Combination Therapy With Canagliflozin Plus Liraglutide Exerts Additive Effect on Weight Loss, but Not on HbA_{1c}, in Patients With Type 2 Diabetes

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OBJECTIVE

To examine the effect of combination therapy with canagliflozin plus liraglutide on HbA_{1c}, endogenous glucose production (EGP), and body weight versus each therapy alone.

RESEARCH DESIGN AND METHODS

Forty-five patients with poorly controlled (HbA_{1c} 7–11%) type 2 diabetes mellitus (T2DM) on metformin with or without sulfonylurea received a 9-h measurement of EGP with [3-^{3}H]glucose infusion, after which they were randomized to receive *1*) liraglutide 1.2 mg/day (LIRA), *2*) canagliflozin 100 mg/day (CANA), or *3*) liraglutide 1.2 mg plus canagliflozin 100 mg (CANA/LIRA) for 16 weeks. At 16 weeks, the EGP measurement was repeated.

RESULTS

The mean decrease from baseline to 16 weeks in HbA_{1c} was −1.67 ± 0.29% (P = 0.0001), −0.89 ± 0.24% (P = 0.002), and −1.44 ± 0.39% (P = 0.004) in patients receiving CANA/LIRA, CANA, and LIRA, respectively. The decrease in body weight was −6.0 ± 0.8 kg (P < 0.0001), −3.5 ± 0.5 kg (P < 0.0001), and −1.9 ± 0.8 kg (P = 0.03), respectively. CANA monotherapy caused a 9% increase in basal rate of EGP (P < 0.05), which was accompanied by a 50% increase (P < 0.05) in plasma glucagon-to-insulin ratio. LIRA monotherapy reduced plasma glucagon concentration and inhibited EGP. In CANA/LIRA-treated patients, EGP increased by 15% (P < 0.05), even though the plasma insulin response was maintained at baseline and the CANA-induced rise in plasma glucagon concentration was blocked.

CONCLUSIONS

These results demonstrate that liraglutide failed to block the increase in EGP caused by canagliflozin despite blocking the rise in plasma glucagon and preventing the decrease in plasma insulin concentration caused by canagliflozin. The failure of liraglutide to prevent the increase in EGP caused by canagliflozin explains the lack of additive effect of these two agents on HbA_{1c}.

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Sodium–glucose cotransporter 2 inhibitors (SGLT2is) lower plasma glucose concentration in patients with type 2 diabetes mellitus (T2DM) by inhibiting renal glucose reabsorption and producing glucosuria (1,2). We (3) and others (4) previously have shown that the administration of SGLT2is in patients with T2DM causes a "paradoxical" increase in endogenous glucose production (EGP), which was accompanied by a small but significant decrease in the fasting plasma insulin concentration and an increase in plasma glucagon concentration. Thus, the ratio of plasma glucagon to insulin concentration was markedly increased by 50–100%. The increase in EGP following SGLT2i administration has important clinical implications since it returns to the circulation an amount of glucose that equals ~40–50% of the amount of glucose that is lost in the urine (3), ameliorating the decrease in HbA_{1c} caused by SGLT2is. Because of the important role of insulin and glucagon in the regulation of EGP (5,6), we hypothesized that the increase in plasma glucagon-to-insulin ratio, at least in part, contributes to the increase in EGP caused by SGLT2is, and preventing the increase in EGP following SGLT2i administration would amplify the decrease in HbA_{1c} caused by the drug.

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) inhibit glucagon secretion and enhance glucose-stimulated insulin secretion (7,8). We, therefore, hypothesized that administration of a GLP-1 RA in combination with an SGLT2i in patients with T2DM would stimulate insulin secretion and inhibit glucagon secretion, thus preventing the increase in plasma glucagon-to-insulin ratio and the increase in EGP caused by SGLT2is and amplifying the decrease in plasma glucose concentration. We recently reported that acute administration of liraglutide plus canagliflozin, though it prevents the change in plasma insulin and glucagon concentration caused by canagliflozin, failed to prevent the increase in EGP (9). The aim of the current study was to examine the long-term effect of treatment with the combination of liraglutide plus canagliflozin versus each therapy alone on EGP and HbA_{1c} in patients with T2DM.

RESEARCH DESIGN AND METHODS

Patients

Forty-five patients with T2DM participated in the study. Except for diabetes, all patients were in good general health on the basis of their medical history, physical examination, blood chemistries, CBC, thyroid function, urinalysis, and electrocardiogram. Patients had stable (±1.5 kg) body weight in the 3 months before the study, and none participated in any excessively heavy exercise programs. Patients were drug naive ($n = 6$) or on a stable dose of metformin with or without a sulfonylurea ($n = 39$) (Supplementary Table 1). Patients with evidence of proliferative diabetic retinopathy, serum creatinine >1.4 mg/dL (females) or >1.5 mg/dL (males), or estimated glomerular filtration rate <60 mL/min/1.73 m^2 were excluded. The study was approved by the University of Texas Health Science Center at San Antonio institutional review board, and informed written consent was obtained from all participants before the study.

