wk + dapagliflozin 10 mg/d, exenatide + oral placebo, dapagliflozin + injected placebo.	Dulaglutide 1.5 mg sc/wk, dulaglutide 0.75 mg/wk, placebo.	Semaglutide 1 mg sc/wk *vs.* placebo
Change in HbA1c	-1.75% with Exenatide + dapagliflozin, -1.38% with exenatide, -1.23% with dapagliflozin. P significant between Exenatide + dapagliflozin *vs.* exenatide or *vs.* dapagliflozin	-1.34% with dulaglutide 1.5 mg, -1.21% with dulaglutide 0.75 mg, and -0.54% with placebo. P significant between dulaglutide 1.5 mg and 0.75 mg *vs.* placebo	-1.5% with semaglutide *vs.* –0.1% with placebo (P<0.0001)
Proportions of patients with HbA1c <6.5% at the end of study	26.3% with exenatide + dapagliflozin, 17.2%, exenatide + placebo, and 8.7%, with dapagliflozin + placebo	50% with dulaglutide 1.5 mg, 38% with dulaglutide 0.75 mg and 14% with placebo	56% with semaglutide and 4% with placebo
Change in weight (kg)	-3.31 with exenatide + dapagliflozin, -1.51 with exenatide, -2.28 with dapagliflozin. P significant between exenatide + dapagliflozin *vs.* exenatide, but nonsignificant *vs.* dapagliflozin	-3.1 with dulaglutide 1.5 mg, -2.6 with dulaglutide 0.75 mg, -2.1 with placebo. P significant between dulaglutide 1.5 mg *vs.* placebo	-4.7 kg with semaglutide *vs.* -0.9 with placebo (P<0.0001)
Change in systolic blood pressure (mmHg)	-4.5 with exenatide + dapagliflozin, -0.7 with exenatide, -2.7 with dapagliflozin. P significant between exenatide + dapagliflozin *vs.* exenatide, but nonsignificant *vs.* dapagliflozin	-4.5 with dulaglutide 1.5 mg, -3.2 with dulaglutide 0.75 mg, -1.4 with placebo. P significant between dulaglutide 1.5 mg *vs.* placebo	-4.7 with semaglutide *vs.* + 1.6 with placebo (P<0.0001).
Hypoglycemia	**Minor hypoglycemia 1.3% with exenatide + dapagliflozin, 0.4% with dapagliflozin, 0% with exenatide	Blood glucose < 70 mg/dl in 4% with dulaglutide 1.5 mg, 4% with dulaglutide 0.75 mg, and 3% with placebo.	11.3% with semaglutide *vs.* 2.0% with placebo. Severe hypoglycemia: 2.7% with semaglutide, 0% with placebo (P value not reported)
Gastrointestinal adverse effects	17.7% with exenatide + dapagliflozin, 19.6% with exenatide + placebo, and 14.2% with dapagliflozin + placebo.	32.0% with dulaglutide 1.5 mg, 21.0% with dulaglutide 0.75 mg, and 17.0% with placebo	37.2% in semaglutide group and 13.2% in placebo group
Genital infections	4.8% with exenatide + dapagliflozin, 1.7% with exenatide + placebo, and 5.2% with dapagliflozin + placebo	Not reported	Not reported
Withdrawal due to adverse effects	4.3% with exenatide + dapagliflozin, 5.2% with exenatide + placebo, 3.4% with dapagliflozin + placebo	3% with dulaglutide 1.5 mg, 0% with dulaglutide 0.75 mg, and 0% with placebo	8.7% with semaglutide *vs.* 2.0% with placebo (P value not reported).

Note: Data are means.
* Most common SGLT2 inhibitors are empagliflozin 10 mg/d, and dapagliflozin 10 mg/d
**Minor hypoglycemia defined as blood glucose < 54 mg/dl, and no loss of consciousness

changes were reported with respect to high-density lipoprotein cholesterol (HDL-C) [9].

Post-hoc analysis of the DURATION-8 study showed that the combination of exenatide once weekly plus dapagliflozin showed stronger effects on markers of liver steatosis and fibrosis compared with each drug alone after 28 weeks of treatment [14].

SGLT2 inhibitors are known to enhance ketosis and increase serum ketones leading uncommonly to development of diabetic ketoacidosis [15]. Interestingly, the addition of exenatide once weekly to dapagliflozin abolished the dapagliflozin-induced rise in serum ketones. Meanwhile, the addition of exenatide maintained beneficial effects of dapagliflozin such as glycosuria and increase hematocrit after 52 weeks of treatment [16].

