Insights into insulin resistance from metabolomics analysis following bariatric surgery. Charles F. Burant, MD, PhD University of Michigan, Ann Arbor, MI, 48103

Significant improvement in insulin resistance, cardiovascular risk factors and resolution of diabetes can found following weight loss. Roux-en-Y (RY) gastric bypass is more effective than either Gastric Banding (GB) or the institution of Very Low Calorie Diets (VLCD). We have conducted a series of metabolomic studies to understand the alteration in plasma metabolite levels in obesity and changes following weight loss and their relationship to improvement in metabolic parameters. In initial experiments, we assessed the levels of plasma and cerebral spinal fluid levels of amino acids and fatty acids in overweight and obese individuals at baseline and following 10% weight loss. We found that the fall in most amino acids in the CNS paralleled the expected fall in the plasma, but the relative reduction in CSF amino acids was greater in the more obese individuals.

We next used directed metabolomics to profile plasma amino acid levels in 3 groups of non-diabetic women during a mixed meal challenge: 4 lean (BMI=21.1±1.5), 6 before (BMI=53.3±11.0) and after (BMI=36.6±3.8) Roux-en-Y (RY) bypass, and 5 before (BMI=40.8±5.0) and after (BMI=34.5±5.2) Gastric Banding (GB). Fasting BCAA were higher at baseline in the RYGB and LAGB subjects compared with lean (17 and 24%, respectively), consistent with previous observations and decreased following wt loss in both groups. We find a linear relationship between BCAA (and the individual branched chain amino acids) and insulin resistance, in lean and obese pre- and post-surgery.In contrast, there was an inverse relationship between fasting glycine levels and HOMA. We also assessed the dynamic changes in plasma amino acid levels in response to Optifast challenge, before and following surgical weight loss. A consistent alteration in the amino acid curves post-RYGB was seen, with a sharper and higher rise in most amino acids compared to the profiles in LAGB patients after surgery (Figure 8A).This unique profile is likely due to the Roux-en-Y operative procedure and not due to alteration in body weight as final weight was identical in following surgery in both groups. A simple but potentially physiologically important explanation is that the diversion of nutrient absorption past the duodenum results in upregulation of intestinal transporters causing more rapid absorption.

In an initial analysis to identify additional metabolites that may contribute to satiety signals and glucose homeostasis following RYGB, we analyzed fasting and 30min post-prandial plasma from individuals at baseline and 12 mos following RYGB (24.5% wt loss). When fasting samples were compared we found 24(out of 239)metabolites were statistically different. Notable decreases were fatty acids, glucose and ketone bodies and vitamin D metabolites. Significant increases were seen in arginine, which is not detected in our standard amino acid assay and the catecholamine metabolite vanillylmandelic acid which has previously been reported to fall following wt loss induced by diet (74). Interestingly, vanillylmandelic acid was reduced 30 minutes following RYGB-induced weight reduction.When we compared the levels of metabolites 30min after meal in presurgical subjects, we found a significant change in a number of metabolites (Table). Additional data from GB patients suggest a procedure-specific change in metabolite dynamic. The data show that we will be able to further elucidate the relationship between amino acids and other metabolites with body wt, insulin resistance, wt loss and modality of weight loss. These data also emphasize the importance of examining post-meal changes after surgery that have not been previously reported.

	Number	UP	Down	Comment
Baseline Pre vs post	**24**	**7**	**17**	**Down primarily fatty acids and derivatives.**
Baseline 0 to 30 min MMTT	**52**	**25**	**27**	**Increases in amino acids, glucose, lactate, bile acids; decreases in fatty acid species**
Wt Loss 0 to 30 min MMTT	**75**	**21**	**54**	**Increases in amino acids, glucose, lactate, bile acids; decreases in fatty acid species, catacholamines**