Experimental Design

All studies were performed at the Texas Diabetes Institute Clinical Research Center (CRC) at 6:00 A.M. after a 10-h overnight fast. Eligible patients received three 9-h measurements of EGP with [3-^{3}H]glucose infusion. In the first study, EGP was measured before any drug administration, which served as the pretreatment study. Seven to 14 days after completing the pretreatment study, participants reported to the CRC for a second EGP measurement, referred to as the start of treatment study. During the second study, after a 3-h tracer equilibration period (see below), participants were randomized to receive *1*) a single dose of 100 mg canagliflozin (CANA), *2*) a single subcutaneous injection of 1.2 mg liraglutide (LIRA), or *3*) 100 mg canagliflozin plus 1.2 mg liraglutide (CANA/LIRA). All drugs were given at time 0 min (i.e., 180 min after the priming/tracer infusion was begun). After completion of this study, participants continued to receive the same treatment that was administered during the second EGP measurement. At week 2, the canagliflozin dose was increased to 300 mg/day and liraglutide to 1.8 mg/day and maintained unchanged until week 16. At the end of the 16-week treatment period, the EGP measurement was repeated. This posttreatment measurement was identical to that described in the second EGP measurement.

The primary outcome of the study was the effect of each therapy on the change from baseline to week 16 in fasting EGP. Secondary outcomes were the change from baseline to week 16 in HbA_{1c} and body weight.

The results of the acute effect of canagliflozin and/or liraglutide on EGP and plasma hormone concentration (i.e., second EGP measurement) in the first 36 patients recruited into the study have previously been reported (9). Since then, an additional 9 patients were enrolled, and all 45 participants completed the 16-week treatment period. In the present publication, we report the results of the long-term (16-week) effect of canagliflozin plus liraglutide versus each agent alone in all 45 participants on EGP, plasma hormone concentrations, HbA_{1c}, and body weight.

Measurement of EGP

Participants reported to the CRC at 6:00 A.M., a catheter was placed into an antecubital vein, and a prime (40 μCi × fasting plasma glucose [FPG] / 100)-continuous (0.4 μCi/min) infusion of [3-^{3}H]glucose was started and continued until 3:00 P.M. At 8:00 A.M., a second catheter was inserted retrogradely into a vein on the dorsum of the hand, which was placed in a heated box (70°C) for sampling of arterialized blood. After 3 h of tracer equilibration, arterialized blood samples were drawn at −30, −20, −15, −10, −5, and 0 (time 0 = drug administration) minutes. At 9:00 A.M. (time 0), plasma samples were obtained every 20 min for 360 min for determination of plasma glucose, insulin, and glucagon concentrations and [3-^{3}H]glucose-specific activity. At 6:00 A.M., participants voided, and the urine was discarded. Urine was collected from 6:00 A.M. to 9:00 A.M. and from 9:00 A.M. to 3:00 P.M. Urinary volume and glucose concentration were measured to determine urinary glucose excretion (UGE). At 3:00 P.M., participants received a meal and returned home.

Treatment Period and Follow-Up Visits

After completing the second EGP measurement, participants continued to receive the treatment that was started during the EGP treatment for 16 weeks. The study intervention (CANA, LIRA, or CANA/LIRA) was added to the baseline therapy, which was continued without change throughout the entire treatment period. During the 16-week treatment period, participants were seen every

2 weeks during the first 8 weeks and every 4 weeks thereafter. Medical history, physical examination, body weight, FPG, and HbA_{1c} were measured during each follow-up visit. At 16 weeks, the EGP measurement was repeated as described above; the treatment drug was administered at time 0 during the repeat EGP measurement.

Analytical Methods

Plasma glucose was measured using the glucose oxidase method (International Point of Care, Toronto, Ontario, Canada); plasma insulin (IBL America, Minneapolis, MN) and C-peptide (MP Biomedicals, Santa Ana, CA) were measured with immunoradiometric assays. Plasma glucagon (MilliporeSigma, Burlington, MA) was measured by radioimmunoassay, with a coefficient of variation <5% and cross-reactivity with other peptides (e.g., oxyntomodulin) <0.1%.

