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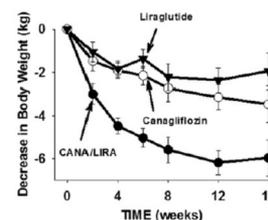
Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Combination of Liraglutide and Canagliflozin Reduces Weight in Type 2 Diabetes but Not HbA_{1c}

A combination of liraglutide and canagliflozin over 16 weeks appears to result in significant reductions in weight and blood pressure in individuals with type 2 diabetes, according to Ali et al. (p. 1234). At the same time, however, the combination failed to reduce HbA_{1c} more than liraglutide alone. The authors suggest that the results may further explain the effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors on glucose control in diabetes. The study included 45 individuals with poorly controlled type 2 diabetes who received either daily canagliflozin, liraglutide, or a combination of the two drugs over a study period of 16 weeks. Endogenous glucose production was determined prior to the study and also at the end via a glucose tracer method. The mean decrease in HbA_{1c} with the combination over 16 weeks was ~1.67%. This compared to decreases of ~1.44% with liraglutide alone and ~0.89% with canagliflozin alone. In terms of weight, the decrease with the combination reached ~6.0 kg after 16 weeks, ~3.5 kg with canagliflozin, and ~1.9 kg with liraglutide. The authors noted similar patterns of reduction in systolic and diastolic blood pressure. They also found that canagliflozin alone did result in increased endogenous glucose production and that there was an increase in the glucagon/insulin ratio as well. Liraglutide alone resulted in a decrease in glucagon concentrations and inhibited endogenous glucose production. The combination, meanwhile, still resulted in an increase in endogenous glucose production, while insulin levels remained at baseline and the expected rise in glucagon due to the canagliflozin was blocked. Commenting more widely, author Ralph DeFronzo told us: “These results provide strong evidence that neither glucagon nor insulin changes can explain the decrease in endogenous glucose production observed with SGLT2 inhibitors. Defining the mechanisms of this ‘paradoxical’ increase in endogenous glucose production is of great clinical importance since it would provide insight about how to employ combination therapy to maximize the reduction in HbA_{1c}.”



Effect of canagliflozin alone, liraglutide alone, and combined treatment (CANA/LIRA) on body weight over 16 weeks.

Ali et al. Combination therapy with canagliflozin plus liraglutide exerts additive effect on weight loss, but not on HbA_{1c}, in patients with type 2 diabetes. *Diabetes Care* 2020;43:1234–1241

Troponins Predict Mortality Risk in Older Individuals With Diabetes

High-sensitivity cardiac troponins are robustly associated with cardiovascular, respiratory, and other major outcomes in older individuals with diabetes, according to Tang et al. (p. 1200). Additionally, it appears that high-sensitivity cardiac troponin tests are predictive of mortality risks beyond traditional cardiovascular risk factors, which might mean they can be used to objectively measure mortality risk to more accurately guide clinical care of older adults with diabetes. These findings come from further analysis of the Atherosclerosis Risk in Communities (ARIC) Study that looked at the associations between two high-sensitivity cardiac troponins (I and T) and cardiovascular, renal, respiratory, mental, and physical comorbidities. The analysis covered 1,835 older individuals with diabetes. The authors found that elevations in either troponin were associated with various heart and renal outcomes, as well as pulmonary disease, hypoglycemia, hypertension, dementia, and frailty. They also found that over the ~6 years of follow-up, higher levels of either troponin allowed them to improve stratification of mortality risk beyond that achievable with comorbidities alone. In short, individuals with higher levels of troponin and comorbidities had the highest mortality risk. In addition, even individuals with a lower burden of comorbidities but raised troponin levels still had increased mortality risk. Individualizing treatment in older individuals beyond what is possible using only comorbidities is important according to the authors, because patient recall of medical history can be incomplete, particularly at an older age. They suggest that the objective nature of measuring troponins to assess mortality risk should help guide care and supplement the overall clinical impression of patients. Commenting more widely, author Elizabeth Selvin told us: “Our data add to the growing evidence that high-sensitivity cardiac troponin testing can be used to monitor risk. These tests may have particular value in diabetes populations to help guide decision-making, for example, prescribing of newer cardioprotective glucose-lowering medications.”

