Title: Metformin slows intestinal glucose absorption in type 2 diabetes, irrespective of the timing of its administration

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Abstract:

Background
Standard practice is to ingest metformin, the first-line therapy for type 2 diabetes (T2D), with meals. However, in a recent study, we demonstrated that metformin, administered 30 or 60 min before a small intestinal glucose load, reduced the glycaemic excursion more than when given concurrently with glucose, associated with augmented glucagon-like peptide-1 (GLP-1) secretion[1]. The effects of metformin on postprandial GLP-1 secretion and glucose lowering may in part reflect its inhibition on intestinal glucose absorption[2]. We therefore retrospectively assessed the impact of varying the timing of metformin administration on intestinal glucose absorption in T2D.

Aim
To evaluate 1) the impact of varying the timing of metformin administration on the rate of glucose absorption in T2D and 2) the contribution of metformin-induced inhibition of glucose absorption on enhanced GLP-1 release with pre-meal administration of metformin.

Methods
16 participants with metformin-treated T2D (2 female, aged 69.9 $\pm$ 1.9 years, BMI 28.7 $\pm$ 1.0 kg/m^2, HbA1c 6.6 $\pm$ 0.1% / 48.2 $\pm$ 1.6 mmol/mol), were studied in a double-blinded, randomised, placebo-controlled, crossover design. On each study day, participants received metformin 1g via a nasoduodenal catheter at t = -60, -30 or 0 min or saline control, followed by an intraduodenal infusion of 45g glucose + 5g 3-O-methylglucose (3-OMG, a non-metabolised glucose analogue, used as a marker of intestinal glucose absorption) from t = 0 - 60 min. Serum 3-OMG concentrations were measured at t = 60, 90 and 120 min. Comparisons between treatments were made using two-factor repeated measures ANOVA with treatment and time as factors and post hoc comparisons adjusted by Bonferroni's correction. The analyses were performed using Prism 10.4 software (GraphPad, USA). A P value < 0.05 was considered statistically significant.

Results
After intraduodenal glucose administration, serum 3-OMG increased with peak levels at t = 90 min, followed by a modest decline at t = 120 min (time effect: P < 0.001 for all study days). There was a significant treatment effect (P = 0.012) as well as a treatment by time interaction (P = 0.008) for metformin on serum 3-OMG concentrations, which were lower than control at t = 90 min on all metformin days (P <0.05), and at t = 120 min when metformin was administered 30 min before the glucose infusion (P = 0.006). Furthermore, 3-OMG concentrations at t = 120 min were lower when metformin was administered 30 min, compared to 60 min, before intraduodenal glucose (P = 0.014). However, serum 3-OMG concentrations did not differ significantly between the three metformin study days[3].

Conclusion
Our findings suggest that metformin reduces the rate of intestinal glucose absorption in a manner unrelated to the timing of its administration and that the enhanced postprandial glucose-lowering and GLP-1 release associated with pre-meal metformin administration are unrelated to the rate of glucose absorption in T2D.

References:

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