Data Analysis

EGP was calculated as previously described (3,7). Under steady-state postabsorptive conditions, the basal endogenous glucose R_a equals the [3-^{3}H]glucose infusion rate divided by steady-state plasma tritiated glucose–specific activity. After drug administration, non–steady-state conditions for [3-^{3}H]glucose-specific activity prevail, and the total body glucose R_a is calculated using the Steele equation. The change from baseline to 16 weeks in each parameter (e.g., EGP, HbA_{1c}, and body weight) was tested in each group using a paired *t* test. Differences between the two studies (EGP measured in the pretreatment and treatment studies) and changes in HbA_{1c} and BMI were compared among the three treatment groups with ANCOVA. Post hoc testing was done with the Bonferroni correction. Similar comparisons were made for the change in plasma insulin and glucagon concentrations during each study and for the change from baseline to 16 weeks. Simple Pearson correlation was used to assess the relationship between continuous variables. All values are presented as mean ± SEM, except for patient characteristics, which are presented as mean ± SD. $P < 0.05$ was considered statistically significant.

Power Calculation

The primary outcome of the study was the effect of therapy on EGP at the fasting states at 16 weeks. In previous study, the change in the fasting EGP from baseline to 2 weeks was 0.36 ± 0.31. We computed that 15 completers would provide 80% power to detect a similar increase in EGP at week 16 at $P < 0.025$.

RESULTS

Baseline patient characteristics of the three treatment groups are presented in Supplementary Table 1. Patients were well-matched for age, sex, BMI, diabetes duration, and baseline HbA_{1c}. After 16 weeks of treatment, CANA and CANA/LIRA caused an increase in UGE to 92 ± 9 and 87 ± 9 g/24 h, respectively ($P <$ 0.0001 for both). No increase in UGE was observed in participants receiving LIRA (0.3 ± 0.2 g/24 h, *P* not significant).

All three treatments improved glucose control and reduced the HbA_{1c}. The decrease from baseline to 16 weeks in mean HbA_{1c} was −1.67 ± 0.29% ($P =$ 0.0001), −0.89 ± 0.24% ($P = 0.002$), and −1.44 ± 0.39% ($P = 0.004$) for CANA/LIRA, CANA, and LIRA, respectively. Figure 1*A* depicts the time course of the decrease in HbA_{1c} caused by the three treatments over the 16-week treatment period. The decrease in HbA_{1c} with CANA/LIRA was greater than with CAN alone ($P = 0.05$) but did not differ from that with LIRA alone.

All three treatments caused significant weight loss. The decrease in body weight was −6.0 ± 0.8 kg ($P <$ 0.0001), −3.5 ± 0.5 kg ($P <$ 0.0001), and −1.9 ± 0.8 kg ($P = 0.03$) in participants receiving CANA/LIRA, CANA, and LIRA, respectively. Unlike the decrease in HbA_{1c}, the decrease in body weight caused by combination therapy with CANA/LIRA was additive and significantly greater than that caused by CANA alone ($P = 0.01$) and LIRA alone ($P = 0.002$) (Fig. 1*B*).

Likewise, both CANA and LIRA reduced blood pressure, and CANA/LIRA caused additive reduction in systolic blood pressure. The decrease in systolic blood pressure at week 16 was −5.2 ± 2.2 mmHg ($P = 0.005$), 5.1 ± 3.8 mmHg ($P < 0.05$), and −14.1 ± 3.0 mmHg ($P <$ 0.0001) for CANA, LIRA, and CANA/LIRA, respectively. Further, the decrease in systolic blood pressure caused by CANA/LIRA was significantly greater ($P = 0.03$) than that cause by CANA and LIRA monotherapy. Similarly, all three therapies reduced diastolic blood pressure. However, the decrease in diastolic blood pressure cause by CANA/LIRA was not significantly greater than each agent alone ($P = 0.11$). Participants in the LIRA and CANA/LRA groups experienced a small increase in heart rate (3 beats), with no change in heart rate in those receiving CANA alone.

Effect of Therapy on FPG and EGP

FPG concentration is an important determinant of the HbA_{1c}, and FPG is influenced highly by basal hepatic glucose production (bHGP) (5). To understand the mechanisms responsible for the lack of additive effect of CANA/LIRA on HbA_{1c} despite very distinct mechanisms of action, we measured both the FPG and the basal EGP (bEGP) before the start and at the end of each therapy at 16 weeks (Fig. 2).

All three treatments significantly lowered FPG (Fig. 3*A* and Supplementary Fig. 1). The decrease in FPG from baseline to 16 weeks was −57 ± 11 mg/dL ($P <$ 0.0001), −48 ± 7 mg/dL ($P <$ 0.0001), and −36 ± 10 mg/dL ($P <$ 0.001) in participants receiving CANA/LIRA, CANA,

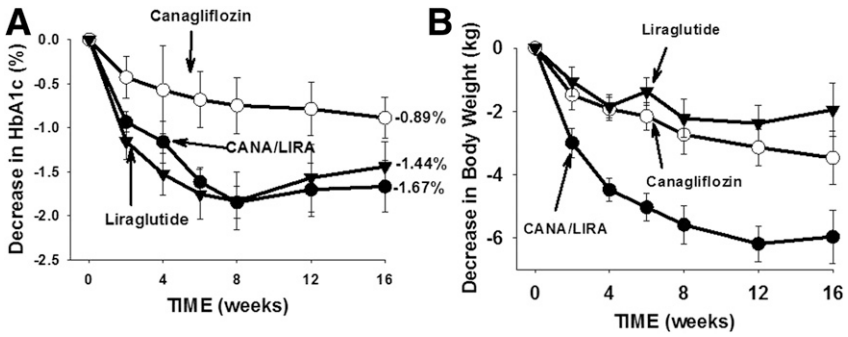

Figure 1—Effect of CANA alone, LIRA alone, and combined CANA/LIRA treatment on the decrease in HbA_{1c} (*A*) and on the decrease in body weight (*B*).