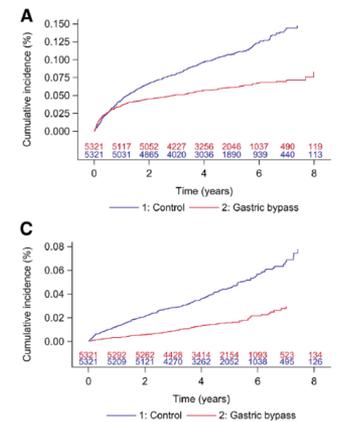
Tang et al. Performance of high-sensitivity cardiac troponin assays to reflect comorbidity burden and improve mortality risk stratification in older adults with diabetes. *Diabetes Care* 2020;43:1200–1208

Meaningful Weight Loss Linked to a Wide Range of Cardiorenal Risk Reduction in Diabetes and Obesity

Weight loss following gastric bypass surgery results in wide-ranging benefits in terms of numerous renal and cardiovascular outcomes in individuals with obesity and type 2 diabetes, according to Liakopoulos et al. (p. 1276). The findings come from a study that used linked data from a series of Swedish registries to identify 5,321 individuals with type 2 diabetes who had gastric bypass surgery and 5,321 matched control subjects who had not had surgery. The authors then looked at 15 different cardiorenal outcomes in the years following surgery. They found that in the first 2 years following surgery there were marked reductions in both BMI and HbA_{1c} as well as smaller reductions in creatinine and micro- and macroalbuminuria compared to the control group. Estimated glomerular filtration rate (eGFR) remained stable in the surgery group while it declined in the control group. Following surgery, 305 individuals went on to develop macroalbuminuria, compared with 575 individuals in the control group—a total risk reduction of 45%, according to the authors. In terms of incidence rates, all but 2 of the 15 cardiorenal outcomes registered significant risk reductions, with hazard ratios between 0.22 and 0.82. They also stratified according to eGFR and found that risks for most key outcomes were lower following surgery irrespective of strata, even among individuals with the very lowest eGFR. They conclude that the findings strongly support intentional weight loss (whether or not via surgery) as a strategy to prevent both renal and cardiac outcomes in people with diabetes and obesity, provided that meaningful weight reduction can be maintained. Commenting more widely, author Vasileios Liakopoulos told us: “Effective weight loss for people with obesity and type 2 diabetes has good effects on many hard outcome measures, and it is possible that many of these are mediated more via cardiorenal mechanisms rather than effects on atherosclerosis. This study strengthens obesity surgery as a method to achieve these effects and may also be considered in some people with renal impairment.”

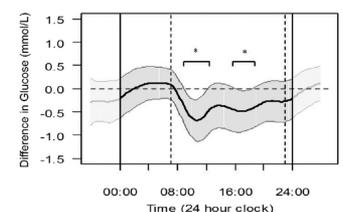
Continuous Glucose Monitoring Data Reveal Detailed Glucose Differences During Pregnancy in Type 1 Diabetes

Functional data analysis (FDA) applied to 24-h glucose profiles obtained by continuous glucose monitoring (CGM) can identify differences in glucose control that are often masked by summary statistics, according to Scott et al. (p. 1178). Using data from the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT), they examined daily glucose profiles in 200 pregnant women with type 1 diabetes who were randomly assigned to use CGM or self-monitoring of blood glucose. Data were collected at baseline (~12 weeks) and at 24 and 34 weeks of gestation. Just under half of the women included used insulin pumps, while just over half had large for gestational age (LGA) births. The authors found that CGM use resulted in significantly lower glucose levels for 7 h during the day compared with self-monitoring. Compared with women who used multiple daily injections of insulin, women who used insulin pumps had significantly higher glucose levels for 12 h per day at 24 weeks but no difference at 34 weeks. Women who had LGA births had higher glucose across gestation and for a majority of time in late gestation. Commenting further, author Eleanor Scott told us: “Much of the utility of CGM for an individual person with diabetes comes from seeing where changes in glucose occur across the 24-h day, and not the average glucose value, as it allows them to carefully direct the changes they make. It is important therefore not to lose this valuable information when analyzing population-level CGM data, as it gives insights into where differences in glucose temporally occur in relation to clinical outcomes. This allows us to understand what aspects of diabetes management need changing, to potentially improve these outcomes. In the case of this pregnancy study, it is behavior around managing mealtime glucose excursions. Whilst this study examines pregnancy outcomes, the technique of functional data analysis lends itself to the population-based study of CGM glucose in relation to any clinical outcomes.”



Cumulative incidence rates during 9 years of follow-up in control subjects (blue) and gastric bypass patients (red) of macroalbuminuria (A) and congestive heart failure (C).

Liakopoulos et al. Renal and cardiovascular outcomes after weight loss from gastric bypass surgery in type 2 diabetes: cardiorenal risk reductions exceed atherosclerotic benefits. *Diabetes Care* 2020;43:1276–1284



Differences in mean temporal glucose levels across 24 h, assessed by FDA. Dark wavy line indicates difference between CGM and self-monitoring of glucose (dotted straight line). Gray area is 95% CI.

Scott et al. Continuous glucose monitoring in pregnancy: importance of analyzing temporal profiles to understand clinical outcomes. *Diabetes Care* 2020;43:1178–1184