Effects on CV outcomes and mortality

Clinical trials designed to evaluate the effects of the combination of GLP-1 RAs and SGLT2 inhibitors on CV, renal and mortality outcomes are lacking. However, the available limited data suggest that this combination might reduce CV events. Thus, in the DURATION-8 trial, adjudicated CV events were reported in 1 (0.4%), 3 (1.3%), and 3 patients (1.3%) randomized to exenatide + dapagliflozin, exenatide + placebo, and dapagliflozin + placebo, respectively after 52 weeks [7]. In addition, post hoc sub-

Table 2 Advantages and limitations of treatment of type 2 diabetes.

Advantages	Limitations
Greater HbA1c reduction compared with each class alone	No data is available regarding effects of the combination on cardio-renal outcomes and mortality
Weight loss and reduction in systolic blood pressure appear to be additive with combination therapy	Increased cost
No increase in hypoglycemia risk overall, except when using semaglutide [9].	Increase treatment burden
	Unknown drug interaction between the 2 classes

group analysis of the EXSCEL, a large CV trial, showed nominally significant reduction in risk of all-cause mortality among patients who received combination of weekly exenatide plus a SGLT2 inhibitor as compared with placebo (hazard ratio 0.38, 95% CI 0.16-0.90), or with weekly exenatide alone (hazard ratio 0.41, 95% CI 0.17-0.95) [17]. Rates of CV death showed similar direction [17]. Moreover, the previous drug combination was more effective than placebo or weekly exenatide alone in slowing progression of diabetic nephropathy as reflected by the improvement in slope of estimated glomerular filtration rate (eGFR) [17]. Although these preliminary results are encouraging, they have to be confirmed by dedicated randomized trials.

Safety of the combination of GLP-1 RA plus SGLT2 inhibitor

The combination of SGLT2 inhibitors and GLP-1 RAs are generally well-tolerated, with no evidence of emergence of unexpected adverse effects or safety signals. The least tolerated combination includes semaglutide, as reflected by the relatively high discontinuation rates due to adverse effects **(Table 2).** The most common adverse effects occurring after the addition of GLP-1 RAs to SGLT2 inhibitors are gastrointestinal, mainly nausea and diarrhea, generally described as mild to moderate in intensity **(Table 1).** However, 6.7% of semaglutide-treated patients discontinued treatment prematurely due to gastrointestinal adverse effects compared to none in the placebo group [9]. Incidence of hypoglycemia was minimally increased with addition of exenatide or dulaglutide to SGLT2 inhibitors **(Table 2)** [7,8]. Yet, risk of hypoglycemia was substantially increased with the addition of semaglutide to SGLT2 inhibitors [9]. In fact, 17 patients (11.3%) randomized to semaglutide reported hypoglycemia compared with 3 patients (2.0%) receiving placebo [9]. Severe or blood glucose-confirmed hypoglycemia < 55.8 mg/dl occurred in 4 patients (2.7%) in the semaglutide group and in none in the placebo group [9]. Diabetic ketoacidosis, an uncommon adverse effect of SGLT2 inhibitors, was not reported so far with the use of the agents with GLP-1 RAs.

Discussion and Conclusion

The combination of GLP-1 RA/SGLT2 inhibitor represents a promising approach for treatment of type 2 diabetes. However, this approach is not without limitations. The concomitant use of this combination provides significant reduction in HbA1c levels, body weight and SBP beyond that achieved by monotherapy alone. Hence, the best candidate for this combination would be a patient with type 2 diabetes uncontrolled on metformin who suffers from weight gain and/or hypertension. Recently, the American Diabetes Association (ADA) and the European Association for the study of diabetes (EASD) recommended using the combination therapy of SGLT2 inhibitor + GLP-1 RA in a subgroup of patients with type 2 diabetes. This subgroup consists of patients with suboptimal glycemic control on monotherapy and has established atherosclerotic CV disease, heart failure or chronic kidney disease. In the meantime, both Associations admitted lack of evidence for the latter recommendation from randomized clinical trials. Such trials are urgently needed to evaluate the effects of the GLP-1 RA/SGLT2 inhibitor combination on cardio-renal outcomes and mortality, to determine the optimum drug combination, and characterize patients likely to derive most of the benefit from this combination. In addition, any possible interaction between the 2 drug classes that might emerge with long-term follow should be carefully studied.

Conflict of Interest

The author has no conflict of interest to declare.

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