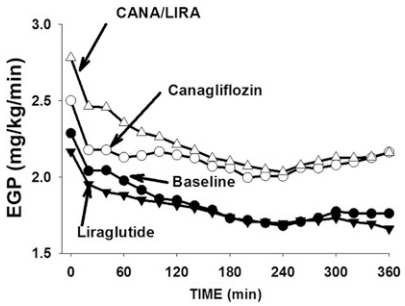

Figure 2—Effect of CANA alone, LIRA alone, and combined CANA/LIRA treatment on the bEGP.

and LIRA, respectively, with no significant difference among the three treatments (*P* not significant by ANOVA).

Since bHGP is the primary determinant of FPG (5) and since we previously have shown that SGLT2is cause a paradoxical increase in the basal rate of EGP (3), we measured bEGP before the start and at the end (16 weeks) of therapy. Consistent with previous studies (3,4), the decrease in the FPG concentration at 16 weeks caused by CANA (Supplementary Fig. 2) was associated with a small but significant increase in bEGP from 2.29 ± 0.07 to 2.50 ± 0.15 mg/kg/min (3.59 ± 0.21 to 3.90 ± 0.17 mg/kg$_{\text{free-fat mass [FFM]}}$/min, $P = 0.05$) (Fig. 3*B*), which was associated with a small but significant decrease in fasting plasma insulin concentration (14.9 ± 1.6 to 12.0 ± 1.6 μU/mL, $P = 0.01$) and 21% increase in fasting plasma glucagon concentration (56 ± 6 to 68 ± 6 ng/mL, $P = 0.01$) (Fig. 4*A* and *B*). Thus, the ratio of plasma glucagon concentration to insulin concentration increased by 50% in participants receiving CANA therapy after 16 weeks (4.7 ± 0.8 to 7.1 ± 1.0, $P = 0.002$) (Fig. 4*C*).

Unlike CANA, the reduction in FPG concentration after 16 weeks of LIRA treatment was associated with a small (8%) decrease in the rate of bEGP (2.36 ± 0.08 to 2.17 ± 0.11 mg/kg/min, $P = 0.02$) (3.42 ± 0.18 to 3.32 ± 0.17 mg/kg$_{\text{FFM}}$/min, *P* not significant) (Fig. 3*B*). During the bEGP measurement following 16 weeks of LIRA treatment, there was a small, nonsignificant decrease in fasting plasma glucagon concentration (76–69 pg/mL, *P* not significant) (Fig. 4*B*) and a small, nonsignificant increase in fasting plasma insulin concentration (20–22 μU/mL, *P* not significant) (Fig. 4*A*). Thus, liraglutide monotherapy for 16 weeks caused a small, nonsignificant decrease in the glucagon-to-insulin ratio (4.6–3.7, *P* not significant) (Fig. 4*C*).

The fasting plasma insulin (18.4 vs. 17.7 μU/mL) and fasting plasma glucagon (72 vs. 77 ng/mL) concentrations remained unchanged in participants receiving CANA/LIRA for 16 weeks. Thus, the plasma glucagon-to-insulin ratio remained unaltered (4.1 vs. 4.4) (Fig. 4). Nonetheless, CANA/LIRA was associated with a robust 16% increase in bEGP (2.40 ± 0.14 to 2.78 ± 0.16 mg/kg/min) (3.85 ±

