Impact of metformin timing on glucose and GLP-1 response

Glucose-lowering effects in response to normal-release metformin are greater when the drug is given 30 or 60 minutes before, rather than with, food, according to this small study in people with well-controlled type 2 diabetes published in *Diabetologia*. Endogenous GLP-1 secretion increased when metformin 1000 mg was given 30 or 60 minutes prior to a glucose infusion, whereas there was no increase when the metformin was administered at the same time as the glucose. The results suggest that, if tolerated, administering standard-release metformin before meals may lead to improved postprandial glycaemic control.

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Historically, metformin was believed to lower blood glucose levels only by decreasing hepatic glucose production, and this mechanism does indeed contribute to the drug's effects on fasting glucose levels. Recent studies, however, have suggested that metformin's postprandial glucose-lowering effect is achieved through multiple actions on the gut, including stimulation of GLP-1 release, suppression of glucose absorption from the intestine and effects on the gut microbiome. The increased endogenous GLP-1 secretion in turn suppresses glucagon release from the alpha-cells and stimulates insulin secretion from the beta-cells of the pancreas, as well as slowing gastric emptying and reducing appetite.

In this "proof-of-concept" study in people with type 2 diabetes, Cong Xie and colleagues sought to identify whether the glucose-lowering effects of metformin on a standardised intraduodenal glucose load would differ depending on the timing of metformin administration and, if so, whether this difference would be related to metformin's effects on endogenous GLP-1 and insulin secretion.

Method

In this double-blind, randomised, placebo-controlled study, 16 people with type 2 diabetes well controlled with metformin monotherapy (mean age 69 years, HbA_{1c} 48.2 mmol/mol, diabetes duration 10.4 years) were studied in a crossover design, on four separate days, each at least 7 days apart. Participants were randomly allocated to receive 1000 mg of metformin in 50 mL of normal saline via a nasoduodenal tube at different time points on each occasion: 60 or 30 minutes before, or at the same time as, an intraduodenal glucose load. Normal saline was administered at the other two time points, and at all three time points in the control arm (in which no metformin was administered), to ensure blinding of participants and researchers. In total, 45 g of glucose in 180 mL of water was infused into the duodenum over 60 minutes, at a rate of 3 kcal/minute.

Although "unphysiological", administering metformin and glucose via nasoduodenal tube ensured accurate timing and standardised dosing of the drug and glucose reaching the duodenum. Glucose, insulin and total GLP-1 levels were measured every 30 minutes from 60 minutes prior to the glucose load until 120 minutes after. Nausea and appetite sensations were monitored using a 10 cm visual analogue scale.

Results

When metformin was given 60 or 30 minutes before the glucose load, there were greater glucose reductions than when given at the start of the glucose load. Peak plasma glucose levels (60 minutes after initiation of the glucose infusion) were significantly lower when metformin was given 30 or 60 minutes prior to the glucose load, and they were significantly lower in those receiving metformin 60 minutes prior to glucose compared with metformin given 30 minutes before glucose.

There was a lower glucose area under the curve with metformin administered at all three

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Impact of the timing of metformin administration on glycaemic and glucagon-like peptide-1 responses to intraduodenal glucose infusion in type 2 diabetes: A double-blind, randomised, placebo-controlled, crossover study

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time points compared with controls, but this reduction was greater when metformin was given 60 or 30 minutes before glucose compared to metformin administered at the same time as glucose.

Following the glucose load, plasma GLP-1 levels rose promptly and peaked at 60 minutes. Greater rises in GLP-1 levels were seen when metformin was administered 30 or 60 minutes prior to the glucose load, but not when co-administered with the glucose.

Insulin levels did not change according to metformin timing but increased promptly after the glucose load, peaking at 60 minutes on the control day and at 90 minutes after all three doses of metformin. Insulin levels were higher at 90 minutes after glucose initiation when metformin was given 60 or 30 minutes prior to the glucose than when it was given at the beginning of the glucose infusion.

Nausea scores remained low throughout the study and there was no difference in scores between the various metformin timings; scores of appetite sensations only differed slightly.

Discussion

Building on previous human and animal studies, the authors propose a number of possible mechanisms responsible for their findings, including that the beneficial effects of earlier metformin administration may reflect the time taken for metformin to influence glucose transporters in the upper small intestine, reducing glucose absorption, and that this may link to increased GLP-1 secretion.

There were several limitations to the study. The authors acknowledge that administering the metformin and glucose intraduodenally was "unphysiological"; however, it was necessary to ensure standardisation of dosing and timings. Use of metformin solution means that this study is likely to be less relevant to those taking modified-release formulations of metformin.

As oral metformin slows gastric emptying, this may mean that oral dosing could have a greater impact on reducing postprandial glucose levels by slowing absorption. Finally, it is not clear whether varying the timing of metformin would have the same effects on mixed meals rather than just glucose, as used here.

Implications for practice

In people with well-controlled diabetes (HbA_{1c} <64 mmol/mol), postprandial glucose contributes more to HbA_{1c} than fasting glucose levels, whereas fasting glucose has a greater impact in those with HbA_{1c} over 64 mmol/mol. Increased postprandial glucose rises are an independent predictor of cardiovascular disease, so it is important to reduce them (ElSayed et al, 2023).

Currently we recommend taking metformin with food, in order to minimise gastrointestinal intolerance. In contrast, this small study suggests that in those with well-controlled type 2 diabetes, standard-release metformin may be more effective at lowering glucose levels and increasing endogenous GLP-1 levels if it is administered 30–60 minutes before meals. There was no significant increase in gastrointestinal side effects in this small group of people who were already treated with – and therefore known to be tolerant of – normal-release metformin. However, it will be important to monitor tolerance if we recommend anyone to take metformin 30–60 minutes prior to meals.

It is always difficult to know when to change entrenched practice. This was a small study in which metformin and glucose were administered as a single dose, intraduodenally – a very artificial scenario. It is not clear how this would translate to long-term use of the drug taken twice daily. However, since there appears to be no downside to changing the dose timing, except perhaps increased risk of gut symptoms (which hopefully would reverse if switched back), and no evidence from the studies reviewed that preprandial metformin will be less effective, I will certainly discuss this with practice and secondary care colleagues, try it with a few people and gather some real-world results.

For people on standard metformin where only a small reduction in HbA_{1c} is required to reach our agreed goal, particularly if additional therapies are likely to be onerous (e.g. gliclazide), this will certainly be worth exploring. ■

ElSayed NA, Aleppo G, Aroda VR et al; American Diabetes Association (2023) 6. Glycemic targets: Standards of Care in Diabetes – 2023. *Diabetes Care* **46**(Suppl 1): S97–110

Xie C, Iroga P, Bound MJ et al (2024) Impact of the timing of metformin administration on glycaemic and glucagon-like peptide-1 responses to intraduodenal glucose infusion in type 2 diabetes: A double-blind, randomised, placebo-controlled, crossover study. *Diabetologia* **67**: 1260–70