

DIABETES

A closer look at the mechanisms of action of colestevlam in humans

Colesevelam, a bile-acid sequestrant, lowers glucose levels in patients with type 2 diabetes mellitus (T2DM) by a mechanism that is associated with increased incretin secretion and improved β -cell function, but not with reduced gluconeogenesis or glucose absorption. These findings resulted from a trial conducted at KineMed and sponsored by Daiichi Sankyo.

Colesevelam is approved by the FDA as a treatment to lower LDL-cholesterol levels, but the drug has also been shown to lower glucose levels in patients with T2DM. The mechanisms responsible for this effect, however, are not well known.

The new double-blind randomized study involved 60 patients with T2DM from three US clinical sites. Patients were given 3.75 g of colestevlam per day or placebo for 12 weeks. Glucose and lipid kinetics were analysed by stable-isotope mass-spectrometric kinetic assays.

“The most important conclusion we found was that colestevlam improved

the clearance of glucose by tissues in the fasting state and also during a meal, but had no effect on glucose absorption,” say investigators Carine Beysen and Marc Hellerstein. “We showed for the first time in humans that the improvement in glucose control with colestevlam may be mediated by an increase in incretin secretion.”

“More work is required to assess the mechanisms of action of colestevlam in humans,” comments Daniel Drucker (Samuel Lunefeld Research Institute, Toronto, Canada), who was not involved in the study. “These mechanisms may include activation of the TGR5 or FXR receptors, or possibly recruitment of additional downstream factors.”

Of these potential mechanisms, the researchers favor mediation of changes in glucose metabolism through activation of TGR5 rather than FXR, as they did not observe an effect of colestevlam on gluconeogenesis (although they



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acknowledge that such an effect cannot be completely ruled out).

“Our preliminary results suggest that colestevlam improves glucose control differently from other approved oral diabetes medications,” conclude the researchers. Therefore, “colestevlam might complement other agents for clinical use”.

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Original article Beysen, C. *et al.* Effect of bile acid sequestrants on glucose metabolism, hepatic de novo lipogenesis, and cholesterol and bile acid kinetics in type 2 diabetes: a randomised controlled study. *Diabetologia* doi:10.1007/s00125-011-2382-3