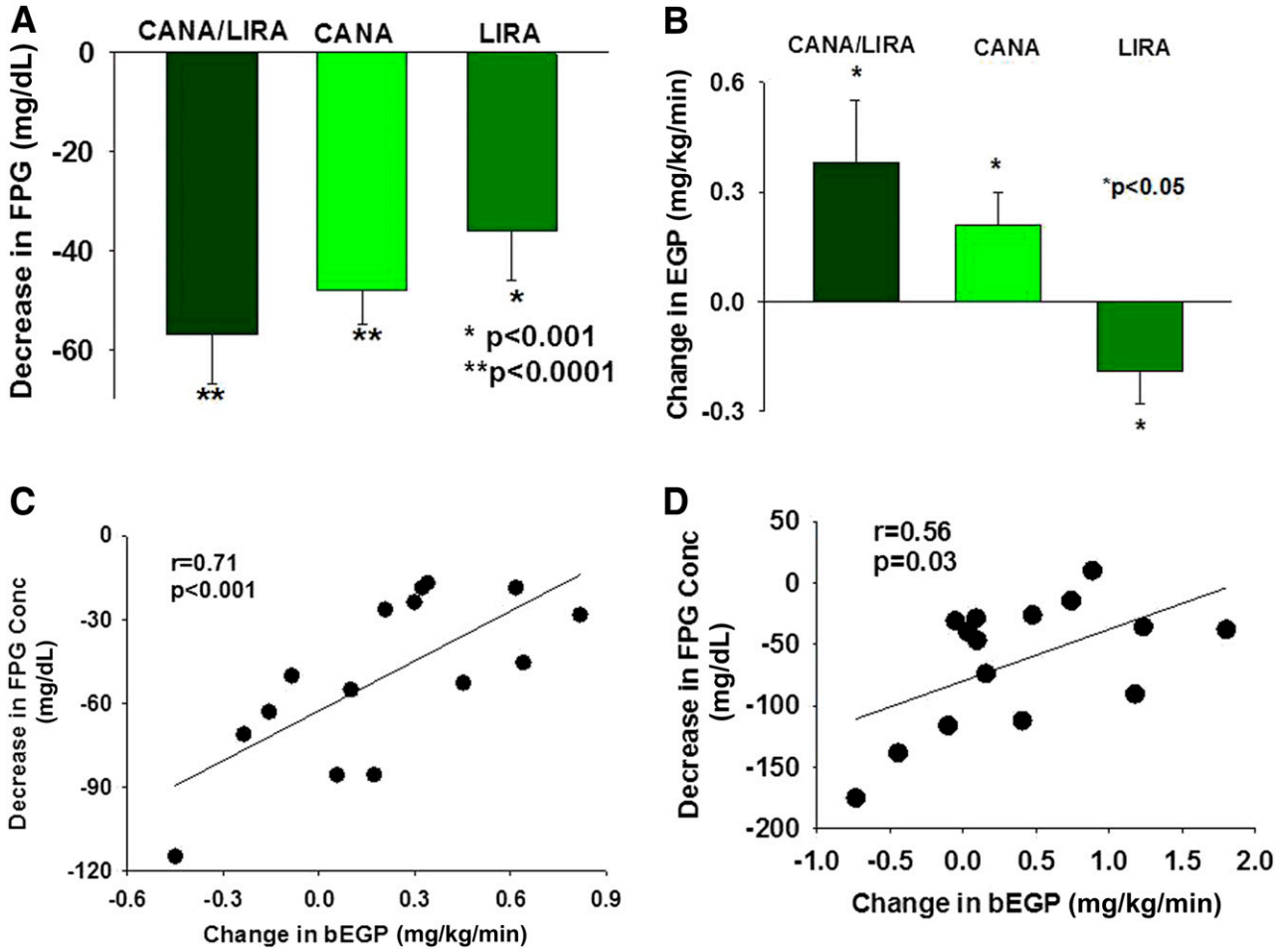

Figure 3—The decrease in FPG (*A*) and change in bEGP (*B*) caused by CANA alone, LIRA alone, and combined CANA/LIRA treatment. The relationship between the decrease in FPG and change in bEGP in participants receiving CANA alone (*C*) and CANA/LIRA (*D*). Conc, concentration.

