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Abstract

Roux-en-Y gastric bypass (RYGB) is commonly used to treatment obesity and type 2 diabetes mellitus (T2DM). Many patients, but not all, experience T2DM remission after the procedure. The exact mechanism of improved glycemic control after RYGB is not fully elucidated and potential mediators include enhanced post-prandial secretion of glucagon-like peptide 1 (GLP-1), a potent insulin secretagogue, and alterations in bile acid (BA) levels and composition. However, these two mechanisms have not been studied directly in individuals with or without diabetes remission after RYGB. In Aim 1, the role of endogenous GLP-1 on β-cell function will be tested in 30 individuals prior to surgery and at 3 and 12 months after RYGB. Glycemic control, insulin secretion rates, and β-cell glucose sensitivity will be assessed in response to an oral glucose challenge, with and without the infusion of exendin$_{9\text{-}39,}$ a competitive GLP-1 receptor antagonist. We will test the hypothesis that the role of GLP-1 on glucose control is greater in remitters than in non-remitters and that the improvement in β-cell function after RYGB can be blocked by exendin$_{9\text{-}39}$. In Aim 2, we will measure BA levels and composition from two large cohorts who underwent distinct modes of weight loss (RYGB (n=278) versus adjustable gastric banding (AGB) or lifestyle intervention (LSI) (total n=272)) to assess temporal changes in BA in individuals with and without T2DM remission with up to 5 years follow-up. We hypothesize that BA will increase more in those with T2DM remission than without remission and in those who underwent RYGB compared to AGB/LSI. Remitters and RYGB subjects will also have lower levels of 12α-hydroxylated BA which are associated with insulin resistance. The change in BA after RYGB may explain its superior effect on glycemic control. Data from this study will help identify mediators of the short- and long-term mechanism of diabetes remission, or lack of, after RYGB, and potentially lead to the development of new molecular targets for the treatment of T2DM.