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Weight loss (WL) improves obesity-related co-morbidities such as type 2 diabetes mellitus (DM). Unfortunately, WL through life-style interventions has a high degree of recidivism and the paucity of safe, effective and affordable pharmacotherapy together with an increase in the prevalence of morbid obesity has led to a rise in bariatric procedures. Clinical trials in patients with DM show that improvements in glycemia vary between procedures and occur in the following order: Roux-en-Y gastric bypass (RYGB) > sleeve gastrectomy (SG) > laparoscopic adjustable gastric banding (LAGB) > medical/life-style therapy. This order mirrors the amount of WL with each intervention and is a major driver of glycemic improvement. We have shown profound changes unique to RYGB and SG in levels of hormones that make up the “gut-brain” and “enteroinsular” axes. The association of some of these hormones with insulin sensitivity (IS) and glycemia independent of WL strongly suggests that glycemic improvements after surgery occur in part through pathways that are distinct from just calorie restriction. A new direction of this application builds on our results showing that levels of fibroblast growth factor 19 (FGF19), a protein secreted by intestinal cells, are increased after RYGB and SG but not after low calorie diet (LCD). One of the effects of FGF19 is to improve IS, which in rodents occurs via suppression of agouti-related protein (AgRP) neurons in the hypothalamus. Another finding in rodents is that FGF19 ameliorates activation of the hypothalamic-pituitary-adrenal (HPA) axis, further adding to the growing evidence that operating on the gut changes brain activity. We have shown that measurement of plasma AgRP reflects central activity. Thus, in AIM ONE we will explore the “gut-brain-HPA” axis in humans and test the hypothesis that diet-induced WL causes an increase in plasma AgRP and activation of the HPA axis whereas equivalent WL after RYGB or SG do not produce such an increase. These findings are of clinical significance as preventing activation of the HPA axis may control hunger and allow for long-term maintenance of WL. In AIM TWO we will utilize proteomic analysis to further extend our investigations of WL dependent and independent mechanisms that may account for differences in metabolic outcomes between LCD, RYGB and SG. A number of experimental paradigms indicate that protein secreted from the proximal small intestine induces insulin resistance which provides a possible explanation as to why RYGB, which excludes this segment of the intestine, produces superior results compared with SG that are independent of WL. In the proposed Aims subjects will be carefully characterized with frequently sampled intravenous glucose tolerance tests and mixed meal tolerance tests. We expect results that will tease out mechanisms related to improvements in IS and beta-cell function that are independent of weight reduction and specific to RYGB or SG with the ultimate goal of optimizing surgical procedures and providing new non-surgical therapeutic targets for the treatment of DM and obesity.