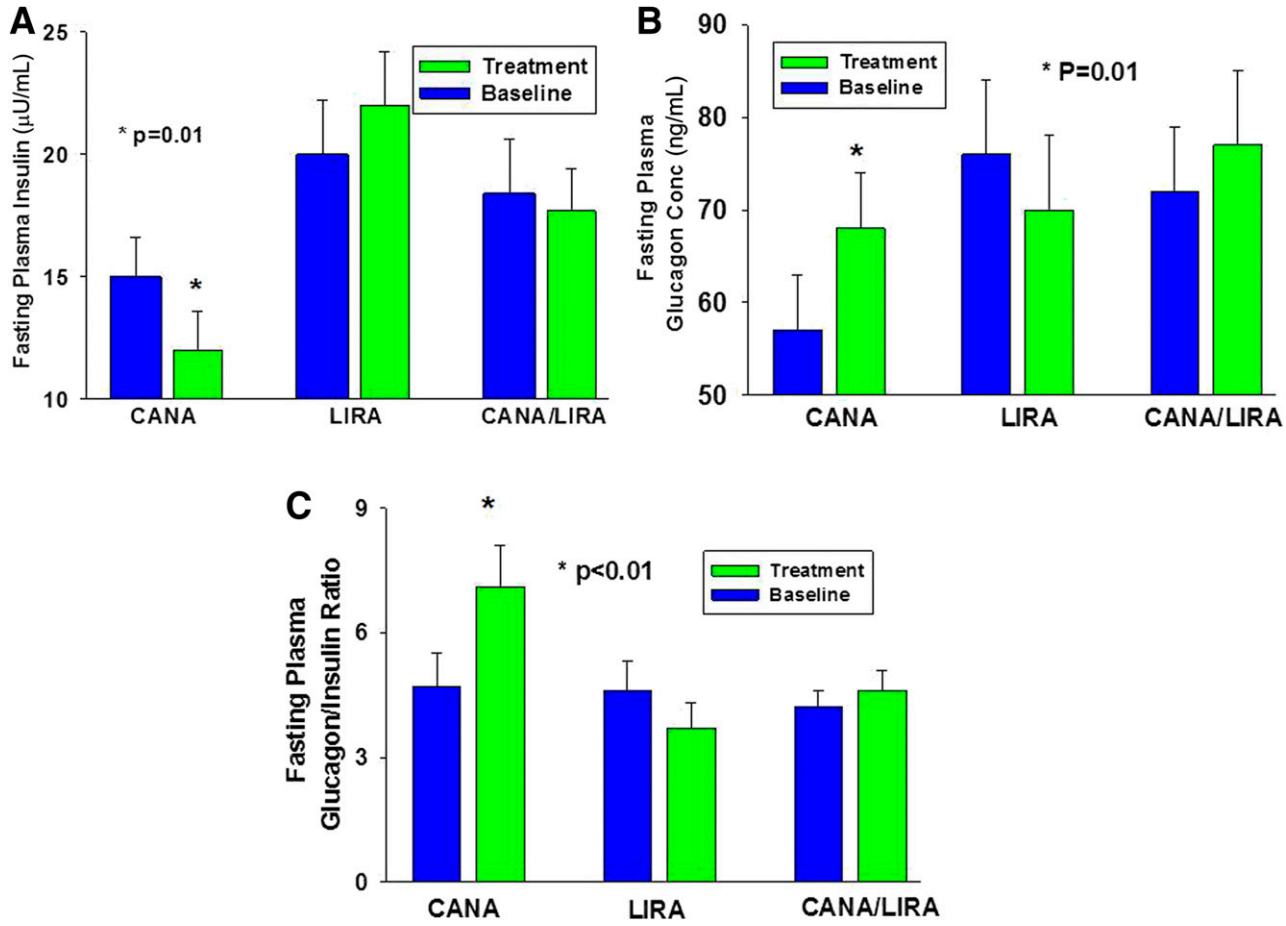

Figure 4—The change in the fasting plasma insulin (*A*) and fasting plasma glucagon (*B*) concentrations and the fasting plasma glucagon-to-insulin ratio (*C*) in participants receiving CANA alone, LIRA alone, and combined CANA/LIRA therapy. Conc, concentration.

0.18 to 4.48 ± 0.29 mg/kg_{FFM}/min, $P < 0.01$) (Fig. 3*B*). The increase in EGP caused by CANA/LIRA (0.38 ± 0.17 mg/kg/min) treatment was not statistically significant than that caused by CANA alone (0.21 ± 0.09 mg/kg/min) ($P = 0.42$). However, it was highly significant compared with that caused by LIRA alone (−0.19 ± 0.11 mg/kg/min) ($P = 0.002$).

Relationship Between UGE and Increase in EGP and Decrease in FPG

The mean increase in the bEGP in participants receiving CANA alone after 16 weeks was 0.21 mg/kg/min. This increase in EGP returns to the systemic circulation 35 g of glucose over 24 h, which is equivalent to ∼40% of the amount of glucose lost in the urine in participants receiving CANA alone. Further, the change in EGP caused by CANA at 16 weeks significantly correlated with the amount of glucose lost in the urine (Supplementary Fig. 3), and this relationship between the increase in EGP and UGE was not affected by LIRA (Supplementary Fig. 3).

The change in EGP caused by CANA at week 16 significantly correlated ($r = 0.71$, $P < 0.001$) with the decrease in FPG at 16 weeks (Fig. 3*C*) (i.e., the greater was the increase in EGP caused by CANA, the smaller was the decrease in FPG concentration). The correlation between the increase in bEGP and decrease in FPG was slightly attenuated in participants receiving CANA/LIRA but remained significant ($r = 0.56$, $P = 0.03$) (Fig. 3*D*). The correlation between the increase in bEGP and decrease in HbA_{1c} did not reach statistical significance ($r = 0.35$, $P = 0.09$).

