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Effects of Tirzepatide, a Dual GIP and GLP-1 RA, on Lipid and Metabolite Profiles in Subjects With Type 2 Diabetes

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Abstract

Context: Tirzepatide substantially reduced hemoglobin A1c (HbA1c) and body weight in subjects with type 2 diabetes (T2D) compared with the glucagon-like peptide 1 receptor agonist dulaglutide. Improved glycemic control was associated with lower circulating triglycerides and lipoprotein markers and improved markers of beta-cell function and insulin resistance (IR), effects only partially attributable to weight loss.

Objective: Assess plasma metabolome changes mediated by tirzepatide.

Design: Phase 2b trial participants were randomly assigned to receive weekly subcutaneous tirzepatide, dulaglutide, or placebo for 26 weeks. Post hoc exploratory metabolomics and lipidomics analyses were performed.

Setting: Post hoc analysis.

Participants: 259 subjects with T2D.

Intervention(s): Tirzepatide (1, 5, 10, 15 mg), dulaglutide (1.5 mg), or placebo.

Main outcome measure(s): Changes in metabolite levels in response to tirzepatide were assessed against baseline levels, dulaglutide, and placebo using multiplicity correction.

Results: At 26 weeks, a higher dose tirzepatide modulated a cluster of metabolites and lipids associated with IR, obesity, and future T2D risk. Branched-chain amino acids, direct catabolic products glutamate, 3-hydroxyisobutyrate, branched-chain ketoacids, and indirect byproducts such as 2-hydroxybutyrate decreased compared to baseline and placebo. Changes were significantly larger with tirzepatide compared with dulaglutide and directly proportional to reductions of HbA1c, homeostatic model assessment 2-IR indices, and proinsulin levels. Proportional to metabolite changes, triglycerides and diglycerides were lowered significantly compared to baseline, dulaglutide, and placebo, with a bias toward shorter and highly saturated species.

Conclusions: Tirzepatide reduces body weight and improves glycemic control and uniquely modulates metabolites associated with T2D risk and metabolic dysregulation in a direction consistent with improved metabolic health.

Trial registration: ClinicalTrials.gov NCT03131687.

Keywords: diabetes; glucose metabolism; insulin signaling.

Comment in

Tirzepatide as an Insulin Sensitizer.
Ferrannini E.
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