CONCLUSIONS

The current study has several novel findings. First, despite very different mechanisms of action, the combination of GLP-1 RA plus SGLT2i does not produce an additive reduction in FPG concentration or HbA_{1c} in patients with T2DM. The decrease in both the FPG concentration and the HbA_{1c} at week 16 produced by combined liraglutide and canagliflozin therapy was not additive compared with each agent alone. Although the reduction in HbA_{1c} caused by canagliflozin plus liraglutide was significantly greater than that caused by canagliflozin alone (−0.89 vs. −1.67%, $P = 0.05$), it did not differ from that produced by liraglutide alone (−1.44%). Further, the clinical significance of the reduction in HbA_{1c} caused by combination therapy versus liraglutide alone is questionable (1.67 vs. 1.44%). These results are consistent with other studies that have examined the effect of combination therapy with incretin-based therapies (i.e., GLP-1 RAs, dipeptidyl peptidase 4 inhibitors) plus SGLT2is. In DURATION-8 (10), once-weekly exenatide plus dapagliflozin caused a 2.0% reduction in HbA_{1c} compared with a 1.6% reduction caused by exenatide monotherapy. The higher baseline HbA_{1c} in DURATION-8 (9.3%) compared with the current study

(8.2%) most likely explains the slightly greater absolute reduction in HbA_{1c} in DURATION-8. However, EGP and plasma glucagon concentration were not measured in the study. Combination therapy with dapagliflozin plus saxagliptin added to poorly controlled, metformin-treated patients with T2DM blocked the increase in plasma glucagon concentration caused by dapagliflozin (11). However, single-dose coadministration of dapagliflozin plus saxagliptin failed to prevent the increase in plasma glucagon concentration (12). Although EGP was not measured in these studies, the combination of saxagliptin plus dapagliflozin failed to produce an additive effect on HbA_{1c} (13). The decrease in HbA_{1c} produced by dapagliflozin plus saxagliptin was 1.44% compared with a 1.2% reduction produced by dapagliflozin monotherapy (13). Collectively, these results are consistent with those of the current study and suggest that combination therapy with incretin-based therapy plus an SGLT2i prevents the increase in plasma glucagon concentration but fails to produce an additive reduction in HbA_{1c}.

Second, the opposing actions of SGLT2is and GLP-1 RAs on EGP can explain the lack of additive benefit of these two classes of antidiabetic agents on glucose control in patients with T2DM. Liraglutide caused a small decrease (8%) in bEGP, which did not reach statistical significance when expressed per FFM, whereas canagliflozin caused a significant 9.2% increase in bEGP. Because of the important role of bEGP in determining the FPG concentration (5), the decrease in bEGP caused by liraglutide could contribute to the decrease in FPG and HbA_{1c}.

Conversely, the decrease in the FPG caused by canagliflozin was accompanied by a paradoxical increase in EGP, and the increase in EGP produced by canagliflozin was significant whether EGP was expressed per body weight or per FFM. These results are consistent with the previously described stimulatory effect of other members of the SGLT2i class (dapagliflozin and empagliflozin) on EGP reported by us (2) and others (3). Further, the strong correlation between the increase in bHGP and decrease in FPG (Fig. 3*C* and *D*) in canagliflozin-treated participants emphasizes the clinical importance of this observation and demonstrates that the glucose returned to the systemic circulation by the increase in bEGP attenuates the decrease in the FPG concentration caused by this drug class. The failure of liraglutide to block the increase in bEGP caused by canagliflozin could contribute to the lack of additive effect of SGLT2is and GLP-1 RAs on FPG and HbA_{1c}.

Although the magnitude of increase in EGP caused by liraglutide plus canagliflozin (0.38 $\pm$ 0.17 mg/kg/min) was numerically greater than that caused by canagliflozin alone (0.21 $\pm$ 0.09 mg/kg/min), the difference between the two did not reach statistical significance ($P = 0.42$). Biologic variation in canagliflozin action in patients with T2DM most likely contributed to this small, nonstatistically significant difference. Conversely, the increase in EGP caused by liraglutide plus canagliflozin was highly statistically different than that caused by liraglutide alone ($P = 0.002$), suggesting that the stimulatory action of canagliflozin on EGP overcomes that of liraglutide and emphasizes the clinical importance of blocking the increase in EGP caused by SGLT2is.

Similar to previous studies (2,3), the increase in EGP caused by canagliflozin was accompanied by a small decrease in plasma insulin concentration and a modest increase in plasma glucagon concentration. Thus, the ratio between plasma glucagon and insulin was markedly increased by ~50% with canagliflozin (Fig. 4). Liraglutide failed to prevent the increase in EGP caused by canagliflozin. The increase in bEGP at 16 weeks in participants who received combination therapy with liraglutide plus canagliflozin was even greater than that caused by canagliflozin alone (16 vs. 9.2%), although the decline in plasma insulin concentration was prevented and the rise in plasma glucagon concentration blocked.

Neither plasma free fatty acids (FFAs) nor ketones were measured in the current study, and we are unaware of studies in T2DM where the ability of liraglutide (or other GLP-1 RAs) to block the SGLT2i-induced rise in plasma FFAs or ketones was examined. In patients with type 1 diabetes mellitus, acute liraglutide administration was shown to decrease both plasma FFA and ketone concentrations (14). However, when chronically liraglutide-treated patients with type 1 diabetes mellitus received dapagliflozin for 12 weeks, the SGLT2i-induced rise in plasma FFA and ketone was not blocked (15). It remains unknown, however, whether the addition of a GLP-1 RA to SGLT2i can inhibit the rise in plasma FFA and ketones observed in patients with T2DM.

Third, the results of the current study argue against an important role of pancreatic hormones (insulin and glucagon) in mediating the increase in bEGP caused by SGLT2is. We (3) and others (4) previously have shown that the increase in EGP caused by SGLT2is is associated with a small decrease in plasma insulin concentration and a large increase in plasma glucagon concentration. Thus, the ratio between plasma glucagon and insulin was markedly increased by SGLT2is. Because of the important role of both insulin and glucagon in the regulation of EGP (6), it has been hypothesized that the change in plasma insulin and glucagon concentration could explain the increase in EGP. However, similar to the acute administration of liraglutide plus canagliflozin (9), chronic (16-week) treatment with combined canagliflozin and liraglutide therapy failed to prevent the increase in EGP caused by canagliflozin. Thus, the results of the current study provide strong evidence against this hypothesis since combination therapy with canagliflozin plus liraglutide was associated with a robust increase in bEGP. These findings suggest that mechanisms other than the decrease in plasma insulin and increase in plasma glucagon concentration (e.g., renal nerves) play an important role in mediating the increase in EGP. It should be noted that the organ responsible for the increase in bEGP caused by SGLT2is never has been determined (kidney vs. liver) in man. Thus, it is possible that an increase in renal gluconeogenesis is responsible for the increase in EGP caused by SGLT2. A study in experimental animals has demonstrated that dapagliflozin treatment for 24 weeks enhances both hepatic and renal gluconeogenesis (16). Alternatively, it is possible that SGLT2is exert a direct action on the liver (e.g., off-target effect) to stimulate HGP.

Finally, liraglutide and canagliflozin produced an additive effect to reduce body weight and systolic blood pressure. Thus, the decrease in body weight at week 16 in participants treated with liraglutide plus canagliflozin was greater

than the sum of weight loss in participants receiving liraglutide alone or canagliflozin alone, as was the decrease in systolic blood pressure. This can be explained by the different and complementary mechanisms by which each agent promotes weight loss. Increased UGE is responsible for weight loss caused by SGLT2is, while appetite suppression and decreased energy intake primarily account for the weight loss with GLP-1 RAs. Of note, despite continuous urinary glucose loss during SGT2i treatment, body weight stabilizes at ~6 months after starting SGLT2i therapy (11,12). This suggests a "compensatory" increase in food intake caused by SGLT2is. Indeed, studies in experimental animals and in man have reported an increase in food intake following SGLT2i treatment (17,18). Although food intake was not measured in the current study, we hypothesize that liraglutide prevented the increase in food intake caused by long-term canagliflozin therapy. Therefore, participants receiving therapy with liraglutide plus canagliflozin continue to experience negative energy balance, leading to an additive or even synergistic reduction in body weight. The additive decrease in body weight caused by canagliflozin and liraglutide therapy could have contributed to the additive decrease in systolic blood pressure. These results are consistent with previous studies that have reported an additive effect of combined SGLT2i/GLP-1 RA therapy on weight loss in both patients with T2DM and patients with prediabetes (10,19,20). Similarly, combination therapy with canagliflozin plus phentermine, a centrally acting amine that stimulates satiety, produced an additive effect on weight loss (21). Collectively, these results support the hypothesis that the combination of SGLT2is plus agents that suppress appetite (e.g., GLP-1 RA, phentermine) produce an additive decrease in body weight compared with each agent alone.

One limitation of the current study is the lack of a placebo group to determine possible changes in EGP, HbA_{1c}, and body weight over the 16-week treatment period. Further, food intake and physical activity were not measured in the current study. Thus, a more controlled study with regard to energy balance is warranted to examine the impact of combination therapy with an SGLT2i plus GLP-1 RA on body weight. Participants in the current study were obese, with a mean BMI of ~34 kg/m^2. However, the increase in EGP caused by canagliflozin did not correlate with BMI ($r = 0.09$, P not significant). It will be of interest to examine whether the increase in EGP by SGLT2is is influenced by obesity.

In summary, the combination of liraglutide plus canagliflozin failed to prevent the increase in bEGP caused by canagliflozin and produced a markedly less-than-additive decrease in HbA_{1c}. However, this combination produced greater weight loss than each therapy alone. Although combination therapy with agents from these two classes of antidiabetic drugs did not exert an additive action on glucose control in the current study, they could be very beneficial in obese patients with T2DM with respect to weight loss and blood pressure.

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